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Letter to the Editor

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The volume of distribution of bromide is often used to estimate the volume of extracellular water in the body. The "corrected" bromide space (CBS) is assumed to equal the volume of extracellular water. To calculate the CBS, the dose of bromide (Br dose) is divided by the equilibrium concentration of bromide in extracellular fluid ($[Br]_e$), with a correction for the amount that is assumed to be distributed in non-extracellular sites (principally erythrocytes):

$$CBS = \frac{\text{Br dose} \times 0.90}{[Br]_e}$$

Because $[Br]_e$ cannot be measured directly, it is calculated from the concentration of bromide in serum ($[Br]_s$) by applying two additional correction factors: the Donnan equilibrium factor 0.95 (8, 11, 12), and the concentration of water in serum (7, 8, 12), which is approximately 94% (12). Thus,

$$[Br]_e = \frac{[Br]_s}{0.95 \times 0.94}$$

and, therefore

$$CBS = \frac{\text{Br dose}}{[Br]_s} \times 0.90 \times 0.95 \times 0.94$$

These corrections are not needed when one uses bromide to estimate total body chloride (10) because the Donnan factors for these two elements are the same, and both are measured in the same serum sample.

Several authors (1, 4, 7, 9, 13, 14) have applied one or two of these three factors incorrectly, multiplying rather than dividing $[Br]_s$ by the Donnan factor and the serum water correction. The result in most cases has been a large, systematic overestimation of extracellular water. When both the Donnan factor and the serum water correction are used incorrectly (1, 4, 9, 13, 14) the resulting errors are additive; extracellular water is then systematically overestimated by 25–31%, depending on the factor used for the serum water correction (0.92–0.94). It should be noted, parenthetically, that even with correct application of these factors there is a slight overestimation of the bromide space if no correction is made for bromide lost in urine before the serum sample is obtained.

Table 1 shows the corrected bromide space results for infants as reported (1, 4, 9, 13, 14) and the values that would have been obtained with correct application of the Donnan and serum water factors. The mean extracellular water volume calculated by Brans *et al.* (1) was 335 ml/kg, higher than the "expected" volume of 286 ml/kg (ref. 1, Table 3). They concluded that "infants with congenital heart disease appear to have . . . slightly expanded volumes of extracellular water" (1). This conclusion seems to have been drawn erroneously as a result of the aforementioned errors in correcting the bromide space (unless the "expected" volume was also calculated incorrectly).

Table 1. *Corrected bromide space (CBS) of infants*

Authors	Subjects	Mean CBS as reported (ml/kg)	Correctly calculated* mean CBS (ml/kg)
Cassady (4)	TermAGA†	376	296
	Premature AGA†	424	334
Brans *et al.* (1)	Infants with CHD‡	335	264
Thornton *et al.* (13)	Term	504	397
	Premature	640	504
Thornton *et al.* (14)	Normocythemic	510	402
	Polycythemic	520	409
Cheek *et al.* (9)	TermV§	358	273
	TermC ‖	354	270

* Using same Donnan factor and serum water correction used by original authors: Donnan factor 0.95 (1, 4, 9, 13, 14); serum water factor 0.934 (1, 4, 13, 14) or 0.92 (9).

† AGA, appropriate birth weight for gestational age, less than 24-h-old.

‡ CHD, congenital heart disease.

§ V, vaginally delivered, 24-h-old.

‖ C, delivered by cesarean section, 24-h-old.

The extent of these errors is not known because many authors report only that corrections were made for the Donnan equilibrium and serum water, without giving details of the calculations. It must be presumed, however, that other papers (2, 3, 5, 6) citing the method of Cassady (4) or Thornton *et al.* (14) also contain bromide space results that were incorrectly calculated. In some cases extracellular water was incorrectly estimated from bromide space and then subtracted from total body water to yield intracellular water (1, 2, 5, 6, 9, 14). This, of course, led to underestimation of intracellular water by the same amount. For example, the mean intracellular water of 328 ml/kg reported by Brans *et al.* (1) should have been 399 ml/kg.

As far as we know, the most recent experimental paper to correctly use and describe the three corrections for bromide space was published in 1954 (8). Most of our information regarding the extracellular water of infants is based on bromide space measurements. Many of these data are demonstrably wrong (1, 7, 9, 13, 14); others cannot be judged because the details of bromide space correction were not given. We conclude that infants contain less extracellular water than was previously thought.

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Response

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Doctors Bell, Ziegler, and Forbes must be congratulated for realizing that over a period of 30 yr the various factors used to correct the bromide space have been at times *apparently* misapplied (3). The correct equation should be written as follows:

$$\text{Corrected bromide space} = \frac{\text{Amount of bromide administered}}{\text{Bromide concentration in plasma}} \times 0.90 \times 0.95 \times 0.94$$

where 0.90 corrects for the amount of intracellular bromide; 0.95 corrects for the Donnan equilibrium; and 0.94 corrects for the proportion of water in plasma.

Their letter triggered an extensive review of data in our three laboratories. Dr. Cassady recalculated the data from all studies performed in his laboratory (1, 2, 4–6) and found that the correct formula was indeed used. Dr. Cheek also used that formula in all his work (7–9). Unfortunately, typographic errors in the "Materials and Methods" sections of several articles suggested that some of the correction factors were misapplied (1, 4, 6, 9). Dr. Bell and his colleagues are therefore incorrect in concluding that "infants contain less extracellular water than was previously thought" and the "corrected" values given in his table are in fact erroneous. In Dr. Bran's laboratory, however, the incorrect formula reported by Cassady (4) and Cheek (9) was used:

$$\text{Corrected bromide space} = \frac{\text{Amount of bromide administered}}{\text{Bromide concentration in plasma}} \times \frac{0.90}{0.95 \times 0.94}$$

An overestimation of both the corrected bromide space (CBS) and the interstitial water (IW) resulted (10). Because the same error was applied to the two study groups being compared (preterm *versus* term neonates), the overestimation did not affect the comparisons. Likewise, in the regression analysis, the errors affected the slope and y-intercept of the regression lines, but not the correlation coefficient nor the $S_{y.x}$. For the record, however, corrected values are as follows:

CBS (ml/kg): 400 ± 67.0 in term *versus* 501 ± 61.0 in preterm babies
IW (ml/kg): 352 ± 63.0 in term *versus* 449 ± 59.4 in preterm babies

$\%\Delta MT = 0.064\ CBS - 1.3$
$\%\Delta SS = 0.081\ CBS - 7.2$
$S\Delta MT \times 10^4 = 0.087\ CBS - 5.8$
$S\Delta SS \times 10^4 = 0.077\ CBS + 0.2$
$\%\Delta MT = 0.066\ IW + 1.0$
$\%\Delta SS = 0.083\ IW - 4.0$
$S\Delta MT \times 10^4 = 0.090\ IW - 2.7$
$S\Delta SS \times 10^4 = 0.080\ IW + 3.0$

These corrections do not affect the validity of the conclusions of the study.

We cannot agree that significant amounts of bromide are lost in the urine during the 3 h of the study. In our experience urine losses amount to less than 1% of the administered dose of bromide. Finally, Bell *et al.*'s conclusion that "infants contain less extracellular water than was previously thought" is not supported by the facts.

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