

**BLOOD VOLUME IN NORMAL INFANTS AND CHILDREN**

Dan C. Darrow, ... , Herbert C. Soule, Thomas E. Buckman

*J Clin Invest.* 1928;5(2):243-258. <https://doi.org/10.1172/JCI100156>.

Research Article

**Find the latest version:**

<https://jci.me/100156/pdf>



## BLOOD VOLUME IN NORMAL INFANTS AND CHILDREN

BY DAN C. DARROW, HERBERT C. SOULE, AND THOMAS E. BUCKMAN

*(From the Pediatric Service of the Boston City Hospital and Washington University, and St. Louis Children's Hospital)*

(Received for publication October 4, 1927)

Knowledge concerning blood volumes has been limited until recent years by the lack of any reliable method that could be applied to living patients. Information about the blood volume is desirable both for the study of anemia and of disturbances in the water metabolism. The work reported in this and the three subsequent papers was undertaken from the latter viewpoint.

There are two reliable methods of determining blood volumes which may be applied to patients. They are (a) the carbon monoxide method, first adapted to man by Haldane and Smith (1) and (b) the dye method of Keith, Rowntree and Geraghty (2). The former method gives results that are probably a little lower than the actual blood volume whereas the latter gives results a little higher than the actual blood volumes. The high results by the dye method have been shown by Smith (3) to be due to transfusion of part of the dye into the lymph. However, the amount of dye disappearing in the lymph is small and fairly constant and the method is accurate for comparative results.

Our knowledge of blood volumes has been recently reviewed by Erlanger (4). In the present paper, only such results as seem to concern this work will be mentioned. The findings of the various workers seem fairly concordant and indicate that adults tend to have about 50 milliliters of plasma and 83 milliliters of blood per kilogram of body weight, as determined by the dye method (Keith, Rowntree and Geraghty (2) Bock (5), Brown and Rowntree (6)). Bock has emphasized the fact that the plasma volume is more constant than the blood volume and has found it to be about 50 milliliters per kilogram of body weight in conditions showing such widely varying volumes of red cells as pernicious anemia and polycythemia. However, a minimum volume of red cells is necessary to maintain the plasma volume.

Robertson and Bock (7) found in soldiers who had lost large amounts of blood that the plasma volume returns quickly to normal unless the volume of the red cells has reached a certain low minimum. If the loss of the red cells is below this minimum, the plasma volume cannot be maintained until the red cell volume has been restored. Obese adults have low plasma volumes per kilogram of body weight (Brown and Keith (8)) but the plasma volume per square meter of surface area of obese adults was found to be essentially the same as for normal adults. A formula relating the blood volume to the surface area times a constant was worked out by Dreyer and Ray (9), the constant being different for different species of animals. These workers felt that since fat is a relatively avascular tissue, surface area would be a better measure of blood volume than weight.

Reports of actual blood volume determinations in infants are confined to three papers. None have been reported on older children. Lucas and Dearing (10) determined blood volumes by the dye method on infants during the first year of life. Their results expressed in milliliters per kilogram of body weight are: blood volume in newly born infants 107 to 195, average 147; plasma volume in newly born infants, 42 to 77, average 59; blood volume in older infants, 90 to 126, average 110; plasma volume, 57 to 78, average 67. In the first weeks of life, a wider variation in the plasma volume was found than later, and the whole blood volume was higher. However, the high whole blood volume in the newly born is entirely accounted for by the high volume of the red cells. The plasma volume is actually lower in the newly born than in infants over six weeks old. Bakwin and Rivkin (11) obtained similar results. They found the average for the blood volume to be 101 milliliters per kilogram of body weight and for the plasma 69 milliliters. In nineteen cases, the average blood volume was 1700 milliliters per square meter of surface area. Marriott and Perkins (12) found 91 cc. of whole blood per kilogram of body weight in seven normal babies, under one year of age, and 80 cc. per kilogram of body weight in babies with severe undernutrition. All the papers agree in finding slightly higher blood volumes per kilogram of body weight in babies than has been found in adults.

The blood volumes here reported were estimated by the method of Keith, Rowntree and Geraghty (2). The cell volumes were deter-

mined by hematocrit tubes made from small burettes which were 5 millimeters in diameter and calibrated. Oxalated venous blood kept under mineral oil was used to minimize the errors due to loss of carbon dioxide. Serum or plasma protein concentration was estimated in some of the later determinations by the Abbe refractometer (13). The surface area was computed by the formula of Lissauer (14) for the infants under one year of age. In the other patients, the surface area was obtained from the table of Benedict and Talbot (15) based on this formula.

The data of the present study were obtained from essentially normal infants and children. The older children were suffering from fractures, or had recovered from some minor illness. The babies had recovered from upper respiratory infections or were in the hospital for some minor complaint. Most of the infants were slightly undernourished and fed on modified cows' milk. The results reported here and to be reported in the subsequent papers indicate that moderate undernutrition makes no difference in the plasma volume per kilogram of body weight. The data found on these patients are given in detail in tables 1 and 2, but the general trend and significance may be appreciated best by examining the two charts.

Chart 1 represents the blood and plasma volumes in milliliters per kilogram of body weight as related to age. As there were not enough determinations to permit conclusions concerning the blood and plasma volumes during the first six weeks of life, the lower relative plasma volume at this age is represented in accordance with previous work (Lucas and Dearing (10) and Bakwin and Rivkin (11)). The plasma volume per kilogram of body weight as related to age describes a curve as indicated on chart 1. This curve starts at about 50 milliliters per kilogram of body weight and rises rather rapidly to 62 milliliters by the sixth month of life, remains high well into the second year, and then gradually returns to 50 milliliters by the beginning of the fourth year. Thereafter the plasma volume per kilogram of body weight agrees well with the adult figure, cited above. The whole blood volume tends to describe a similarly shaped curve, but, due to variations in the volumes of the red cells, the whole blood volume cannot be predicted very accurately. In general the blood volume per kilogram is 25 to 35 milliliters more than the plasma volume for the

TABLE 1

| Case number | Date               | Diagnosis      | Sex | Age          | Weight<br>kgm. | Sur-<br>face<br>area<br>sq. m. | %Vol-<br>umes<br>per<br>cent<br>of<br>cells | Blood volume |                    |              | Blood volume per kilogram |                    |              | Blood volume per square meter of surface |                    |
|-------------|--------------------|----------------|-----|--------------|----------------|--------------------------------|---|--------------|--------------------|--------------|---------------------------|--------------------|--------------|--|--------------------|
|             |                    |                |     |              |                |                                |   | Blood<br>ml. | Plas-<br>ma<br>ml. | Cells<br>ml. | Blood<br>ml.              | Plas-<br>ma<br>ml. | Cells<br>ml. | Blood<br>ml.                             | Plas-<br>ma<br>ml. |
| 1           | July 26, 1923      |                | F.  | 1 wk.        | 3.6            | 0.24                           | 45.0  | 284          | 156                | 128          | 79.0                      | 43.0               | 36.0         | 1,180                                    | 647                |
| 2           | December 13, 1922  |                | M.  | 1 mo.        | 3.4            | 0.23                           |   | 221          | 221                |              | 65.0                      |                    |              |  | 950                |
| 3           | July 13, 1923      | Undernutrition | F.  | 2 mos.       | 3.1            | 0.21                           | 27.0  | 214          | 156                | 58           | 69.0                      | 50.4               | 18.7         | 984                                      | 710                |
| 4           | July 20, 1923      | Undernutrition | M.  | 2 mos.       | 4.2            | 0.27                           | 27.5  | 301          | 218                | 83           | 71.7                      | 52.0               | 19.7         | 1,120                                    | 814                |
| 5           | September 10, 1923 | Undernutrition | M.  | 2 mos.       | 3.5            | 0.24                           | 27.0  | 271          | 198                | 73           | 77.7                      | 56.5               | 21.1         | 1,180                                    | 835                |
| 6           | April 7, 1924      | Normal         | M.  | 6 wks.       | 3.3            | 0.23                           |   | 180          | 180                |              | 54.0                      |                    |              |  | 785                |
| 7           | August 8, 1925     | Normal         | F.  | 10 wks.      | 3.7            | 0.24                           | 30.0  | 321          | 225                | 96           | 87.5                      | 61.1               | 26.0         | 1,340                                    | 920                |
| 8           | December 3, 1922   | Undernutrition | M.  | 3 mos.       | 3.0            | 0.21                           | 19.0  | 240          | 194                | 46           | 80.0                      | 64.5               | 15.3         | 1,140                                    | 905                |
| 9           | December 1, 1922   | Undernutrition | M.  | 3 mos.       | 4.2            | 0.27                           | 34.0  | 400          | 264                | 136          | 95.3                      | 63.0               | 32.4         | 1,480                                    | 985                |
| 10          | November 29, 1922  | Undernutrition | M.  | 3 mos.       | 3.0            | 0.21                           | 25.0  | 215          | 161                | 54           | 71.6                      | 53.6               | 18.0         | 1,020                                    | 753                |
| 11          | September 17, 1923 | Undernutrition | F.  | 3 mos.       | 3.5            | 0.24                           | 24.0  | 246          | 188                | 58           | 70.3                      | 53.7               | 16.5         | 1,040                                    | 794                |
| 12          | July 12, 1923      | Normal         | F.  | 5 mos.       | 4.7            | 0.29                           | 34.5  | 389          | 255                | 134          | 82.6                      | 54.3               | 28.5         | 1,340                                    | 883                |
| 13          | July 19, 1923      | Normal         | F.  | 5 mos.       | 4.3            | 0.27                           | 29.0  | 372          | 264                | 108          | 86.5                      | 61.4               | 25.2         | 1,380                                    | 967                |
| 14          | September 13, 1923 | Normal         | F.  | 6 mos.       | 5.4            | 0.32                           | 28.4  | 475          | 340                | 135          | 88.0                      | 63.0               | 25.0         | 1,530                                    | 1,070              |
| 15          | September 19, 1923 | Undernutrition | F.  | 9 mos.       | 7.2            | 0.38                           | 33.5  | 662          | 440                | 222          | 91.8                      | 61.0               | 30.8         | 1,740                                    | 1,145              |
| 16          | September 20, 1924 | Undernutrition | F.  | 1 yr.        | 5.5            | 0.32                           | 28.5  | 475          | 340                | 135          | 86.7                      | 62.0               | 24.7         | 1,480                                    | 1,060              |
| 17          | November 27, 1925  | Normal         | M.  | 1 yr. 2 mos. | 10.5           | 0.50                           | 35.5  | 969          | 624                | 345          | 92.3                      | 59.5               | 32.9         | 1,940                                    | 1,250              |
| 18          | December 1, 1925   | Normal         | M.  | 1 yr. 2 mos. | 8.6            | 0.44                           | 29.0  | 665          | 473                | 192          | 76.5                      | 55.0               | 22.4         | 1,510                                    | 1,078              |
| 19          | December 17, 1925  | T. B. adenitis | M.  | 1 yr. 2 mos. | 9.5            | 0.47                           | 32.6  | 739          | 498                | 241          | 77.8                      | 52.5               | 25.4         | 1,570                                    | 1,060              |
| 20          | December 10, 1925  | Undernutrition | M.  | 1 yr. 2 mos. | 6.3            | 0.34                           | 28.0  | 511          | 368                | 143          | 81.1                      | 58.4               | 22.7         | 1,500                                    | 1,080              |
| 21          | December 8, 1925   | Undernutrition | M.  | 1 yr. 4 mos. | 9.6            | 0.46                           | 30.0  | 647          | 453                | 194          | 67.4                      | 47.2               | 20.2         | 1,410                                    | 986                |
| 22          | September 15, 1923 | Normal         | M.  | 1 yr. 6 mos. | 10.0           | 0.49                           | 31.1  | 897          | 618                | 280          | 89.8                      | 61.8               | 28.0         | 1,830                                    | 1,260              |
| 23          | June 23, 1923      | Normal         | M.  | 2 yrs.       | 12.6           | 0.57                           | 34.2  | 1,058        | 696                | 362          | 84.0                      | 55.3               | 28.7         | 1,860                                    | 1,220              |

|    |                    |                |    |          |      |       |                        |       |       |                  |                  |                  |                  |
|----|--------------------|----------------|----|----------|------|-------|------------------------|-------|-------|------------------|------------------|------------------|------------------|
| 24 | September 14, 1923 | Normal         | F. | 2 yrs.   | 14.0 | 0.62  | 30.61, 1,038           | 720   | 318   | 74.0             | 51.4             | 22.71, 6701, 160 |                  |
| 25 | December 6, 1924   | Undernutrition | F. | 2 yrs.   | 7.2  | 0.39  | 46.0                   | 759   | 408   | 351              | 105.2            | 56.5             | 48.61, 9401, 050 |
| 26 | December 10, 1924  | Undernutrition | F. | 2 yrs.   | 8.6  | 0.44  | 30.0                   | 672   | 470   | 282              | 78.4             | 54.8             | 23.61, 5301, 068 |
| 27 | September 21, 1923 | Normal         | M. | 2.7 yrs. | 13.0 | 0.59  | 37.51, 0,224           | 640   | 384   | 78.8             | 49.2             | 29.61, 7401, 085 |                  |
| 28 | September 22, 1923 | Normal         | M. | 3 yrs.   | 14.6 | 0.63  | 30.2                   | 960   | 670   | 290              | 65.7             | 46.0             | 19.81, 5401, 060 |
| 29 | July 7, 1923       | Normal         | F. | 4 yrs.   | 15.0 | 0.65  | 38.01, 200             | 744   | 456   | 80.0             | 49.6             | 30.41, 8401, 140 |                  |
| 30 | June 19, 1923      | Normal         | M. | 5 yrs.   | 14.4 | 0.63  | 36.41, 170             | 745   | 426   | 81.4             | 51.7             | 29.61, 8501, 185 |                  |
| 31 | July 10, 1923      | Normal         | M. | 5 yrs.   | 27.2 | 1.00  | 31.91, 9821, 350       | 632   | 72.9  | 49.6             | 23.21, 9821, 350 |                  |                  |
| 32 | June 5, 1923       | Normal         | F. | 6 yrs.   | 24.0 | 0.92  | 43.42, 340             | 1,327 | 1,013 | 97.5             | 55.3             | 42.32, 5401, 440 |                  |
| 33 | June 27, 1923      | Normal         | M. | 6 yrs.   | 20.0 | 0.83  | 34.71, 347             | 880   | 567   | 67.4             | 44.0             | 23.41, 6301, 065 |                  |
| 34 | July 25, 1923      | Normal         | M. | 6 yrs.   | 18.4 | 0.76  | 34.01, 394             | 920   | 474   | 75.7             | 50.0             | 25.71, 8401, 210 |                  |
| 35 | August 2, 1923     | Normal         | M. | 6 yrs.   | 19.0 | 0.79  | 33.51, 407             | 936   | 471   | 74.0             | 49.2             | 24.81, 7801, 180 |                  |
| 35 | August 6, 1923     | Normal         | M. | 6 yrs.   | 18.4 | 0.77  | 33.51, 407             | 936   | 471   | 76.4             | 50.8             | 25.61, 8201, 210 |                  |
| 36 | July 21, 1923      | Normal         | M. | 6 yrs.   | 17.0 | 0.74  | 33.61, 327             | 880   | 447   | 78.0             | 51.7             | 26.21, 7901, 190 |                  |
| 37 | June 8, 1923       | Normal         | F. | 7 yrs.   | 21.0 | 0.84  | 34.41, 450             | 951   | 499   | 69.0             | 45.3             | 23.71, 7201, 134 |                  |
| 38 | June 13, 1923      | Normal         | F. | 7 yrs.   | 18.9 | 0.76  | 31.41, 430             | 981   | 449   | 75.7             | 51.9             | 23.81, 8801, 290 |                  |
| 39 | July 12, 1923      | Normal         | M. | 7 yrs.   | 24.1 | 0.93  | 34.01, 8181, 200       | 618   | 75.4  | 49.8             | 25.61, 9501, 290 |                  |                  |
| 40 | July 10, 1923      | Normal         | M. | 8 yrs.   | 22.2 | 0.88  | 36.01, 5951, 020       | 575   | 71.8  | 46.0             | 25.81, 8101, 160 |                  |                  |
| 41 | July 11, 1923      | Normal         | M. | 8 yrs.   | 28.4 | 1.06  | 35.42, 1501, 390       | 760   | 75.8  | 49.0             | 26.82, 0201, 310 |                  |                  |
| 42 | July 20, 1923      | Normal         | M. | 8 yrs.   | 27.2 | 1.05  | 33.62, 1191, 404       | 713   | 77.9  | 51.6             | 26.22, 0201, 340 |                  |                  |
| 43 | July 28, 1923      | Normal         | M. | 8 yrs.   | 23.0 | 0.906 | 38.01, 7611, 092       | 669   | 76.6  | 47.5             | 29.01, 9451, 200 |                  |                  |
| 44 | August 1, 1923     | Normal         | M. | 8 yrs.   | 23.4 | 0.91  | 31.81, 8701, 275       | 595   | 80.0  | 54.5             | 25.42, 0301, 400 |                  |                  |
| 45 | July 10, 1923      | Normal         | M. | 9 yrs.   | 22.7 | 0.89  | 37.01, 6761, 056       | 620   | 73.8  | 46.5             | 27.31, 8801, 190 |                  |                  |
| 46 | July 19, 1923      | Normal         | F. | 9 yrs.   | 21.5 | 0.82  | 37.01, 562             | 984   | 578   | 72.6             | 45.8             | 26.81, 9001, 200 |                  |
| 47 | July 23, 1923      | Normal         | M. | 9 yrs.   | 24.0 | 0.93  | 37.01, 9111, 204       | 707   | 79.8  | 50.3             | 29.52, 0301, 290 |                  |                  |
| 48 | July 4, 1923       | Normal         | M. | 10 yrs.  | 24.5 | 0.94  | 35.01, 8771, 220       | 657   | 76.6  | 49.7             | 26.82, 0001, 300 |                  |                  |
| 49 | July 5, 1923       | Normal         | F. | 10 yrs.  | 29.0 | 1.05  | 38.02, 3381, 450       | 888   | 80.6  | 50.0             | 30.62, 2201, 380 |                  |                  |
| 50 | July 23, 1923      | Normal         | M. | 10 yrs.  | 33.0 | 1.18  | 39.02, 5981, 5841, 014 | 78.7  | 48.0  | 30.72, 2001, 340 |                  |                  |                  |
| 51 | July 28, 1923      | Normal         | M. | 10 yrs.  | 22.3 | 0.84  | 38.01, 8261, 132       | 694   | 81.9  | 50.8             | 30.12, 1801, 350 |                  |                  |
| 52 | July 25, 1923      | Normal         | M. | 11 yrs.  | 30.0 | 1.11  | 33.02, 2401, 500       | 740   | 74.7  | 50.0             | 24.62, 0901, 350 |                  |                  |

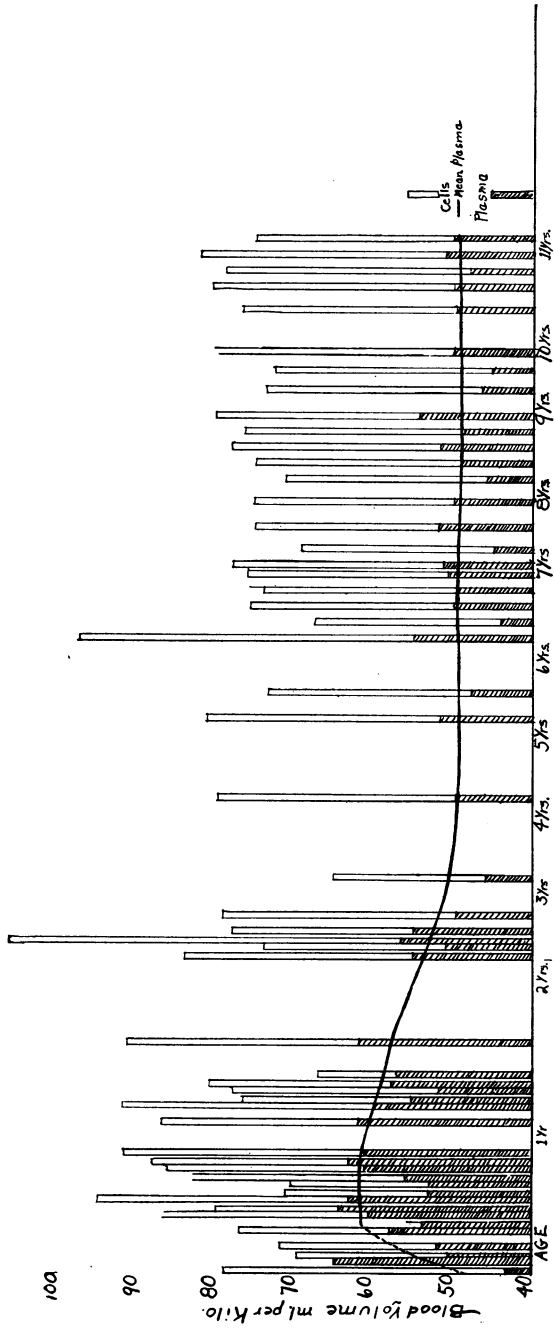


CHART 1. THE RELATION OF BLOOD AND PLASMA VOLUMES PER KILOGRAM AT DIFFERENT AGES

respective age. An exception to this statement is not shown in chart 1, but is brought out best in the paper of Lucas and Dearing (10). During the first 3 to 4 weeks of life, the proportion of the blood represented by the red cells is 45 to 70 per cent; while during the rest of the first year of life, it is only 30 per cent. The high proportion of red cells makes the total blood volume correspondingly high. It will be noticed also that the plasma volume per kilogram of body weight varies more widely during the first year of life, than later. This variability cannot be explained from our present knowledge of infant physiology. This physiological constant must, therefore, be classified with the other physiological constants that manifest greater variability in infants than in adults.

TABLE 2

| Case number | Protein  |                    | Case number | Protein  |                    |
|-------------|----------|--------------------|-------------|----------|--------------------|
|             | Per cent | Grams per kilogram |             | Per cent | Grams per kilogram |
| 5           | 6.62     | 3.74               | 19          | 8.65     | 4.54               |
| 7           | 7.96     | 4.86               | 20          | 6.98     | 4.08               |
| 16          | 7.26     | 4.50               | 21          | 8.05     | 3.80               |
| 17          | 7.42     | 4.40               | 25          | 7.78     | 4.40               |
| 18          | 7.63     | 4.20               | 26          | 9.60     | 5.25               |

The red cell volume per kilogram of body weight after the first six weeks of life, is about 25 to 35 milliliters. This is somewhat lower than in adults, and is in keeping with the lower hemoglobin and red cell count.

The total serum protein per kilogram of body weight is given on a few cases in table 2. The average for the second year is 4.2 grams per kilogram of body weight, whereas Bakwin and Rivkin (11) found 3.6 grams for the first year. From our knowledge that the serum protein concentration remains about the same after the first year of life, one may assume that the average for the rest of life will be about 4 grams per kilogram of body weight. This figure, though probably not very exact, will be useful for comparison with the findings obtained from patients suffering from various diseases.

The blood and plasma volume per square meter of body surface as related to age is shown in chart 2. It is realized that the methods for



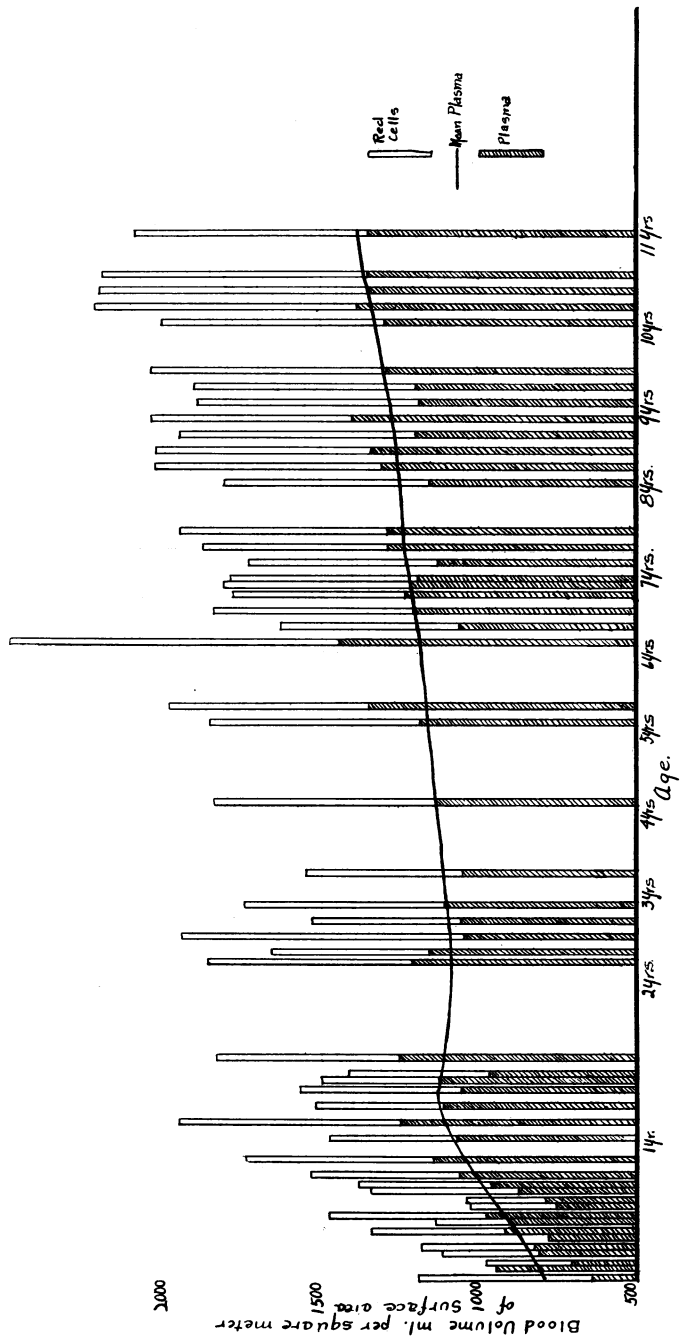


CHART 2. THE RELATION OF BLOOD AND PLASMA VOLUMES PER SQUARE METER OF SURFACE AREA AT DIFFERENT AGES

computing the surface area are not yet sufficiently accurate to give a very exact estimate of the surface area in a given child. However, the figures are sufficiently accurate to show the general relation of the blood and plasma volume to the surface area. As will be noticed, the plasma volume per square meter of body surface as related to age rises rapidly during the first year from 750 milliliters to 1110 milliliters and then remains constant during the second year, perhaps decreasing a little. Thereafter, there is a steady rise to about 1375 milliliters, by the twelfth year of life. That this rise continues till adult life is indicated by the fact that the adult average of the plasma volume per square meter of surface area is 2000 milliliters (Brown and Keith (8)).

The variability of the red cell volume makes the curve of the blood volume per square meter of surface area more irregular. In general the whole blood volume describes a curve similar in shape to the one described by the plasma volume.

The question as to whether weight or surface area is better correlated with the plasma volume has not been settled and the data in this paper only bring out new facts. Table 3 shows the standard deviation<sup>1</sup> from the average and the percentage standard deviation from the average of the plasma volume as related to both weight and surface area. The plasma volume per kilogram of body weight was not used in the six youngest babies in making this table because the data for this age are not sufficiently numerous. No figures are given for the first year for the standard deviation of the plasma volume per square meter of surface area because at this age the average plasma volume per square meter is changing too rapidly to allow such a computation from the data of this paper.

<sup>1</sup>Standard deviation is calculated according to the well known formulae:

$$\delta = \sqrt{\frac{\sum (x - x_1)^2}{n}}$$

$\delta$  = standard deviation

$x$  = mean measurement

$x_1$  = given measurement

$N$  = number of measurements

$\Sigma$  = Sum of the different quantities  $(x - x)^2$ .

Percentage standard deviation =  $\frac{100\delta}{x}$ .

The average of the percentage standard deviations for each age is the same (5.4) whether plasma volume is compared with weight or surface area. However, since weight is more variable than surface area, the same degree of correlation would indicate a closer relationship between weight and plasma volume, than surface area and plasma volume. However, there are not enough cases in this series to draw conclusions from small differences. The main fact brought out is that surface area cannot be correlated with the plasma volume unless the age of the individual is also taken into account, but weight may be correlated with the plasma volume after the third year, since the plasma volume is constant at 50 milliliters per kilogram of body weight, after this age (see charts 1 and 2).

TABLE 3

|  | Age |     |     |     |   |      |      |     |     |     |     |
|--|-----|-----|-----|-----|---|------|------|-----|-----|-----|-----|
|  | 1   | 2   | 3   | 4   | 5 | 6    | 7    | 8   | 9   | 10  | 11  |
| Standard deviation per kilogram of weight.....               | 4.8 | 3.7 | 3.1 | 3.1 | 0 | 2.1  | 3.7  | 2.7 | 3.9 | 4.0 | 1.0 |
| Percentage standard deviation per kilogram of weight.....    | 7.7 | 7.5 | 5.7 | 6.2 | 0 | 4.1  | 7.4  | 5.4 | 7.8 | 8.0 | 2.0 |
| Standard deviation per square meter of surface.....          |     | 89  | 65  | 13  | 0 | 127  | 126  | 61  | 72  | 90  | 21  |
| Percentage standard deviation per square meter of surface... |     | 7.3 | 5.9 | 1.3 | 0 | 10.9 | 10.5 | 4.9 | 5.7 | 7.0 | 1.5 |

## DISCUSSION

The shape of the curve of the plasma volume per kilogram of body weight as related to age suggests a relationship between the plasma volume and the metabolic rate. It will be noted that the shape of this curve is similar to that of the basal metabolic rate per square meter of surface area as related to age (Benedict and Talbot (16)). There is both a rise in the metabolic rate and in the plasma volume during the first year of life and both remain high during the second year. The basal metabolic rate drops rather rapidly till the beginning of the fourth year and continues to decrease slowly during the rest of childhood. The plasma volume per kilogram of body weight decreases rapidly till the fourth year but then seems to be quite constant.

However, the figures for adults tend to be slightly lower than those for children reported in this paper (see previous references) and the comparatively small number of cases reported here may not have been sufficient to indicate a slight tendency to a decrease in the plasma volume after the third year. Thompson (17) found in nine patients with myxedema that treatment with thyroid extract caused an increase in the total plasma volume as follows: average increase in the total plasma volume 22 per cent; average increase in the plasma volume per kilogram of body weight 28 per cent; average increase in plasma volume per square meter of body surface 22 per cent. Furthermore, the plasma volume while the patients were suffering from myxedema, in general, was low. These facts seem to indicate that the higher the metabolic rate, the larger the amount of water in the blood stream, and the lower the metabolic rate, the smaller the amount of water in the blood stream.

The fact that the metabolic rate is so closely related to the surface area and that the surface area has a relation to the plasma volume which varies with the age of the child demands some explanation. The work of Brown and Keith (8) on obese patients would lead one to expect a close correlation between plasma volume and surface area. These facts may be reconciled by assuming that the plasma volume is related primarily to the mass of the body tissues and that there is only a secondary relation between the plasma volume and the metabolic rate. Thus weight becomes the better measure of the plasma volume when individuals of widely different sizes are chosen, but with individuals of about the same weight, the surface area may be a better measure of the plasma volume than weight.

The red cells play an important part in the regulation of the blood volume. In normal individuals, the volume of the red cells is large enough to maintain the plasma volume. However, a minimum volume of red cells is necessary to carry and hold water in the blood stream. (Robertson and Bock (7) Keith (18)). The dependence of the body on red cells to transport water is suggested by the appearance of edema in severe cases of anemia. Based on the increased depression of the freezing point which accompanies an increase in the tension of the carbon dioxide to which blood is exposed, Buckman and Darrow (19) have advanced the hypothesis that amongst the other varied

functions of the red cells must be added that of being the chief carrier of water.

The mechanism of maintaining and carrying the blood and plasma water may be explained in part as follows. Given an adequate volume of red cells circulating through the body, the following events tend to take place. When the oxygenated blood reaches the systematic capillaries, a certain amount of fluid is filtered out of the blood stream by hydrostatic pressure; the red cells lose oxygen and take up carbon dioxide, as a result of the increased tension of carbon dioxide. This causes an increase in the osmotic pressure of the plasma and presumably of the red cells which become swollen with water taken from the plasma. The increased osmotic pressure of the plasma enables it to take up water from the tissues to replace the loss of water to the red cells. In the lung capillaries all the factors favor an accumulation of water in the pulmonary tissues. In addition to the hydrostatic filtration process, the loss of carbon dioxide decreases the osmotic pressure of the plasma and thus favors the transfusion of water into the alveolar tissues. This probably accounts for the fact that the lungs contain a higher proportion of water than any other body tissue. The extent of the tendency of the circulating blood to take up water from the systemic tissues will depend ultimately on the amount of carbon dioxide carried by the blood. Although, in the plasma alone, bicarbonate is formed on exposure to carbon dioxide, and this reaction is accompanied by an increase in the osmotic pressure and is a reversible reaction, it is the presence of hemoglobin in the red cells, which so greatly enhances the efficiency of this reaction. The hemoglobin under the influence of carbon dioxide loses oxygen and becomes more alkaline, and conversely, the presence of oxygen frees carbon dioxide through the formation of oxyhemoglobin which is more acid than reduced hemoglobin. This property of hemoglobin explains the efficiency of blood not only as a carbon dioxide but also as a water carrier. Thus the amount of water taken up by the blood from the tissues should be related to (1) the amount of carbon dioxide produced or the basal metabolic rate and (2) the efficiency of the blood as a carbon dioxide and water carrier which under ordinary circumstances is dependent on the circulating mass of red cells.

Based on the above described mechanism of water transport, one

may conceive of six classes of disturbances which may affect the blood volume and water distribution. They are as follows: (1) disturbances in carbon dioxide production as in diseases of the thyroid gland, fever, etc., (2) disturbances of the transporting mechanism of the blood such as occurs in anemia and changes in the acid-base equilibrium leading to too high or too low initial bicarbonate levels, (3) disturbances in carbon dioxide and water excretion in the lungs, as in emphysema, pulmonary edema, heart disease, pneumonia, etc., (4) disturbances in the excretion of water by the sweat glands, gastrointestinal canal and kidneys as in heat stroke, diarrhea and perhaps some forms of nephritis, (5) disturbances in the water absorption as in vomiting, and perhaps some forms of diarrhea, (6) disturbances in the rate of blood flow.

The manner in which all the above types of disturbances may affect water balance is fairly obvious, and only the third and sixth need any elaboration. Since venous blood undergoes an increase in osmotic pressure over that of arterial blood which is directly proportional to the increase in bicarbonate content, it is apparent that the tendency of the venous blood to take up water from the tissues depends on the increase in the bicarbonate content of the venous blood over that of the arterial blood, what one might call the potential difference between arterial and venous blood. In some unpublished experiments by Buckman and Darrow it was found that an increase in bicarbonate of the plasma of one volume per cent is accompanied by a lowering of the freezing point of about 0.001 degree centigrade. This corresponds to an increase in osmotic pressure of 9.1 millimeters of mercury, and when one takes into account the usual difference in bicarbonate content of venous and arterial blood, one would expect an increase in osmotic pressure of venous blood over that of arterial blood of the same order of magnitude as the fall in hydrostatic pressure from arterial to capillary blood. It is obvious that, with the same rate of carbon dioxide production, the difference in bicarbonate content between arterial and venous blood will become less the more rapid the rate of blood flow. If the increase in bicarbonate or osmotic pressure becomes small enough, an equilibrium between the osmotic pressure of the tissue and plasma cannot take place in the short period of time that it takes the blood to pass through the tissues. Since hydrostatic

pressures remain about the same, water tends to accumulate in the tissues at the expense of the plasma under such conditions. Apparently this is what happens with a too rapid rate of blood flow. Similarly with a slow circulation, the increase in osmotic pressure may be great enough to increase the rate of water diffusion back into the plasma. Thus, when the water carrying mechanism of the blood is compensated, apparently a slow rate of blood flow leads to increased plasma water content, and diminished tissue water content, whereas a rapid rate of blood flow leads to a diminished plasma water content and an increased tissue water content. However, due to the shape of the carbon dioxide curve, which shows diminishing increments in bicarbonate with increasing carbon dioxide pressure, the carbon dioxide carrying and water carrying mechanism would tend to break down with too slow a rate of blood flow, and, in such cases, one would expect an accumulation of water in both the tissues and plasma. Data supporting these views will be given in subsequent papers in cases of pneumonia and heart disease.

When carbon dioxide excretion is interfered with in the lungs, as in cases of pulmonary edema, the first obvious change in the blood is an increase in arterial bicarbonate and decrease in arterial oxygen. This lessens the difference in bicarbonate content of venous and arterial blood by making the blood work at a higher carbon dioxide pressure, and as noted above, this diminishes the efficiency of the carbon dioxide and water carrying mechanism of the blood. Thus pulmonary edema leads to diminished plasma water content, and increased tissue water content. Evidence of these changes is given in post-influenzal pneumonia and poisoning by war gases by Underhill and Ringer (20) and Underhill (21). In emphysema, the increased red cell concentration leads to greater efficiency of the carbon dioxide and water carrying mechanism of the blood. Only experimental observations can tell whether this is sufficient to overcome the tendency to diminished plasma volume one would otherwise expect.

The above mechanism can only be considered a partial explanation of the transportation and distribution of water. Increased pressure of carbon dioxide in the tissues increases the osmotic pressure of the tissues by a process similar to that observed in the blood, and thus alters the water distribution. Other means of varying the salt binding

power of proteins must occur, but little is known of such processes. Furthermore, our present knowledge does not permit a discussion of the rôle played by differential excretion of electrolytes and other crystalloids by the kidneys, intestines and sweat glands. Also any disturbance in the distribution of colloids should produce a disturbance in the water balance. No explanation of water metabolism can be complete, without considering these factors in addition to the mechanism postulated in this paper.

#### SUMMARY

Blood volumes determined by the dye method are reported on normal infants and children up to twelve years of age. A curve of the plasma volume per kilogram of body weight as related to age shows a rise in the plasma volume from 50 to 62 milliliters during the first year of life, and a return to 50 milliliters, by the fourth year. Thereafter, the plasma volume remains constant at 50 milliliters per kilogram of body weight.

A curve of the plasma volume per square meter of surface area as related to age shows a rapid rise from 750 to 1100 milliliters during the first year of life, and thereafter there is a gradual increase to 1375 milliliters by the twelfth year.

The proportion of the blood represented by the red cells is about 30 per cent, except during the first six weeks of life, when it is 45 to 70 per cent. The whole blood volume cannot be predicted very accurately either from the weight or the surface area because of the variability of the cell volume.

The following hypotheses are advanced: (1) The amount of plasma is primarily dependent on the mass of the body tissues. (2) Within certain limits set by the mass of the tissues, the amount of water in the blood stream varies directly with the metabolic rate.

The mechanism by which the plasma volume is maintained and varied is given a partial explanation.

#### BIBLIOGRAPHY

1. Haldane, J., and Smith, J. L., *J. Physiol.*, 1900, xxv, 331. The Mass and Oxygen Capacity of the Blood in Man.
2. Keith, N. M., Rowntree, L. G., and Geraghty, G. H., *Arch. Int. Med.*, 1915, xvi, 547. A Method for the Determination of Plasma and Blood Volume.



3. Smith, H. P., *Bull. Johns Hopkins Hosp.*, May 1925, xxxvi, 325. The Fate of an Intravenously Injected Dye (Brilliant Vital Red), with Especial Reference to Its Use in Blood Volume Determinations.
4. Erlanger, J., *Physiol. Rev.* i, 177. Blood Volume and Its Regulation.
5. Bock, A. V., *Arch. Int. Med.*, 1921, xxvii, 83. The Constancy of the Volume of the Blood Plasma.
6. Brown, G. E., and Rowntree, L. G., *Arch. Int. Med.*, 1925, xxv, 129. The Volume and Composition of the Blood and the Changes Incident to Diuresis, in Cases of Edema.
7. Robertson, O. H., and Bock, A. V., *J. Exper. Med.*, 1919, xxix, 139. Blood Volume in Wounded Soldiers. I. Blood Volume and Related Blood Changes after Hemorrhage.
8. Brown, G. E., and Keith, N. M., *Arch. Int. Med.*, 1924, xxxiii, 217. Blood and Plasma Volume in Obesity.
9. Dreyer, G., and Ray, W., *Phil. Trans. of the Royal Soc. London B*, 1910, cci, 133. The Blood Volume of Mammals as Determined by Experiments upon Rabbits, Guinea Pigs, and Mice; and its Relationship to the Body Weight, and to the Surface Area Expressed in a Formula.
10. Lucas, W. P., and Dearing, B. F., *Am. J. Dis. Child*, 1921, xxi, 96. Blood Volume in Infants Estimated by the Vital Dye Method.
11. Bakwin, H., and Rivkin, H., *Am. J. Dis. Child.*, 1924, xxvii, 340. The Estimation of the Volume of Blood in Normal Infants and Infants with Severe Malnutrition.
12. Quoted by Marriott, McKim, *Am. J. Dis. Child.*, Dec., 1920, xx, 461. Some Phases of the Pathology of Nutrition in Infancy.
13. Reiss, E., *Ergeb. Inn. Med. u. Kinderh.*, 1913, x, 531. Die refraktometrische Blutuntersuchung und ihre Ergebnisse für die Physiologie und Pathologie des Menschen.
14. Quoted by Murlin, J. R., *Abt's Pediatrics* 591. W. B. Saunders Company, Philadelphia.
15. Quoted by Talbot, F., *Physiol. Rev.*, 1925, v, 483. Basal Metabolism of Children.
16. Quoted by Talbot, F., *Physiol. Rev.*, 1925, v, 487. Basal Metabolism in Children.
17. Thompson, W. O., *J. Clin. Invest.*, 1926, ii, 477. The Blood Volume in Myxedema with a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema.
18. Keith, N. M., *Blood Volume Changes in Wound Shock and Primary Hemorrhage*. London. Med. Research Committee. Special Series 1919.
19. Buckman, T. E., and Darrow, D. C., *J. Clin. Invest.*, 1925, i, 582. An Hypothesis Concerning the Transportation of Water.
20. Underhill, F. P., and Ringer, M., *J. Am. Med. Assoc.*, 1920, lxxv, 1531. Blood Concentration Changes in Influenza.
21. Underhill, F. P., *Arch. Int. Med.*, 1919, xxiii, 753. The Physiology and Experimental Treatment of Poisoning with Lethal War Gases.