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Human Organ/Tissue Growth Algorithms that Include Obese Individuals and Black/White Population Organ Weight Similarities from Autopsy Data

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Physiologically based pharmacokinetic (PBPK) models need the correct organ/tissue weights to match various total body weights in order to be applied to children and the obese individual. Baseline data from Reference Man for the growth of human organs (adrenals, brain, heart, kidneys, liver, lungs, pancreas, spleen, thymus, and thyroid) were augmented with autopsy data to extend the describing polynomials to include the morbidly obese individual (up to 250 kg). Additional literature data similarly extends the growth curves for blood volume, muscle, skin, and adipose tissue. Collectively these polynomials were used to calculate blood/organ/tissue weights for males and females from birth to 250 kg, which can be directly used to help parameterize PBPK models. In contrast to other black/white anthropomorphic measurements, the data demonstrated no observable or statistical difference in weights for any organ/tissue between individuals identified as black or white in the autopsy reports.

Physiologically based pharmacokinetic (PBPK) models are usually constructed to depict the fate of a xenobiotic during a relatively short time frame when compared to the life span of the animal. The age and/or weight of the animal is normally considered a constant during this modeling exercise. However, the average or normal weight for the adult animal and in turn the "normal" weight for the organs and tissues are not necessarily the proper weights for the modeling. These PBPK models need to be able to accommodate the young and old as well as the thin and obese individual. There needs to be a means for relating the appropriate organ/tissue weights with any body weight.

Most PBPK models are developed for a specific xenobiotic. These models assume a variety of appearances, with few to many individual or grouped "organs" being represented depending upon the need of the study. Luecke et al. (2007, 2008) have taken a different approach by developing a generalized PBPK model that can be applied to any xenobiotic in several species including humans. In so doing, the inclusion of most organs/tissues was necessary to ensure the applicability of the model to many different and varied circumstances. In some cases the added detail may be irrelevant, but in other cases a small tissue region may be a focus of consideration. Added detail from a priori sources contributes structure to the model enhancing predictability although in many cases imperceptibly.

All PBPK models depend on a knowledge of organ weights and blood flows in order to calculate the distribution of any xenobiotic. Luecke et al. (2007) derived polynomials that calculated for a normal or "standard" individual estimates for organ/tissue/blood weights that depended only on species, gender, and total body weight. These polynomials were applicable from neonate to adult for humans, dogs, rats, and mice. Upper weight limits were imposed on these polynomial calculations

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based on the available data, which, for the human, came mainly from Reference Man (ICRP, 1975). For humans the upper limits were 65 kg for females and 75 kg for males.

Extension of the PBPK model for xenobiotic concentrations to obese humans requires obtaining organ weight data for higher total body weights. Actual individual autopsy data were the optimal source since most of the literature reported only average information for both the organ/tissue weight as well as the related total body weight. Also literature data on organ or tissue weights for the morbidly obese are almost nonexistent.

Not all organs/tissue weights are documented in autopsy reports—adipose, muscle, and skin, to be more specific. Blood volume is also not reported. And of course cardiac output is not a staple of an autopsy report. Each of these parameters needed to be extended to include reasonable values for a PBPK model of the obese individual. Such data had to be found in the literature.

Differences due to race (specifically black/white differences) had not been anticipated. However, the literature quickly brought this issue to the forefront as almost all relevant reports claimed a body composition difference between blacks and whites.

METHODS

Autopsy records from the University of Arkansas for Medical Sciences between 1964 and 1999 were randomly accessed by hand to obtain organ weights, cause of death, and demographic information of age, body weight, height, and race. In the case of paired organs (i.e., adrenals, kidneys, lungs), the sum of the two organs was recorded. The Arkansas Crime Lab database containing postmortem examinations since 1999 was also accessed for the same information. No personal identifiers were obtained. This study was determined to be not human research and therefore approval was not required by the Institutional Review Board of the University of Arkansas for Medical Sciences and the Research Involving Human Subjects Committee for the Food and Drug Administration.

During the latter stages of data gathering, increased emphasis was given to finding those individuals which were either stated to be obese by the prosector or had a body mass index (BMI) calculated to be greater than 30. An attempt was made to obtain approximately equal numbers of males and females with an equal number of BMI values of <20, 20–30, and >30. All data were maintained and subjected to analyses in an Excel database. No culling of autopsy reports was done based on clinical diagnosis; however, disease state or cause of death was retained as part of the data set and was used to delete specific organ data.

Organ weight data were reviewed in light of the cause of death. In cases where the cause of death was likely to produce an erroneous increase or decrease in the weight of an organ, the specific organ weight was deleted. In all cases where the cause of death was a gunshot wound, the organ weights of organs injured by the projectile(s) were deleted. Organ weights that were abnormally enlarged due to natural disease were also deleted. For example, the weights of the hearts were deleted in all cases of dilated cardiomyopathy, and lung weights were deleted in cases of pneumonia. In the cases where an organ weight was deleted, all other organ weights for that individual remained as part of the data set.

As the autopsy data set was comprised, by chance alone, of approximately an equal number of black and white individuals for each gender, each organ subset was tested to determine if there was a difference due to race. Black/white organ/tissue weight or fractional weight comparisons utilized an SAS (SAS Institute, Inc., Cary, NC) procedure that tested a generalized linear regression model for significance of the effects of body weight, race, and weight by race interaction. Significance was set at the .05 level.

For development of the polynomials, organ weight was plotted as a fraction of the total body weight for each organ versus total body weight for males and females separately. Data previously obtained from Reference Man (ICRP, 1975) and reported in Luecke et al. (2007) were added to each set of autopsy organ weight data. Using an SAS polynomial regression procedure written specifically for this analysis, which adjusted for number of observations for each data point and allowed for easy choice of up to a fifth order polynomial, a functional algorithm was determined for each organ. Only polynomials were considered since the resulting formulas were to be used in an existing PBPK model for calculation of organ weights based on gender and total body weight (Luecke et al., 2007). The lowest order polynomial was chosen that had all coefficients statistically significant at p values <.05.

As these data were gathered specifically to assess the affects of obesity on organ and tissue mass, the weights of adipose and muscle tissues were important factors. Since autopsies are not designed to document total adipose and muscle tissue mass, other literature was searched for relevant data. The literature data for muscle tissue (Aloia et al., 1999; Bosy-Westphal et al., 2004; Heymsfield et al., 1990; Janssen et al., 2000; Kim et al., 2002, 2006; Kyle et al., 2001; Lee et al., 2000, 2004; Proctor et al., 1999; Shen et al., 2004; Wang et al., 1996) and adipose/fat tissue (Aloia et al., 1999; Barlett et al., 1991; Bosy-Westphal et al., 2004; Ferland et al., 1989; Kehayias et al., 1991; Kim et al., 2002; Kvist et al., 1988; Kyle et al., 2001; Lafortuna et al., 2005; McNeill et al., 1991; Proctor et al., 1999; Ross et al., 1993; Salamone et al., 2000; Shen et al., 2004; Sohlstrom et al., 1993; Svendsen et al., 1991) were added to the curves obtained from Reference Man (ICRP, 1975) in order to extend these tissue curves to higher total body weight. The maximum body weight for which adipose tissue weight was found was 163 kg for male and 148 kg for female (Lafortuna et al., 2005), and for muscle tissue the maximum body weight was only 92 kg for female and 107 kg for male (Lee et al., 2000). Since our PBPK model considered total body mass, values for weight and fraction of total weight of nonperfused tissue were also assessed.

Two articles offered formulas to calculate adipose tissue volume. Kvist et al. (1988) utilized the formulas $1.36 \times (\text{wt/ht}) - 42.0$ for adult males and $1.61 \times (\text{wt/ht}) - 38.3$ for adult females to calculate total adipose tissue volumes with weight (wt) in kilograms, height (ht) in meters, and adipose tissue volume in liters. The adipose tissue volume was converted to weight using the specific gravity value of 0.916 (Reference Man, ICRP, 1975). Aloia et al. (1999) proposed slightly different equations for black and white women for body fat (kg) and muscle mass (kg), which included age (yr) as well as weight (kg) and height (cm). All of these formulas were applied to our autopsy data restricted by similar constraints of age and BMI as reported in the original source papers. For the female autopsy data, the adipose calculations from these 2 articles differed on the average by only 8%.

Since the objective was to predict organ and tissue weight up to 250 kg total body weight, extrapolation outside the range of available data was required for some organs. This involved several assumptions:

1. The basis for extrapolation was that autopsy data showed some organ weights increasing slightly up to the maximum autopsy weight available (140 kg for males and 205 kg for females).
2. Organ weights at body weights higher than in this specific autopsy data set were assumed to be constant with further increase in total body weight.
3. Blood and skin weight increased with increasing body weight up to the 250-kg goal.
4. Most of the weight greater than a total body weight of 100 kg was due to increase in adipose tissue (fat).
5. Nonperfused tissue was held to an approximate constant weight after 60 kg total body weight for females and 75 kg for males.
6. The last polynomial equation to be defined was for adipose tissue, and it was determined by material balance with the sum of the organ and tissue weights comprising 100% of the total body weight.

RESULTS

The demographics from the autopsy data are depicted in Table 1. There were a total of 325 autopsy records summarized to form this data set. There were slightly more males than females (192 vs. 133) but approximately the same

TABLE 1
Demographics Describing the Autopsy Data

						Number of useable values per organ/gender		
Total autopsies summarized		325			325			
						Organ	Male	Female
Number of males		192			192	adrenals	147	110
Number of black males	84		Number with BMI < 20 (low)	69		brain	170	115
Number of white males	105		Number with BMI > 20 and < 30 (normal)	66		heart	181	126
Number of other males	3		Number with BMI > 30 (high)	57		kidneys	182	126
						liver	172	126
Number of females		133			133	lungs	146	110
Number of black females	65		Number with BMI < 20 (low)	42		pancreas	142	93
Number of white females	67		Number with BMI > 20 & < 30 (normal)	52		spleen	179	127
Number of other females	1		Number with BMI > 30 (high)	39		thymus	50	27
						thyroid	75	52

Age groups (yr)	Males	Females	Males			Females			Totals		
			Low BMI	Normal	High BMI	Low BMI	Normal	High BMI	Low BMI	Normal	High BMI
<1	47	22	46	1	0	20	2	0	66	3	0
1–<10	11	9	9	2	0	8	1	0	17	3	0
10–<20	11	10	3	7	1	5	4	1	8	11	2
20–<30	21	19	2	13	6	4	11	4	6	24	10
30–<40	26	13	4	7	15	0	8	5	4	15	20
40–<50	27	22	1	9	17	1	5	16	2	14	33
50–<60	26	17	2	15	9	2	11	4	4	26	13
60–<70	10	11	0	7	3	1	6	4	1	13	7
>70	13	10	2	5	6	1	4	5	3	9	11
	192	133	69	66	57	42	52	39	111	118	96

proportion of low (<20), "normal" (20–30), and high (>30) BMI values for each gender. There were about an equal number of black and white individuals in the data set. The number of values for the specific organs (upper right quadrant of Table 1) ranged from a low of 27 for the female thymus to a high of 182 for the male kidneys. The breakdown by age group is also presented. The greatest proportion (~75%) of the low BMI values were observed in the age groups <10 years old.

Since the range of age (birth to 106 yr old) and weight (0.5 to 205 kg) is so broad, no attempt at presenting average weight data for each organ has been made. Even using only the "adult" data, the range of weights is so large as to make any averaging meaningless.

There are many references in the literature that imply that body composition is different between black and white individuals (listing only a few: Aloia et al., 1999; Conway et al., 1995; Gasperino, 1996; Kleerekoper et al., 1994; Yanovski et al., 1996). However, none of these references include organ weights as part of the body composition measurements or calculations. Adipose and muscle mass are most often mentioned in these articles. In an editorial, Reid (1997) stated that when adipose weight was expressed as a fraction of total body weight, the apparent differences between the two racial groups was no longer evident.

The observations and statistical analysis from this autopsy data set do not support differences between black and white organ weights or fractional weights.

As an example, Figure 1 illustrates the apparent visual randomness of the liver data from the autopsy data set (Figure 1a: male liver weight vs. total body weight; Figure 1b: fractional male liver weight vs. total body weight). All other organs for both genders exhibit this visual randomness with no apparent differences between black and white data. Table 2 presents the statistical results (R^2 and Pr > F values) using a generalized linear model for the comparison of the black and white organs/tissues/blood data based on their weights (columns 4–8) and also on their fractional weights (columns 9–13). A p value <.05 was considered statistically significant. The model R^2 is an indication of goodness of fit but also reflects the number of observations (columns 2 and 3) and has little meaning without being coupled with the adjacent Model p value column. The values contained under the column headings of Model, Body weight, Race, and Wt × Race are p values (i.e., Pr > F) and not the β_i values. Under this analysis, the β_i values are of little interest while the p values are infinitely more interesting. A p value <.05 in the Model column indicates that the data fit this generalized linear model. A p value <.05 in the Body weight column indicates that both data sets (i.e., black and white) are statistically dependent on body weight; the same is true for the Race column (i.e., intercepts are different) and the Weight × Race interaction column (i.e., slopes are different). In contrast, a p value >.05 in the Race and Weight × Race columns coupled with the p values <.05 in the Body weight and Model column indicates that the

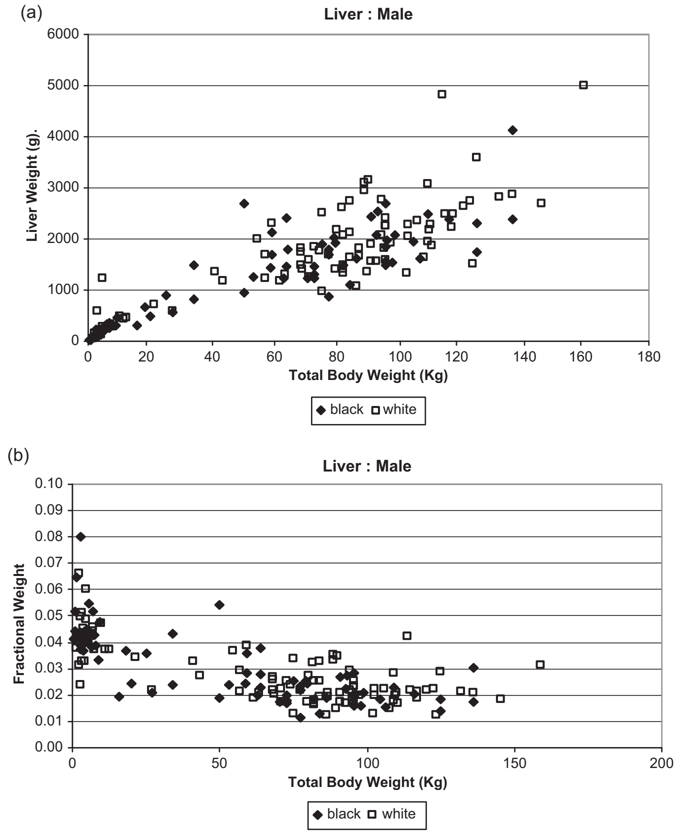

FIG. 1. Comparison of black and white autopsy data for liver from males: (a) liver weight or (b) fractional liver weight vs total body weight.

black and white data slopes and intercepts are not statistically different for that organ/tissue/blood or there is no difference between the black and white data sets. Only the thymus and thyroid data fail to be fitted with a linear model. Logarithmic transformation and/or combining the data across genders failed to provide a linear model for testing, which may be due to the randomness and/or relative sparsity of these two data sets. However, visually it is hard to find any pattern or racial differences for either of these organs.

The fractional weight data set for the male pancreas failed to meet the criteria for a linear model. The data presented for the male in Table 2 are for the combined data set of male and female pancreas, which was linear and dependent only on the body weight, independent of race. This combined black/white comparison was made since the final fractional weight polynomial for the pancreas was calculated for the male and female combined data.

Blood (male and female), adipose (females), and muscle (females) data are included in Table 2 since predictive equations were obtained from the literature that could be applied to this autopsy data set. When comparisons were made using these calculated values, there were no differences found between the races for blood, fat, or muscle.

TABLE 2
Black/White Organ, Tissue, and Blood Comparisons from Autopsy Data Utilizing a Generalized Linear Regression Model from SAS

	Number of observations		Organ weight vs. total body weight					Fractional organ weight vs. total body weight				
	Number black	Number white	Model R^2	Model	Body weight	Race	Wt*Race	Model R^2	Model	Body weight	Race	Wt*Race
Male												
adrenals	68	76	0.562	<0.0001	<0.0001	0.8487	0.6210	0.302	<0.0001	<0.0001	0.3354	0.5427
brain	73	93	0.624	<0.0001	<0.0001	0.1901	0.5996	0.724	<0.0001	<0.0001	0.3060	0.0721
heart	79	99	0.783	<0.0001	<0.0001	0.1358	0.5274	0.316	<0.0001	<0.0001	0.7984	0.5688
kidneys	80	99	0.715	<0.0001	<0.0001	0.3912	0.9492	0.407	<0.0001	<0.0001	0.3180	0.1285
liver	76	94	0.778	<0.0001	<0.0001	0.8904	0.4492	0.237	<0.0001	<0.0001	0.0522	0.2628
lungs	69	76	0.766	<0.0001	<0.0001	0.0825	0.4277	0.287	<0.0001	<0.0001	0.3028	0.9557
**pancreas	105	126	0.588	<0.0001	<0.0001	0.8772	0.1101	0.063	0.0021	0.0038	0.2274	0.8231
spleen	81	95	0.482	<0.0001	<0.0001	0.6647	0.1374	0.073	0.0043	0.0045	0.3909	0.3763
thymus	30	21	0.100	0.1712	0.0483	0.1866	0.0406	0.051	0.4822	0.4226	0.7348	0.6317
thyroid	35	38	0.390	<0.0001	<0.0001	0.4878	0.1252	0.072	0.1591	0.4995	0.3950	0.1122
*blood	72	105	0.959	<0.0001	<0.0001	0.5848	0.5642	0.837	<0.0001	<0.0001	0.4565	0.7491
Female												
adrenals	57	52	0.527	<0.0001	<0.0001	0.6323	0.2876	0.299	<0.0001	<0.0001	0.0840	0.2096
brain	60	55	0.462	<0.0001	<0.0001	0.8132	0.2462	0.552	<0.0001	<0.0001	0.5867	0.9093
heart	63	62	0.685	<0.0001	<0.0001	0.8402	0.4408	0.336	<0.0001	<0.0001	0.3319	0.7382
kidneys	63	62	0.519	<0.0001	<0.0001	0.2951	0.2188	0.427	<0.0001	<0.0001	0.1863	0.2029
liver	63	60	0.642	<0.0001	<0.0001	0.5248	0.6474	0.439	<0.0001	<0.0001	0.1168	0.2183
lungs	55	54	0.507	<0.0001	<0.0001	0.5021	0.6022	0.397	<0.0001	<0.0001	0.0864	0.6294
pancreas	48	44	0.514	<0.0001	<0.0001	0.5841	0.9172	0.118	0.0110	0.0031	0.3093	0.6893
spleen	63	63	0.258	<0.0001	<0.0001	0.5923	0.5403	0.128	0.0008	0.0015	0.1002	0.5681
thymus	13	14	0.299	0.0392	0.2056	0.2535	0.3003	0.116	0.4077	0.9294	0.6277	0.7993
thyroid	33	18	0.424	<0.0001	<0.0001	0.0548	0.0302	0.147	0.0561	0.1141	0.0575	0.0785
*blood	64	67	0.900	<0.0001	<0.0001	0.7405	0.1850	0.773	<0.0001	<0.0001	0.4737	0.8782
*adipose	20	25	0.942	<0.0001	<0.0001	0.2566	0.5056	0.715	<0.0001	<0.0001	0.2199	0.3807
*muscle	20	25	0.776	<0.0001	<0.0001	0.3477	0.6669	0.643	<0.0001	<0.0001	0.2672	0.4717

Note. Values reported are R^2 and Pr > F *for* $Y = \beta_0 + \beta_1$ *Wt + β_2 *Race + β_3 *Wt *Race where Wt = total body weight (g).
Highlighted cells are those that are not consistent with the conclusion that there are no differences between the black and white organ data sets.
*Blood values were calculated from a formula from Lemmens et al. (2006); adipose and muscle values were calculated from formulas from Aloia et al. (1999).
**Pancreas data in this row are for the combined dataset of male and female values.

Since there were no apparent graphical or statistical differences due to race, the organ weight data from black and white individuals were combined for the determination of the fractional weight polynomial algorithms for each organ for each gender.

All of the organ weight data were treated with a similar procedure. The organ weight data were transformed to a fraction of the total body weight since this format lent itself to being represented by polynomial algorithms better than the raw weight data. These polynomials are included within the authors' generalized PBPK model called PostNatal (Luecke et al., 2007, 2008). The fractional weight was then plotted against total body weight for the polynomial construction. Both the autopsy data and the Reference Man (ICRP, 1975) data were combined for the analysis. The SAS program was systematically altered to test a constant fraction (i.e., fractional organ weight = X_0) up to a fifth order polynomial. Both an R^2 and a p value were used to assess the goodness of fit. For all but the most random data, a $p < .0001$ was usually obtained for each coefficient (right side of Table 3).

Figure 2 (a–f) illustrates the fractional organ weight versus total body weight data for selected male and female organs including the curve representing the best-fit polynomial. The coefficients

TABLE 3a

Organ Weight Polynomials for Humans, Expressed as Fraction of Total Body Weight

							p Values that correspond to each coefficient in table on the left						Model
Component	X^0	X^1	X^2	X^3	X^4	X^5	X^0	X^1	X^2	X^3	X^4	X^5	R^2
Male													
Brain	1.41E-01	−5.54E-06	9.30E-11	−6.83E-16	1.80E-21	0	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.0007		0.875
Heart	6.32E-03	−1.67E-08	0	0	0	0	< 0.0001	< 0.0001					0.120
Kidney	7.26E-03	−6.69E-08	3.33E-13	0	0	0	< 0.0001	< 0.0001	< 0.0001				0.747
Liver	4.25E-02	−1.01E-06	1.99E-11	−1.66E-16	4.83E-22	0	< 0.0001	< 0.0001	0.0002	0.0020	0.0075		0.535
Lungs	1.86E-02	−4.55E-08	0	0	0	0	< 0.0001	< 0.0001					0.113
Spleen	3.12E-03	−5.57E-09	0	0	0	0	< 0.0001	0.0310					0.022
Female													
Brain	1.12E-01	−3.33E-06	4.30E-11	−2.45E-16	5.03E-22	0	< 0.0001	< 0.0001	< 0.0001	0.0002	0.0077		0.971
Heart	5.40E-03	−1.07E-08	0	0	0	0	< 0.0001	< 0.0001					0.114
Kidney	7.56E-03	−5.58E-08	1.54E-13	0	0	0	< 0.0001	< 0.0001	0.0059				0.420
Liver	3.34E-02	−1.89E-07	5.34E-13	0	0	0	< 0.0001	< 0.0001	0.0499				0.388
Lungs	1.89E-02	−5.94E-08	0	0	0	0	< 0.0001	< 0.0001					0.170
Spleen	2.96E-03	−7.72E-09	0	0	0	0	< 0.0001	0.0002					0.084
Combined													
Adrenals	8.04E-04	−1.98E-08	2.01E-13	−6.11E-19	0	0	< 0.0001	< 0.0001	< 0.0001	< 0.0001			0.386
Pancreas	1.48E-03	0	0	0	0	0	< 0.0001						0
Thymus	3.70E-03	−1.05E-07	7.94E-13	0	0	0	< 0.0001	< 0.0001	0.0005				0.670
Thyroid	2.42E-04	0	0	0	0	0	< 0.0001						0

Note. Format: $Y = X^0 + X^1 *\mathrm{Wt} + X^2 *\mathrm{Wt}^2 + X^3 *\mathrm{Wt}^3 + X^4 *\mathrm{Wt}^4 + X^5 *\mathrm{Wt}^5$ where Y = organ/tissue and Wt = total body weight (g).

TABLE 3b

Blood and Tissue Weight Polynomials for Humans, Expressed as Fraction of Total Body Weight (Coefficients for *X*0–*X*5)

Male													
Adipose	1.61E-01	−3.59E-06	8.28E-11	−3.57E-16	4.73E-22	0	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		0.920
Muscle	9.68E-02	−3.32E-06	1.83E-10	−1.24E-15	0	0	<0.0001	0.0255	<0.0001	<0.0001			0.932
Skin	1.03E-01	−2.56E-06	3.68E-11	−2.58E-16	8.62E-22	−1.10E-27	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.997
Female													
Adipose	1.84E-01	−6.86E-06	2.46E-10	−2.11E-15	7.58E-21	−9.94E-27	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.924
Muscle	3.65E-02	7.91E-06	−5.74E-11	0	0	0	0.0081	<0.0001	<0.0001				0.537
Skin	9.81E-02	−2.28E-06	2.74E-11	−1.58E-16	4.30E-22	−4.43E-28	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.999
Combined													
Blood	8.97E-02	−3.50E-07	6.54E-13	0	0	0	<0.0001	<0.0001	0.0053				0.521

Note. Format: $Y = X^0 + X^1 *\mathrm{Wt} + X^2 *\mathrm{Wt}^2 + X^3 *\mathrm{Wt}^3 + X^4 *\mathrm{Wt}^4 + X^5 *\mathrm{Wt}^5$ where Y = organ/tissue and Wt = total body weight (g).

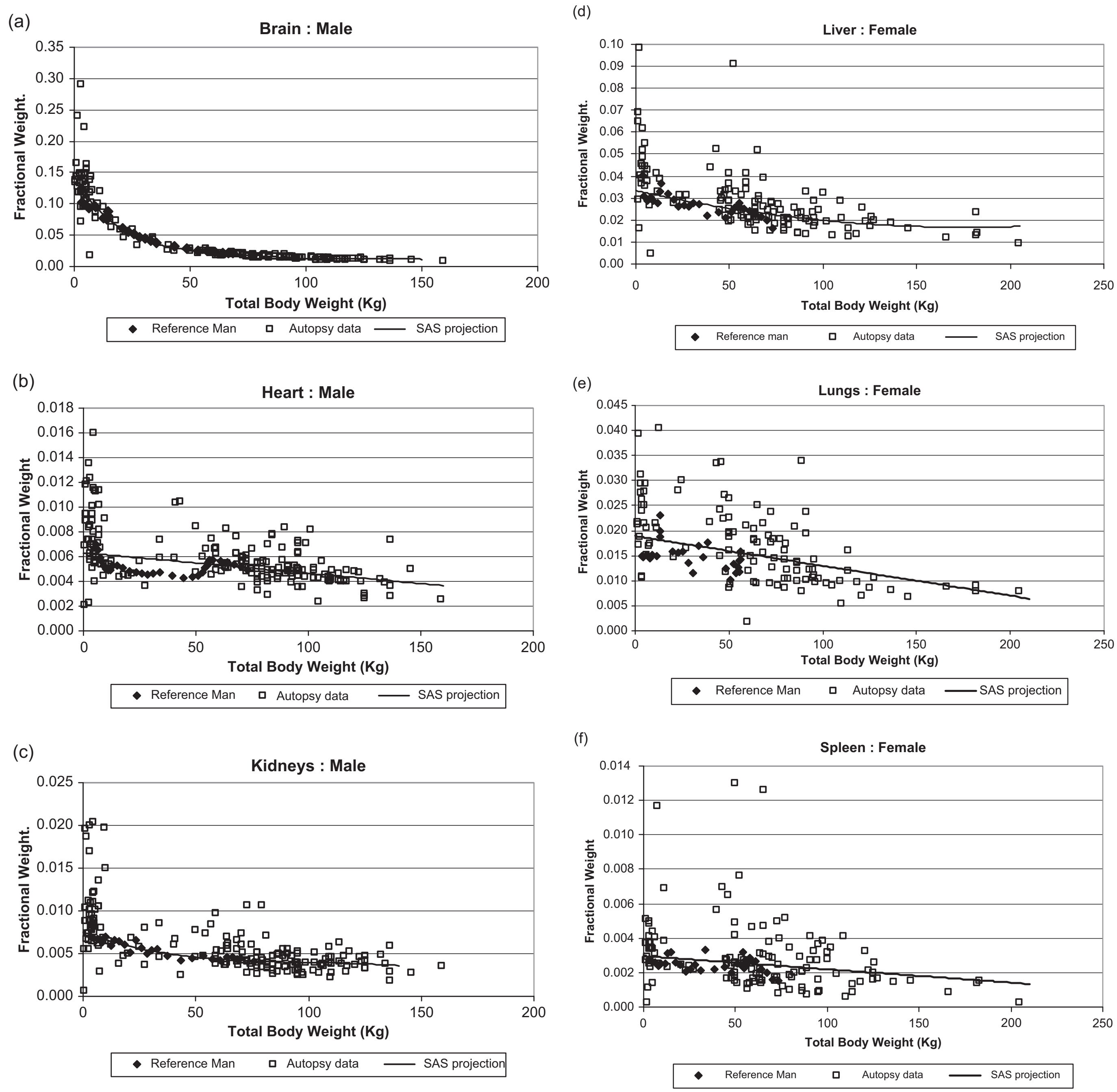

FIG. 2. Fractional organ weight vs total body weight for autopsy and Reference Man (ICRP, 1975) data for (a) male brain, (b) male heart, (c) male kidneys, (d) female liver, (e) female lungs, and (f) female spleen. The solid lines are the polynomials predicted by the SAS projection which are listed in Table 3a.

for the polynomials for all the organs are presented in Table 3a (columns 2–7) along with the corresponding statistical *p* value for each coefficient and R^2 for the equation (columns 8–14). There were no difference between the male and female data for the adrenals, pancreas, thymus, and thyroid; each organ's data from both genders were combined for the polynomial determination. The lowest order polynomial with all coefficients statistically significant ($p < .05$) was chosen for each organ. The values within the left side of the table are the coefficients for the X^i terms of the polynomials. The values within the right side of the table are the *p* values for each coefficient with the R^2 for the polynomial in the last column on the right. One must be cautious when using polynomials as they tend to increase or decrease rapidly outside the data range. At the upper limits of the autopsy data set, the algorithm is terminated and a constant weight for that organ is used for all higher body weights. This strategy implies that increases in total body weight above this limit are the result mainly of increases in adipose (fat).

Table 4 contains organ weight values from 50 to 250 kg total body weight for males and females, calculated mainly from the polynomials presented in Table 3. Bone marrow, diaphragm, gonads, intestines, mammary, and stomach values were carried forward from the polynomials presented by Luecke et al. (2007). The upper limits or cutoff values for the polynomials for each organ/tissue are presented in the far right column of Table 4.

The data with the least scatter across the entire body weight range were for the brain (see Figure 2a). Only the very early data points fall off the SAS projection curve. This early weight variability was seen in all data sets and may have significant implications. Perhaps part of the scatter is due to the large number of autopsy records around birth.

No acceptable polynomial was found for the pancreas or thyroid for either the male or the female. Even when combined, these data did not yield a discernable relationship with total body weight. Therefore a mean constant value taken from all the data was assigned as the algorithm (i.e., $Y = X^0$) to the gender combined data. Note that this constant value does not necessitate a R^2 value (Table 3a).

Adipose and muscle tissues, blood volume, and skin all increase as total body weight increases. None of these tissues or fluids are available from autopsy reports and literature reports are few, and even fewer for the obese individual. However, a few reports were found that allowed for some consideration to be given to the obese individual. Lemmens et al. (2006) reported an equation to calculate blood volume (BV) based on the BMI [i.e., BV = 70/(√(BMI/22))]. This equation was applied to all of our autopsy data, and then the volume was converted to weight using the specific gravity of 1.058 taken from Reference Man (ICRP, 1975). No difference was found between the black and white data from either gender (Figure 3a and Table 2); there was also no difference between the male and female data, and a single polynomial was constructed from the combined data (Figure 3b and Table 3b). The calculated blood weight for the various body weights are given in Table 4.

Skin was a little more challenging since only the polynomials reported by Luecke et al. (2007) were available where each gender's algorithm was based on a Reference Man (ICRP, 1975) theoretical skin curve. However, those polynomials were used to predict skin weights up to a body weight of 100 kg for males and 65 kg for females. Those limited values were used to define a power equation that predicted skin weight to the

TABLE 4a

Male, Organ Weight (g) Projection at Each of the Weights Listed

Body weight (kg)		50	75	100	125	150	175	200	225	250	Cutoff (kg)
Blood		3692	5034	6122	7018	7783	8478	9164	9903	10756	250
Adipose		7355	16666	32066	53056	78001	104687	130874	154848	175977	250
Adrenals		12	14	14	14	14	14	14	14	14	75
Bone marrow	*	2137	2903	2986	2986	2986	2986	2986	2986	2986	78
Brain		1145	1362	1519	1519	1519	1519	1519	1519	1519	94
Diaphragm	*	15	21	21	21	21	21	21	21	21	70
Gonads	*	10	33	33	33	33	33	33	33	33	75
Heart		274	380	465	530	558	558	558	558	558	140
Intestines	*	603	1182	1473	1473	1473	1473	1473	1473	1473	90
Kidneys		237	309	390	390	390	390	390	390	390	100
Liver		1193	1776	2242	2547	2628	2628	2628	2628	2628	130
Lungs		814	1136	1400	1608	1705	1705	1705	1705	1705	140
Muscles		11697	26683	34118	34118	34118	34118	34118	34118	34118	90
Pancreas		74	104	104	104	104	104	104	104	104	70
Skin		1970	2495	3150	3768	4226	4580	5019	5610	5860	250
Spleen		142	203	256	303	327	327	327	327	327	140
Stomach	*	114	137	137	137	137	137	137	137	137	68
Thymus		21	14	14	14	14	14	14	14	14	64
Thyroid		12	18	24	30	34	34	34	34	34	140
Nonperfused***		18483	14532	13467	15333	13931	11196	8884	8580	11348	

Note. Within the shaded area, the individual organ weight does not change as the total body weight increases. *Calculated from polynomials presented by Luecke et al. (2007). **Calculated by difference (i.e., total body weight – sum of all organs/tissues/blood). ***These values are for both genders.

TABLE 4b
Female, Organ Weight (g) Projection at Each of the Weights Below

Tissues/organs Body weight (kg)		50	75	100	125	150	175	200	225	250	Cutoff (kg)
Blood		3692	5034	6122	7018	7783	8478	9164	9903	10756	250
Adipose		11803	28357	50428	74084	96866	118803	141687	166590	189646	250
Adrenals		12	14	14	14	14	14	14	14	14	75
Bone marrow	*	1553	1666	1666	1666	1666	1666	1666	1666	1666	68
Brain		1253	1214	1373	1432	1432	1432	1432	1432	1432	115
Diaphragm	*	15	21	21	21	21	21	21	21	21	70
Gonads	*	28	81	81	81	81	81	81	81	81	70
Heart		243	344	432	507	568	616	624	624	624	180
Intestines	*	623	1152	1168	1168	1168	1168	1168	1168	1168	76
Kidneys		258	318	352	373	397	438	462	462	462	185
Liver		1264	1667	1985	2268	2565	2926	3402	3516	3516	205
Lungs		797	1084	1296	1435	1499	1504	1504	1504	1504	160
Mammary	*	500	750	1000	1250	1500	1750	2000	2250	2500	250
Muscles		14429	21016	21016	21016	21016	21016	21016	21016	21016	68
Pancreas		74	104	104	104	104	104	104	104	104	70
Skin		1771	2043	2491	3057	3581	3954	4188	4423	4840	250
Spleen		129	179	219	250	271	282	284	284	284	192
Stomach	*	114	137	137	137	137	137	137	137	137	68
Thymus		21	14	14	14	14	14	14	14	14	64
Thyroid		12	18	24	30	34	34	34	34	34	140
Nonperfused	**	11409	9788	10058	9076	9284	10563	10999	9758	10182	
Cardiac output (ml/min)***		4454	4781	5276	6407	7845	8786	9078	9117	9119	

Note. Within the shaded area, the individual organ weight does not change as the total body weight increases. *Calculated from polynomials presented by Luecke et al. (2007). **Calculated by difference (i.e., total body weight – sum of all organs/tissues/blood). ***These values are for both genders.

approximate 2/3 power of the body weight. Given its correct theoretical implication to surface area, that power equation was then used to predict skin weights out to 250 kg body weight. The same power exponent was used for the female predictions. These predicted values were then converted to fractional weight values to produce the polynomials presented in Table 3b.

To extend the muscle polynomial to higher total body weights, additional literature was assessed. Numerous citations were found but only a few that contained values that expanded the Reference Man (ICRP, 1975) upper values of 75 kg for male and 64 kg for females. Aloia et al. (1999) provided separate equations for black and white women based on age, weight, and height; these two equations were developed from a cohort of women between the ages of 20 and 70 yr and BMI values between 18 and 30. Application of the equations to the autopsy data set was limited to these same constraints. Figure 4a illustrates the lack of difference between the blacks and whites for the female muscle data based on the autopsy data; Table 2 presents the statistics that support the "no difference" conclusion between the muscle values of black and white females. Similarly, no black/white male muscle comparison data were found.

Figure 5 presents the male (a) and female (b) fractional muscle weight data and resulting polynomials (solid line and Table 3b). Taken collectively the literature data represented 1092 individuals from 8 studies for the male and 1497 individuals from 11 studies for the female assessment.

The literature was also searched for adipose tissue values to expand the polynomial from Luecke et al. (2007) to higher total body weights. Aloia et al. (1999) also provided equations for fat mass for black and white women, which were applied to our autopsy data set. Figures 4b presents this autopsy data projection and again an apparent lack of difference between black and white adipose tissue values. Table 2 presents the statistical values which supports the "no difference" between the black and white female adipose tissue data sets.

The upper limits to the literature values for adipose tissue were 163 kg for males surveyed from 1127 individuals from 10 studies and 148 kg for females surveyed from 1533 individuals from 16 studies. For higher values of total weight up to 250 kg, an estimate for adipose tissue was obtained by a difference calculation. All of the individual organ/tissue/blood values from

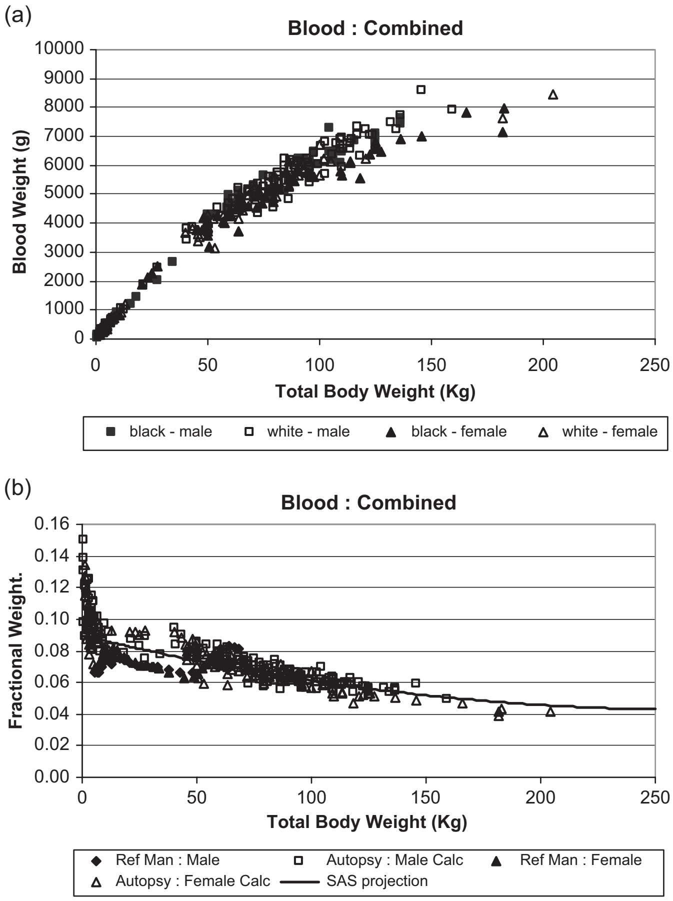

FIG. 3. (a) Comparison of black and white blood weight data calculated from an equation from Lemmens et al. (2006) that was applied to the autopsy data for both genders; (b) fractional blood weight vs. total body weight for the autopsy data presented in (a) plus Reference Man (ICRP, 1975) blood data for both genders. The solid line is the polynomial predicted by the SAS projection, which is listed in Table 3b.

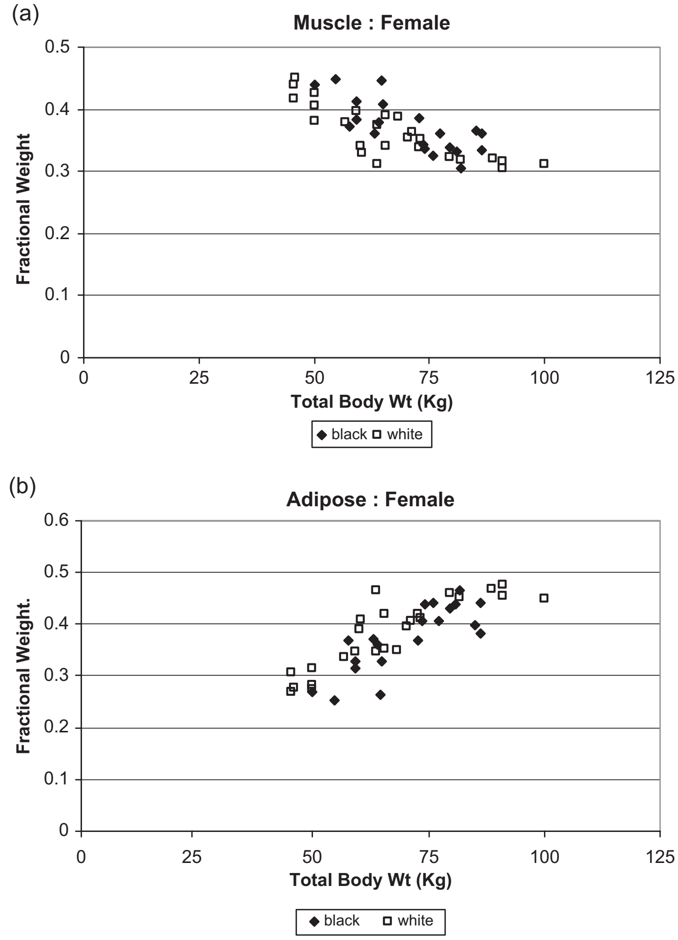

FIG. 4. Comparison of black and white tissue weight data calculated from equations from Aloia et al. (1999) that were applied to limited (i.e., 20–70 yrs old and 18–30 BMI) female autopsy data: (a) fractional muscle weight vs. total body weight and (b) fractional adipose weight vs. total body weight.

Table 4 were summed except for adipose, and that sum was subtracted from the total body weight. The nonperfused tissue was held to a constant weight above 65 kg for females and 75 kg for males for this subtraction calculation. These estimated adipose tissue values were added to the SAS file for calculation of the polynomial for the adipose tissue (large open circles in Figure 6, a and b). Equal regression weight within the SAS regression program based on the number of observations was assigned to the data from Reference Man (ICRP, 1975), calculated values from our autopsy data, the literature values, and the upper range weight values obtained from the subtraction calculation. In turn the polynomial was used to recalculate adipose tissue weights for Table 4. In this circular manner, a final estimate was obtained for the nonperfused compartment. Figure 6 (a and b) presents the fractional weight adipose data and polynomials for the male and female values. Table 3b contains the polynomial coefficients and *p* values for the statistical fit.

Utilizing these algorithms and those previously presented (Luecke et al., 2007) for tissues not included in the autopsy data set, realistic organ weights for a male or female human were calculated up to a total body weight of 250 kg. Organ weights from 50 to 250 kg are presented in Table 4. The last column indicates the total body weight cutoff used for each organ. These are necessarily varied based on the upper values of the autopsy, Reference Man (ICRP, 1975), or other literature data. All organ weights above the cutoff value (shaded area of Table 4) are assumed to be constant for that organ. This is predicated on two issues: (1) no specific organ/tissue weight data available at higher total body weights, and (2) assumption that most of the excess weight in larger individuals is due mainly to adipose tissue. As more data become available, these cutoff values may be raised and the adipose algorithm adjusted accordingly.

The cardiac output polynomial for normal growth (Luecke et al., 2007) overpredicts for the obese individual larger than about 80 kg. An additional literature search

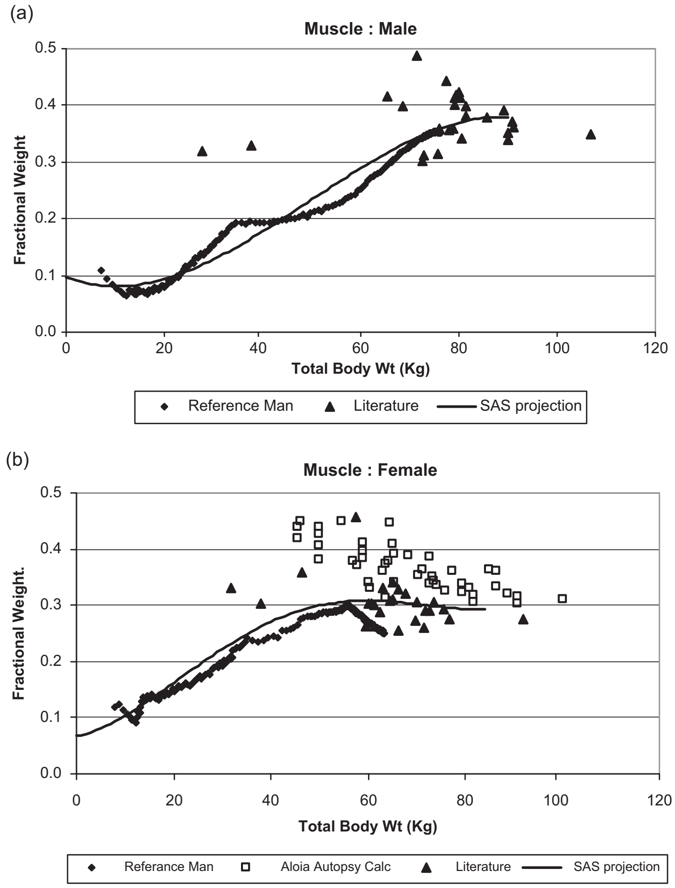

FIG. 5. Fractional muscle weight vs total body weight for male (a) and female (b) autopsy, Reference Man (ICRP, 1975), and literature data. The solid lines are the polynomials predicted by the SAS projection that are listed in Table 3b.

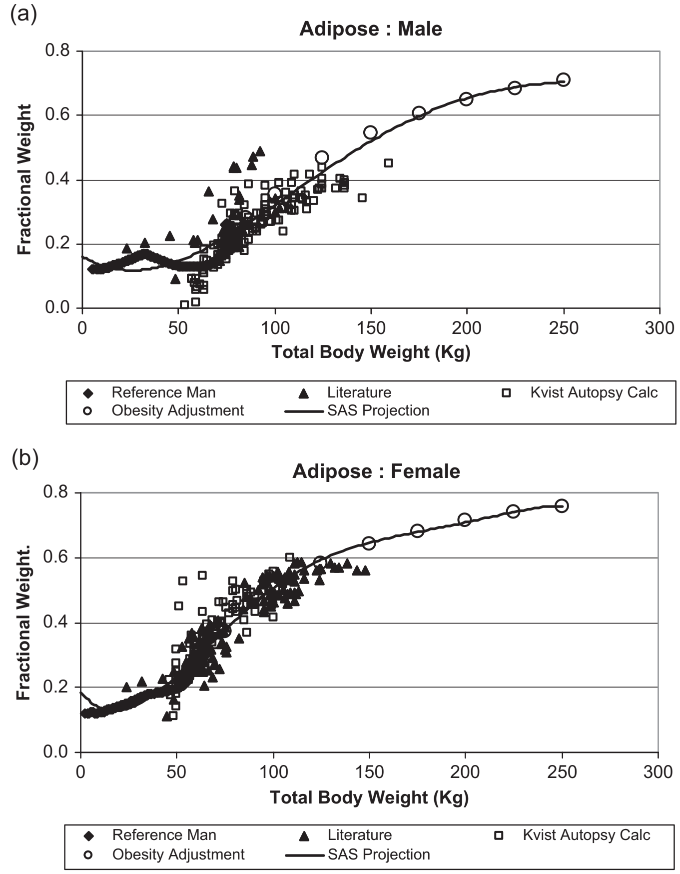

FIG. 6. Fractional adipose tissue weight vs. total body weight for male (a) and female (b) autopsy, Reference Man (ICRP, 1975), and literature data. The solid lines are the polynomials predicted by the SAS projection that are listed in Table 3b.

extends the original normal weight data to include cardiac output values for humans up to 200 kg in total body weight (Alexander et al., 1962–63; Collis et al., 2001; Danias et al., 2003; de Simone et al., 1997; Messerli et al., 1982; Palmieri et al., 2001; Stelfox et al., 2006). The extended data set and cardiac output (CO) algorithm for humans only including the projection to 250 kg are illustrated by Eq. (1) and Figure 7.

$$\mathrm{CO} = f - \exp(a + b^{*}\mathrm{Wt} + c^{*}\,\mathrm{Wt}^2 + d \times \mathrm{Wt}^3) \quad (1)$$

where Wt is total body weight (kg), f = 9119, a = 9.164, b = –2.91E-02, c = 3.91E-04, and d = –1.91E-06. The upper one-fifth of this curve is somewhat speculative but is held constant with the increasing body weight. The projected cardiac output values from this algorithm are displayed at the bottom of Table 4 to match the total body weights at the top of the table.

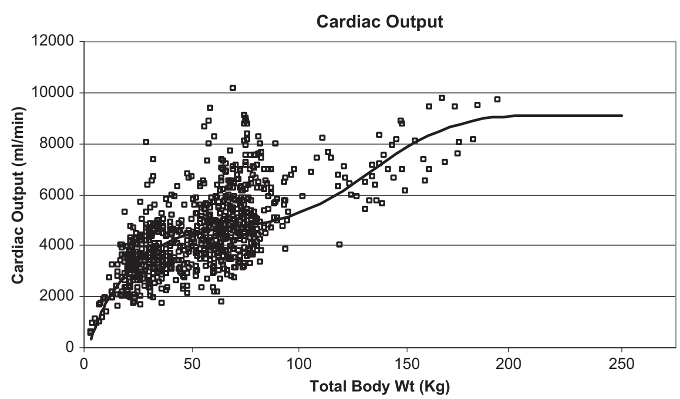

FIG. 7. Cardiac output (ml/min) vs. total body weight for humans. The solid line is calculated from Eq. (1) in the text.

DISCUSSION

The majority of the low BMI values being located in the lower age groups, while troubling at first glance, is consistent with BMI values obtained from growth data from the Centers for Disease Control (CDC, 2000) and also from weight and height data from Stoudt et al. (1960), which is one of the base papers for the data contained in Reference Man (ICRP, 1975). BMI values of <20 are normal for children less than about 15 yr old. Figure 8a indicates that the average BMI values across age have not changed over this 40-yr period for either boys or girls. This is true also for growth (total body weight) versus age from these same two sources (Figure 8b). The concordance of this weight data across time allows the combining of our autopsy data with the data presented in Reference Man (ICRP, 1975) for the present analysis of organ weight growth data. However, it does question the present dogma that obesity is becoming rampant in this country.

The black/white analysis was designed to address the question of whether race has an affect on the relationship between the organ/tissue weights and the body weights. The regression model, $Y = \beta_0 + \beta_1$ (Body weight) + β_2 (Race) + β_3 (Body weight × Race), was applied to all organ/tissue/blood (Y) data sets. The addition of the β_2 (Race) term to the regression model $Y = \beta_0 + \beta_1$ (Body Weight) means that there is a significant difference in the intercepts of the regression models for each race. In the same manner, the addition of the interactive term, β_3 (Body weight × Race), means that there is a significant difference in slopes of the regression models for each race. If the slopes and intercepts of the two data sets (i.e., black vs. white) are the same, then there are no statistical differences in the two sets of data. As indicated by Table 2, there are no differences in the organ weights obtained from these autopsy reports from black or white individuals. Even using separate equations specifically designed to calculate muscle or fat mass for black and white females did not result in statistical differences in the female values for these two tissues. Only thymus and thyroid didn't yield a clear statistical result and that was due to the non-applicability of this generalized linear model.

Autopsy data were the basis for the organ and tissue weights in Reference Man (ICRP, 1975) compiled from data published over the previous 50 yr. The autopsy records for the present data set spanned 43 yr up to 2007. There appears to be fairly good concordance between the two sets of data even though the Reference Man (ICRP, 1975) data were primarily Caucasian and the present autopsy records are about half Caucasian and half Black. Ogiu et al. (1997) reported on 4667 Japanese autopsies reported from 1985–1989 with ages ranging from 0 to 95 yr; exclusion criteria were limited to cadavers with severe postmortem changes, extensive burn injuries, pathological lesions in many organs, or failure to report height or weight. Their data are reported in extensive tables for each organ arranged into 45 uneven age categories. De la Grandmaison et al. (2001) summarized data from 684 adult autopsies limited to a French Caucasoid population, all of whom had died from injury and were without macroscopic evidence of disease. Singh et al. (2004) summarized data from 2025 autopsies from individuals from a specific region of India and were also reported to be without any gross organ pathology. In these latter two references, only broad summary data were presented, and the authors stated that their data were only applicable to a very narrow population and would need to be updated periodically. Figure 9 presents all five sets of data (i.e., Reference Man, Ogiu, de la Grandmaison, Singh, and the present autopsy values) for male liver (Figure 9a) and female kidneys (Figure 9b). The SAS projection based only on the Reference Man (ICRP, 1975) data and the present autopsy data is included with each figure. The agreement of the data from these three literature data sets with our data and that of Reference Man (ICRP, 1975) would imply that this fractional weight algorithm might apply to a much more generalized population. The data from these three literature sources for all organs are in good agreement with all of our data.

Only polynomial functional forms were considered as growth algorithms when fitting these organ/tissue/blood data sets. This was expedient since polynomials are fairly versatile and can be adopted to a variety of shapes by additional terms.

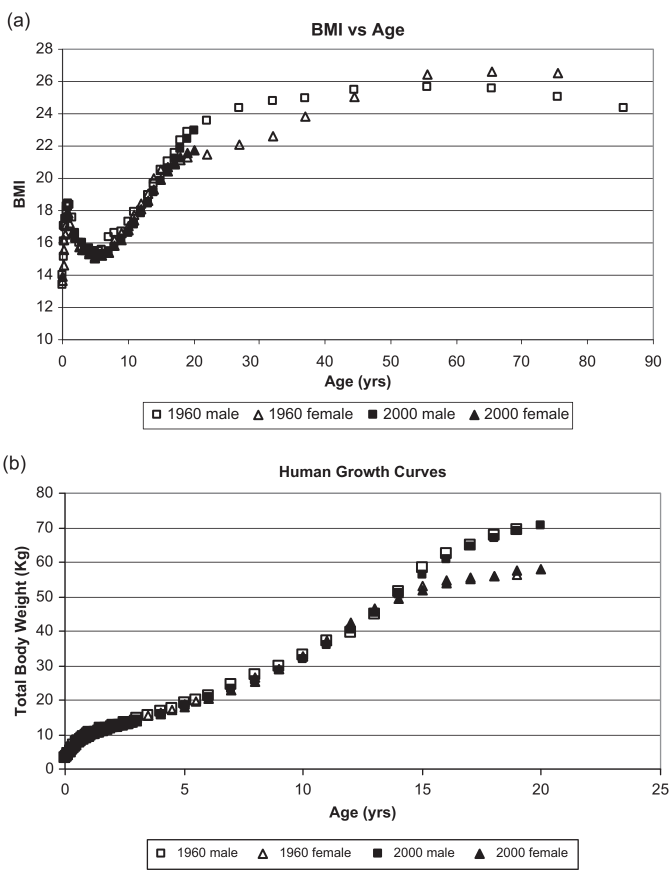

FIG. 8. Comparison of data from Stoudt et al. (1960) and CDC (2000): (a) age vs. BMI for males and females, and (b) age vs. total body weight for males and females.

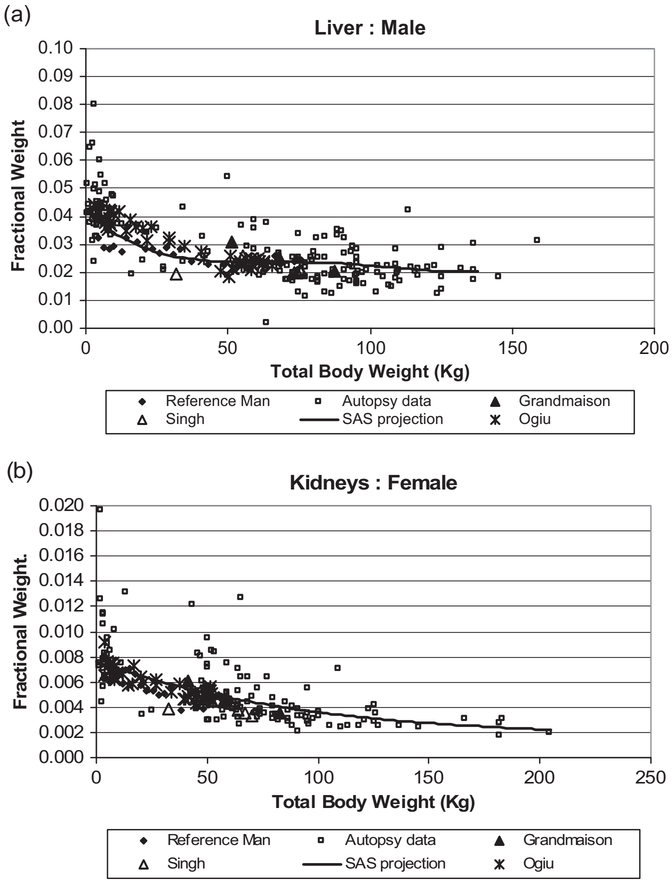

FIG. 9. Fractional organ weight vs. total body weight for male liver (a) and female kidneys (b). The solid lines are the polynomials predicted by the SAS projection that are listed in Table 3a. Superimposed on the Reference Man (ICRP, 1975) and the autopsy data are summary data from Ogiu et al. (1997) (Japanese autopsy data), de la Grandmaison et al. (2001) (French autopsy data), and Singh et al. (2004) (India autopsy data).

In addition, the polynomial coefficients can be easily fit into a two-dimensional matrix format, which had been utilized for the author's PostNatal PBPK program.

The inclusion of many more organs than are routinely incorporated into PBPK models causes no harm and may provide a future modeler with growth data that are already hard to find. The inclusion, exclusion, or lumping of organs into catch-all terms such as slowly perfused organs and rapidly perfused organs is up to the individual modeler and the purpose of the investigation. The down side of including these nonmajor organs in PBPK models is that they must be parameterized for the model to work and are included with this effort to provide those values. If these minor organs are excluded and since most PBPK models account for 100% of the mass, the weight must be assigned to some sort of lumped term. However, the lumped organs must be parameterized also, and with little guidance other than what other researchers have already reported. Often the same authors haven't even used the exact same parameters for weight and blood flow for lumped organs when modeling different xenobiotics. There is also no way to confirm through analytical means what the xenobiotic concentration is in these lumped organs other than measurements in individually identified organs.

The modeler may chose to use these polynomials to calculate organ weights for his or her specific volunteers or might choose to use the values presented in Table 4 if the 25-kg increments is close enough. If lumping is desirable, perhaps the modeler can choose the organs to combine and obtain slowly or rapidly perfused tissue weights in that manner.

Collectively, these algorithms for organ/tissue/blood weight and cardiac output are being utilized to set parameters in a physiologically based pharmacokinetic model (i.e., PostNatal, Luecke et al., 2007, 2008) that can be used for any age human and compensate for the obese individual up to 250 kg total body weight. These adjustments should at least allow some preliminary simulations to explore the affects of a constant dose from the normal to the obese person.

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