Prediction of blood volume in normal human adults

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For many years there has been a diligent search for methods of measuring normal circulating blood associated with attempts to correlate the findings with various body parameters. Accurate information on the normal human being is essential to evaluation of changes that occur in disease states.[2, 9] A survey of the literature indicates that several approaches to the prediction of circulating blood volume have been used. These employ the measurement of circulating plasma volume and/or circulating red blood cell mass and attempts have been made to correlate these measurements with various parameters such as weight alone (with or without correction factors), height and weight, surface area,[2] lean body weight, and, more recently, the cube of height and total body mass.[1] Various anthropometric parameters have been suggested, such as biacromial diameter and skin-fold thickness.

The needs of the physician must be met by a methodology which encorporates readily obtained parameters and a simple technical procedure for the measurement of circulating blood volume. If within these requirements a suitably accurate technique can be set up, then the method is practical. Of necessity, a practical method may carry a certain empiricism and in the technique proposed in this paper attempts were made to estimate blood volume under conditions that simulate the expediency of clinical practice. It is agreed that ideal conditions, including measurement of nude weight and height and other physical parameters, might lead to more accurate estimation of circulating blood volume. Under clinical conditions not all of these requirements can be satisfied and a prediction formula based upon ideal standards might not apply to the critically ill patient. Urgency may even preclude the possibility of accurate weight measurement; anthropometric parameters are not readily utilized by clinicians. For these reasons only the simple, readily-obtained parameters of sex, weight, and height were used. The measurement of plasma volume can be satisfactorily accomplished by estimation of the I^{131}-labeled albumin dilution in plasma. From the concentration of radioactive iodine in whole blood and plasma, estimates of the circulating blood volume, plasma volume, and hematocrit can be obtained. The method is simple, harmless, and reproducible and can be repeated at short intervals.

It has been generally accepted that the only satisfactory method of determining the total circulating blood volume is to tag the red blood cells and measure them separately from tagged plasma; the sum of these two constitutes the total circulating blood volume. This view has been challenged by Chaplin and associates[8] who provided excel-

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lent evidence to indicate the constancy of the ratio of total body hematocrit to venous hematocrit over an observed venous hematocrit range of 9 to 82 per cent. They found the ratio to be 0.910 with a standard deviation of 0.026. Similar ratios have been observed by others.[5, 11, 12, 18] The significance of this work is that it establishes a basis for the estimation of circulating blood volume from a measurement of either the red blood cell volume or plasma volume alone.

This paper reports the results of measurement of the circulating blood volume in 155 normal adult subjects plotted against predicted blood volumes derived from the parameters of sex, height, and weight. It includes a discussion of 3 main prediction bases, weight alone, surface area, and height cubed–body mass. Use is made of the electronic digital computer for the derivation of prediction formulae.

METHODS

Approximately one-half of the normal persons included in this group were ambulatory individuals selected from the hospital staff and personnel and inmates of Angola Prison Farm. The remainder were selected from hospital patients admitted for routine study or minor surgical procedures which could in no way affect the circulating blood volume. None of the subjects gave a history or findings of blood loss, anemia, rapid sedimentation rate, debilitating illness, or malignant disease. There were 92 men and 63 women with an age range of 17 to 90 years. Body weights ranged from 80 to 390 pounds and the heights ranged from 58 to 76 inches. An effort was made to avoid a biased population.

Radioactive I^{131}-labeled albumin was selected because of its ease of application to routine clinical dilution tracer techniques. It is readily available in pyrogen-free sterile solutions. Radioactive counting was performed in a scintillation well counter. The method exhibited an expected standard statistical counting error of about 3 per cent. Syringes which were precalibrated to deliver the volume of tracer material within a 2 per cent error were used. After injection into one antecubital vein, the syringe was rinsed once with blood. All withdrawals of postinjection specimens were obtained from the opposite extremity 10 to 12 minutes after injection. Samples were rejected if there was suspicion of perivenous infiltration, hemolysis, rapid sedimentation of red blood cells, or partial clotting of the specimens. The small error in the technique of injection has been estimated to be about 2 per cent by Hlad and Tanz.[16] Hematocritis were computed from counts on 2 ml. of whole blood and 2 ml. of plasma. The whole blood volume (WBV) and the plasma volume (PV) were calculated from the isotope dilution figures. This "isotope" hematocrit is then represented by:

$$\text{isotope hematocrit} = \frac{\text{WBV} - \text{PV}}{\text{WBV}}$$

The advantages of this method of calculation are obvious. Not only is it independent of "trapped plasma," a factor in centrifuge hematocrit estimates, but it is independent of the g factor of the centrifuge—any centrifuge which separates plasma is adequate. The isotope hematocrits were corrected by the body hematocrit/venous hematocrit ratio, 0.91. Standards were prepared from the same stock bottle used as a source of injection tracer material, which obviated the necessity

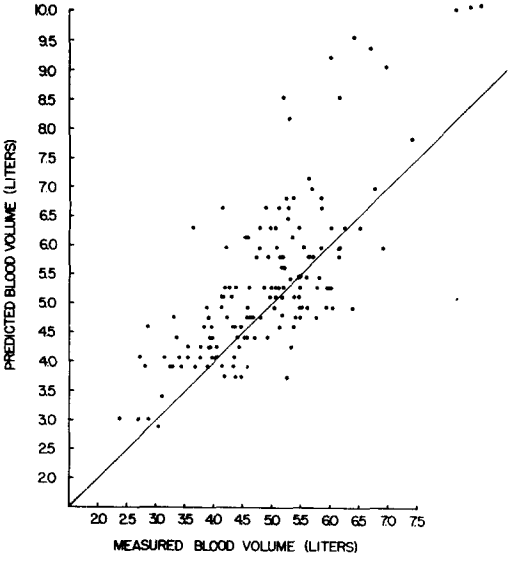


Fig. 1. Measured blood volume (I^{131} HSA) versus 75 ml. per kilogram times body mass (Kg.).

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of meticulous standardization of the stock solutions since the calculations are based on a dilution ratio.

ANALYSIS OF DATA

The determined blood volumes of 155 normal subjects were plotted against calculated blood volumes based on the use of 3 commonly used prediction formulas, (1) body weight formula, (2) surface area formula, and (3) height cubed–body mass formula.

Since a direct ratio between measured and predicted blood volume is sought, a 45 degree line passing through the origin is the only mathematically acceptable line of regression. With perfect correlation, all points would fall on this regression line. The degree of correlation in these scatter plots depends upon the extent to which the points on these plots cluster into an ellipsoid whose major axis approximates collinearity with the 45 degree slope and on the distribution of the points about the major axis (ratio of major to minor axis).

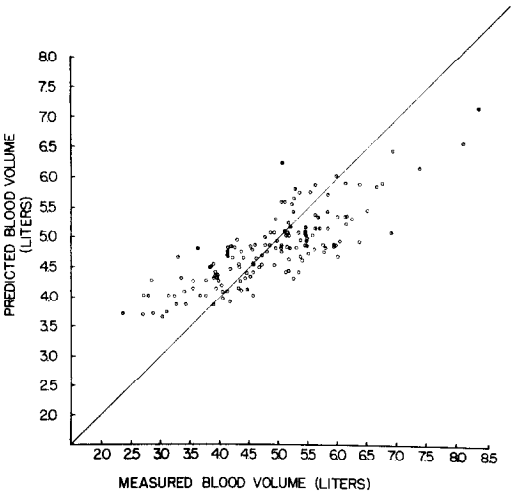


Fig. 2. Measured blood volume (I^{131} HSA) versus 2.68 L. per square meter times surface area.

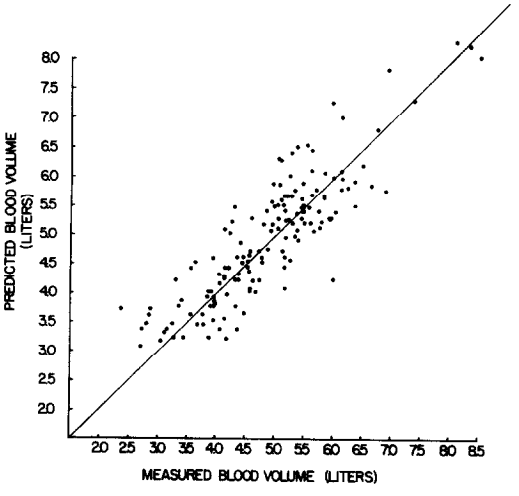


Fig. 3. Measured blood volume (I^{131} HSA) versus height cubed–body mass formula (Allen).

Body weight formula (75 ml. per kilogram times body mass). The normal circulating blood volume has been reported to range from 64 to 79.3 ml. per kilogram of body weight with an average of 75 ml. per kilogram.[13, 20, 21, 23] Women have smaller volumes than men with an average of 66 ml. per kilogram. The sex difference has been explained on the basis of the relatively smaller ratio of metabolically active tissue to fat tissue in women.

Fig. 1 shows our measured blood volumes plotted against body weight as the sole parameter. The lack of ellipsoid clustering of points and the lack of collinearity indicate poor correlation. It is possible to achieve highly inaccurate prediction of blood volume. For example, a male patient weighing 270 pounds with a measured blood volume of 5,990 ml. showed a predicted blood volume of 9,200 ml. The data supply reasonable justification for abandoning the body weight formula as a method of predicting circulating blood volume.

The surface area formula (2.68 L. per square meter times surface area). Baker and his group,[2] using I^{131}-tagged human albumin in 150 clinical subjects, employed 2.68 L. per square meter as a prediction formula. Although they recognized the sex difference in blood volume, no attempt was made to separate men and women; there was no correction for body hematocrit. While their correlation line does not pass through zero, fairly good correlation was obtained.

Fig. 2 shows our measured blood volumes plotted against the predicted volume obtained from the surface area using 2.68 L. per square meter times surface area. The

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points form an ellipsoid of reasonable dimensions, but the major axis is obviously skew to the 45 degree slope regression line—an adequate objection to the acceptance of this formula. Statistical analysis indicates how this formula can be improved.

The height cubed–body mass formula. The major deviations from the mean with formulas 1 and 2 can be largely attributed to differences in adiposity. The work of Behnke and his associates[3, 4] led to the concept of lean body mass being related to total active metabolic tissue as a parameter for the prediction of circulating blood volume. Allen and colleagues[1] studied Chinese subjects by densitometry and skin-fold measurements to determine lean body weight and applied their formula to the prediction of circulating blood volume. With corrections for "trapped" plasma (0.96) and body hematocrit/venous hematocrit ratios (0.91), using the T-1824 dye technique and appropriate correction for the "adiposity factor," the height cubed–body mass formula became:

For men and boys, $BV = 0.417\ H^3 + 0.0450\ TBM - 0.030$ L.

For adult women, $BV = 0.414\ H^3 + 0.0328\ TBM - 0.030$ L.

where BV is blood volume (L.), H is height (M.), and TBM is total body mass (Kg.).

Fig. 3 shows our measured blood volumes plotted against the volumes predicted by Allen's height cubed–body mass formula. While the major axis of the ellipsoid is more nearly collinear with the 45 degree slope regression line, the distribution about this axis is wider than with the surface area formula.

It seemed worthwhile to explore the potential of the IBM electric digital computer in performing a regression analysis. The computer offered an opportunity to compare several formulas—a Herculean task by any other method. The equipment performs a series of approximations to minimize the sums of squares of deviation of the measured blood volume from the predicted blood volume. In essence, there is an automatic performance of the method of least squares. The program of Cates and his group was used.[6] The patients were separated into male and female groups and the surface area and height cubed–body mass formulas were examined by the computer method of regression analysis. The basic surface area formula is of the form:

$$PBV = a_1\ H^{0.725}\ W^{0.425}$$

where PBV is predicted blood volume, a_1 is a constant, H is height (cm.), and W is weight (Kg.).

Using this formula the computer indicated a value for a_1 and a correction factor yielding the following prediction formulas:

For men, $PBV = 0.0236 \times H^{0.725} \times W^{0.425} - 1.229$ (equation 1) where 1.229 L. is the correction factor supplied by the computer to compensate for the skewness shown in Fig. 2.

For women, $PBV = 0.0248 \times H^{0.725} \times W^{0.425} - 1.954$ (equation 2) where 1.954 L. is the correction factor for skewness shown in Fig. 2.

Fig. 4 shows the distribution of data when measured blood volumes of our men and women are plotted against predicted volumes using the computer-corrected formula. Comparison with Fig. 2 shows the loss of skewness. Improvement in correlation is also found (Tables I and II).

The basic height cubed–body mass formula is of the form:

$$PBV = a_1\ H^3 + a_2\ W + a_0$$

where PBV is predicted blood volume, a_1, a_2, and a_0 are constants, H is height (M.), and W is body mass (Kg.).
Regression analysis gave the following formulas:

For men, $PBV = 0.3669\ H^3 + 0.03219\ W + 0.6041$ (equation 3).

For women, $PBV = 0.3561\ H^3 + 0.03308\ W + 0.1833$ (equation 4).

Fig. 5 shows plots of the measured blood volumes of our males and females against volumes predicted by computer-corrected height cubed–body mass formulas. While improvement over the uncorrected height cubed–body mass formulas is difficult to discern visually, statistical data in Tables I and II indicate significant improvement in correlation.

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It was necessary to determine the comparative value of uncorrected and computer-corrected formulas. A statistical program was written for the electronic computer to compare the formulas with the data groups. A portion of the data is given in Tables I and II. The complete statistical analysis will be published elsewhere.[15] The data groups selected were 57 men and 26 women studied by Allen and associates[1] and the 92 men and 63 women in our series.

Table I shows the chi-square data on these 4 groups. The height cubed–body mass formula shows the poorest correlation on our men and the surface area formula shows the poorest correlation for both groups of women. Both of the computer modified formulas show consistently good correlation for all 4 populations.

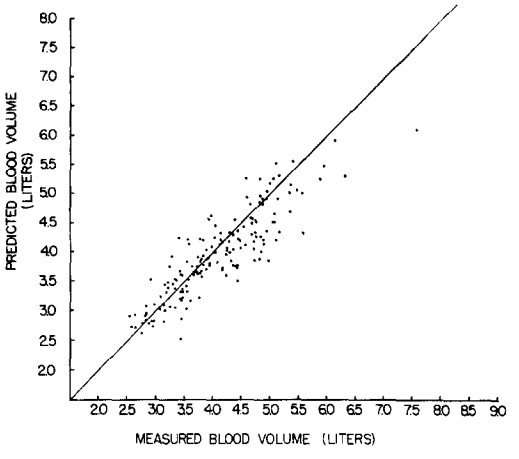


Fig. 4. Measured blood volume (T-1824) versus computer-predicted blood volume.

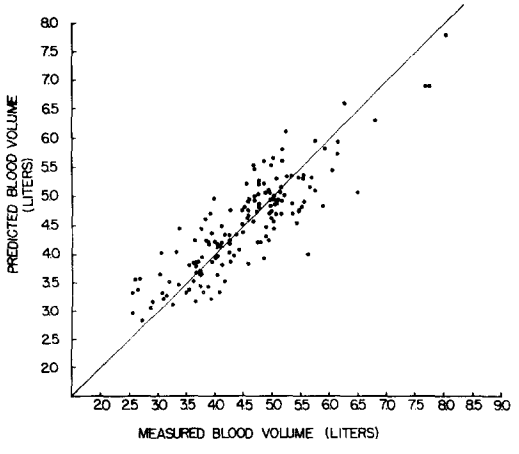


Fig. 5. Measured blood volume (I^{131} HSA) versus computer-corrected height cubed–body mass formula.

Table II shows the standard error of estimate and indicates that based on the chi-square value for our series of 92 men, prediction by the height cubed–body mass leads to the improbable value of 0.048 L. for the standard error of estimate. Similarly, the surface area formula applied to the 26 Allen women leads to the improbable value of 1.638 L. It may be concluded that neither the uncorrected surface area formula nor the uncorrected height cubed–body mass formula will fit all populations. On the other hand, computer modifications of the surface area formula and the height cubed–body mass formula fit all populations equally well. It is not possible to distinguish statistically between the predictions of the computer-corrected surface area formula (equations 1 and 2) and the predictions of the computer-corrected height cubed–body mass formula (equations 3 and 4). Tables III and IV give a schedule of predicted blood volumes based on height and weight for men and women.

Since the measurements in our 155 cases were all done with I^{131} HSA, blood volumes measured by Evans blue dye were plotted against computer-corrected height cubed–body mass formulas. Fig. 6 shows predicted whole volumes on males and females plotted against the measured volumes of 81 patients in Allen's[1] series and 82 cases of Gibson and Evans.[10] Appropriate corrections were made for centrifuge hematocrit and body hematocrit in the latter data. Wennesland and colleagues[25] measured the whole blood of 201 male subjects using Cr^{51} cell tagging and venous hematocrit. Fig. 7 shows predicted whole blood volumes plotted against their measured blood volumes. Hematocrit corrections were applied to their data. Fig. 8 is a composite plot of 518 normal measured blood volumes plotted against predicted blood volumes. It is apparent that the correlation is as good as might be expected from the method, regardless of whether red blood

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cell or plasma tag or dye is used, provided that corrections for centrifuge hematocrit and body hematocrit are applied.

DISCUSSION

The predicted blood volumes depend in part on the isotope measurement, the venous or centrifuge hematocrit measurement and the body hematocrit centrifuge hematocrit ratio. The isotope measurement carries an inherent error of ± 5 per cent because of volume measurements, adsorption on glass, and statistical counting errors.[16, 22] The centrifuge hematocrit measurement has been the subject of some dispute.[7, 24, 25] Corrections for "trapped" plasma in the erythrocyte column vary from 8 to 2 per cent. We have adopted an average correction of 0.96 unless centrifugation under conditions controlled for g factor and time indicate change in this figure.

The correction factor for the ratio body hematocrit/centrifuge hematocrit requires comment since it is used in the calculation of blood volume from either the plasma volume or red blood cell volume according to the equations:

$$BV = PV \times \frac{100}{100 - BH}$$

$$BV = RCV \times \frac{100}{BH}$$

where BV is blood volume, PV is plasma volume, BH is body hematocrit, and RCV is red cell volume.

The blood volume determined from tagged erythrocytes is lower than the blood volume determined from tagged plasma.[5] Thus, the average body hematocrit

$$\frac{RCV}{RCV + PV}$$

is lower than the peripheral venous hematocrit[5, 8, 11, 12, 18] with an average value of 0.91. The absolute value in disease states is still uncertain. If one accepts an inherent ± 5 per cent error in the I^{131} HSA method, the ratio would vary by 3 per cent (0.91 ± 0.027). It is possible, but not proved, that

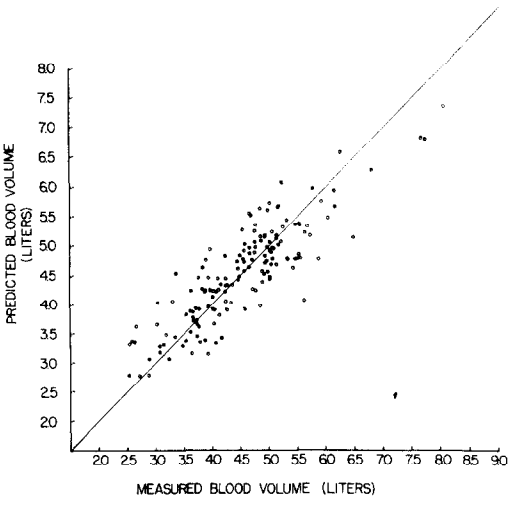


Fig. 6. Measured blood volume (I^{131} HSA) versus computer-corrected surface area formula.

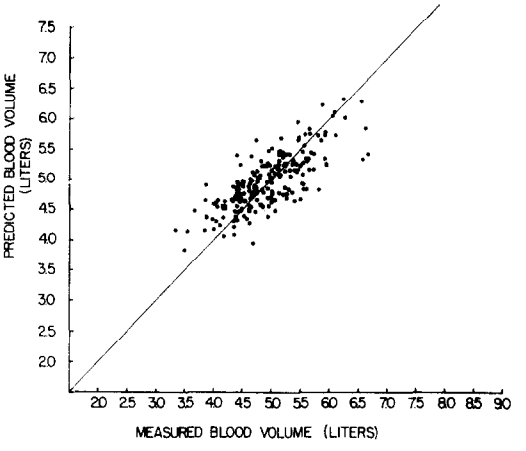


Fig. 7. Measured blood volume (Cr^{51} method) versus computer-predicted blood volume.

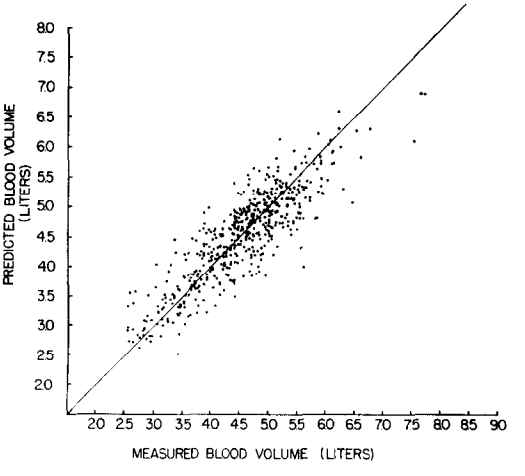


Fig. 8. Measured normal adult blood volume (518 cases) versus computer-predicted blood volumes.

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Table I. *Table of chi square*

Prediction formula used	*Men*		*Women*	
	Our series (92)	*Allen series (57)*	*Our series (63)*	*Allen series (26)*
H^3 – BM	9.90	2.17	3.59	0.36
H^3 – BM, computer	4.61	3.31	3.59	0.35
Surface area	5.03	3.73	9.16	4.01
Surface area, computer	4.67	2.35	3.65	0.49

Table II. *Standard error of estimate (liters)*

Prediction formula used	*Men*		*Women*	
	Our series (92)	*Allen series (57)*	*Our series (63)*	*Allen series (26)*
H^3 – BM	0.048	0.324	0.414	0.169
H^3 – BM, computer	0.392	0.318	0.413	0.168
Surface area	0.397	0.325	0.421	1.638
Surface area, computer	0.393	0.306	0.417	0.171

Table III. *Table of predicted "normal" blood volumes in men (PBV = 0.3669 H^3 + 0.03219 W + 0.6041)*

Weight (lb.)	*Volume by height (in.)*							
	60	*62*	*64*	*66*	*68*	*70*	*72*	*74*
100	3,365	3,500	3,643	3,795	3,957	4,129	4,311	4,503
110	3,512	3,646	3,789	3,941	4,103	4,275	4,457	4,649
120	3,658	3,792	3,935	4,088	4,250	4,422	4,603	4,796
130	3,804	3,938	4,082	4,234	4,396	4,568	4,750	4,942
140	3,951	4,085	4,228	4,380	4,542	4,714	4,896	5,088
150	4,097	4,231	4,374	4,527	4,689	4,860	5,042	5,235
160	4,243	4,377	4,521	4,673	4,835	5,007	5,189	5,381
170	4,389	4,524	4,667	4,819	4,981	5,153	5,335	5,527
180	4,536	4,670	4,813	4,966	5,128	5,299	5,481	5,673
190	4,682	4,816	4,959	5,112	5,274	5,446	5,627	5,820
200	4,828	4,963	5,106	5,258	5,420	5,592	5,774	5,966
210	4,975	5,109	5,252	5,405	5,566	5,738	5,920	6,112
220	5,121	5,255	5,398	5,551	5,713	5,885	6,066	6,295
230	5,267	5,402	5,545	5,697	5,859	6,031	6,213	6,405
240	5,414	5,548	5,691	5,843	6,005	6,177	6,359	6,551
250	5,560	5,694	5,837	5,990	6,152	6,323	6,505	6,698
260	5,706	5,840	5,984	6,136	6,298	6,470	6,652	6,844
270	5,852	5,987	6,130	6,282	6,444	6,616	6,798	6,990
280	5,999	6,133	6,276	6,429	6,591	6,762	6,944	7,136
290	6,145	6,279	6,423	6,575	6,737	6,909	7,091	7,283
300	6,291	6,426	6,569	6,721	6,883	7,055	7,237	7,429
310	6,438	6,572	6,715	6,868	7,030	7,201	7,383	7,575

the ratio varies widely in certain disease states.[14, 17]

The I^{131} HSA isotope hematocrit is derived from the counts on similar volumes of peripheral blood and plasma according to the equation

$$\frac{BV - PV}{BV}$$

The counts on plasma and whole blood are directly related in that the whole blood count represents dilution of the plasma by cells. This value is a direct measure of the peripheral hematocrit but independent of the variables that affect the centrifuge hematocrit. In a large series of cases in health and disease the ratio of isotope hema-

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Table IV. *Table of predicted "normal" blood volumes in women (PBV = 0.3561 H^3 + 0.03308 W + 0.1833)*

Weight (lb.)	Volume by height (in.)							
	60	62	64	66	68	70	72	74
80	2,646	2,776	2,915	3,063	3,220	3,387	3,564	3,750
90	2,796	2,927	3,066	3,214	3,371	3,537	3,714	3,901
100	2,947	3,077	3,216	3,364	3,521	3,688	3,864	4,052
110	3,097	3,227	3,366	3,514	3,671	3,838	4,015	4,201
120	3,247	3,378	3,517	3,665	3,822	3,989	4,165	4,352
130	3,398	3,528	3,667	3,815	3,972	4,139	4,315	4,502
140	3,548	3,678	3,817	3,965	4,123	4,289	4,466	4,652
150	3,698	3,829	3,968	4,116	4,273	4,440	4,616	4,803
160	3,849	3,979	4,118	4,266	4,423	4,590	4,766	4,953
170	3,999	4,129	4,268	4,416	4,574	4,740	4,917	5,103
180	4,150	4,280	4,419	4,567	4,724	4,891	5,067	5,254
190	4,300	4,430	4,569	4,717	4,874	5,041	5,217	5,404
200	4,450	4,581	4,719	4,867	5,025	5,191	5,368	5,554
210	4,601	4,731	4,870	5,018	5,175	5,342	5,518	5,705
220	4,751	4,881	5,020	5,168	5,325	5,492	5,669	5,855
230	4,901	5,032	5,171	5,318	5,476	5,642	5,819	6,005
240	5,052	5,182	5,321	5,469	5,626	5,793	5,969	6,156
250	5,202	5,332	5,471	5,619	5,776	5,943	6,120	6,306
260	5,352	5,483	5,622	5,770	5,927	6,093	6,270	6,457
270	5,503	5,633	5,772	5,920	6,077	6,244	6,420	6,607
280	5,653	5,783	5,922	6,070	6,227	6,394	6,571	6,757
290	5,803	5,934	6,073	6,221	6,378	6,544	6,721	6,908

tocrit to corrected centrifuge hematocrit was 1.0 ± 0.03.[19] Data of Gurney and Bolt,[14] showing wide ranges of body hematocrit/centrifuge hematocrit ratio in disease states, allowed us to calculate the isotope hematocrit/centrifuge hematocrit ratio. The values ranged from 0.835 to 1.20. Since either the centrifuge hematocrit or the isotope measurement is in error the validity and interpretation of their data is open to question.

SUMMARY

The circulating blood volumes in 155 normal adult men and women were determined by the I^{131} HSA method. The measured volumes were plotted against body weight, surface area, and the height cubed–body mass formulas. Significant statistical improvement was attained when the data were plotted against predicted volumes based upon computer-corrected surface area and height cubed–body mass formulas. Both computer-corrected formulas yield the same prediction data when sex, height, and weight are the only parameters used. The usefulness of the prediction formulas was demonstrated when data obtained by other workers using different methods of estimating blood volume showed as good correlation with prediction as did our data.

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