THE CONSTANCY OF THE VOLUME OF THE BLOOD PLASMA *

A. V. BOCK, M.D.
BOSTON

INTRODUCTION

Until about the middle of the nineteenth century no observations as to the total blood mass in the human body were presented by either clinicians or physiologists. In 1854, Welcker [1] attempted to determine the quantity of blood in the bodies of two criminals by means of a washing out method, and he established as normal the figure of $1/13$ of the body weight, which has remained the standard commonly adopted up to the present time. Even today, after a considerable series of investigations of this problem by various workers, figures given for the total blood volume in man are approximate and not absolute. The results usually quoted vary from $1/10$ to $1/21$ of the body weight. This uncertainty regarding the actual amount of circulating blood is largely due to technical difficulties. Clinical methods for determining the blood volume now available, however, yield results consistent enough to furnish a figure approximating the true volume and to afford data from which relative changes in the blood mass may be determined.

It is the purpose of this paper to show that the plasma volume in man, in contradistinction to the total blood volume, tends to be a physiologic constant, except under certain stated conditions. The evidence consists of data obtained by blood volume determinations in five normal and twenty-five abnormal individuals. With reference to changes in the blood, the latter cases include examples of extreme variations in total blood volume, corpuscle content, and so forth.

METHOD

The total mass of circulating blood may be determined by a number of indirect methods. For recent reviews of these, reference may be made to the papers of Keith, Rowntree and Geraghty [2] and Salvesen.[3]

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* From the Medical Clinic of the Massachusetts General Hospital. This is Study 6 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

1. Welcker, H.: Prager Vrtljschr. **4**:145, 1854.

2. Kieth, N. M.; Rowntree, L. G., and Geraghty, J. T.: Arch. Int. Med. **16**:547 (Nov.) 1915.

3. Salvesen, H.: J. Biol. Chem. **40**:109, 1919.

The vital red method was used for the present study. In principle it consists in the colorimetric determination of the dilution in the plasma of a known amount of a dye, vital red, which has been injected intravenously and allowed to circulate for a period of four minutes, when the sample of blood required for the determination is withdrawn. Having obtained the plasma volume in this manner, the total volume may be calculated from the proportion of corpuscles to plasma as shown by the hematocrit.

Remarkably constant results have been obtained with this method in man by Keith, Rowntree and Geraghty, the total blood mass measuring $1/_{11.4}$ of the body weight in a series of eighteen normal men.[2] The same method as modified and used in dogs by Dawson, Evans and Whipple,[4] and the acacia method of Meek and Gasser,[5] show close agreement with each other, and the values reported by these observers for normal dogs per kilogram of body weight approximate those found in man.

Total blood volume determinations have also been made in a variety of conditions with the carbon monoxid method, a method which in the hands of Haldane and Smith[6] gave values ranging from $1/_{30}$ to $1/_{16}$ of the body weight in fourteen cases examined. The value $1/_{30}$ was obtained in a patient of an extremely obese type. Later, Haldane and Douglas[7] made repeated observations with the carbon monoxid method on each other and found a mean value for the total blood volume from which variations did not exceed 8 per cent., in excess or deficiency, except in one instance for each subject. Salvesen[3] obtained an average value for normal men of $1/_{16.8}$ of the body weight, and Plesch[8] found $1/_{18}$ as an average value in four cases with the same method. In anemic conditions Lorrain Smith[9] found values in chlorosis of $1/_{9.2}$ of the body weight and $1/_{8.9}$ for pernicious anemia; volumes which represent enormous increases over the values obtained for normals by the carbon monoxid method. Finally, Douglas[10] secured constant results in rabbits which agreed closely with the Welcker method, approximating $1/_{21}$ of the body weight in male animals.

The difference in results between the vital red and carbon monoxid methods is not easily explained, but an important consideration concerning it will be found at the end of this paper. The variability in

4. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: Am. J. Physiol. **51**:*232*, 1920.

5. Meek, W. J., and Gasser, H. S.: Am. J. Physiol. **47**:302, 1918.

6. Haldane, J. S., and Smith, J. L.: J. Physiol. **25**:331, 1900.

7. Douglas, C. G.; Haldane, J. S.; Henderson, Y., and Schneider, E. C.: Phil. Tr. Roy. Soc., London, Series B, **203**:195.

8. Plesch, J.: Ztschr. f. Exper. Path. u. Therap. **6**:380, 1909.

9. Smith, J. L.: Proc. Physiol. Soc., Dec. 9, 1899, p. 6.

10. Douglas, C. G.: J. Physiol. **33**:493, 1906.

results with the carbon monoxid method may be more apparent than real, as Boycott[11] suggests, but it seems probable that the values generally accepted for the blood volume in anemia, based on Smith's figures, are too great as may be seen by results in similar cases quoted here.

There remains to be mentioned the conception of Dreyer and Ray[12] that the volume of the blood in mammals is directly proportional to the surface area of the body. They believe that the practice of expressing blood volume as a per cent. of body weight is erroneous and misleading, and that it should be expressed in the formula $B.V. = \frac{B.W.^n}{K}$ in which K is a constant which must be worked out for each species. The formula has recently been extended to application in man and used by Bazett[13] in determining the amount of blood lost by operative procedures. As adopted for man the formula is $B.V. = \frac{B.W.^{.72}}{0.67}$. This formula yields a blood volume in man equivalent to approximately $1/_{9.3}$ of the body weight, a higher figure than has been obtained by any of the other methods.

RESULTS IN NORMAL INDIVIDUALS

It is unfortunate that more figures concerning the blood plasma volume in normal men are not available. At present, in addition to the data presented here, the figures of Keith, Rowntree and Geraghty[2] alone may be referred to.

In Table 1 are presented the data of the five normal individuals in this series.[14] The total volume is $1/_{12.2}$, or 8.7 per cent. of the body weight, as compared with 8.8 per cent. as found in the series of Keith, Rowntree and Geraghty. The average plasma volume expressed as a fraction of the body weight is $1/_{19.6}$, or 5.1 per cent., which agrees closely with the figure of $1/_{19.4}$ in the above series. Data of this type as well as that obtained in animals by the vital red method[4] reveal only slight variations in the plasma volume in normal individuals per kilogram of body weight. An investigation by Bogert, Underhill and Mendel[15] concerning the regulation of the blood volume after injections of saline solutions leads to the same conclusion.

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11. Boycott, A. E.: J. Path. & Bacteriol. **16**:485, 1911.

12. Dreyer, G., and Ray, W.: Phil. Tr. Roy. Soc., London **201**:159, 1910.

13. Bazett, M. C.: Medical Research Committee. Wound Shock and Hemorrhage, Report 5. 1919.

14. It must be emphasized again that the figures presented in the tables in this paper are not put forward as absolute values. Their value lies rather in the consistency of results obtained with the vital red method, and they offer a working basis for problems concerned with blood volume. The vital red method and modifications of it are the only methods available by which the plasma volume is directly estimated.

15. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: Am. J. Physiol. **41**:189, 1916.

RESULTS IN POLYCYTHEMIA

In three cases of polycythemia vera, as shown in Table 2, the average total volume is 13.2 per cent., or $1/7.3$ of the body weight, the increase above the normal figure (approximately $1/12$) being entirely due to the great increase in the total number of corpuscles which average 2.5 times the number found in normal men. The plasma fraction of the body weight varied from $1/16.2$ to $1/21.2$, the average being $1/19.3$. Thus, while the plasma volume in polycythemia is the same as in normal individuals, the total blood per kilogram, in the cases studied, averages 47 c.c. more than in the normal. The relatively high plasma volume in Case 8 is difficult to explain. This patient had had a long course of treatment with radium and the roentgen ray.

RESULTS IN PERNICIOUS ANEMIA

The seven cases of pernicious anemia have an average plasma volume of 4.9 per cent., or $1/20.5$ of the body weight, and a total volume of 5.7 per cent., or $1/17.3$ of the body weight (Table 3). The first four cases, with hemoglobin values ranging from 43 to 59, per cent., have plasma volumes averaging 5.4 per cent., or $1/18.5$ of the body weight. Cases 13 and 14 have an average plasma volume of 4 per cent., or $1/25$ of the body weight. It will be observed that in each of these cases the hemoglobin is below 30 per cent., which may account for the low plasma volumes. The condition seems to parallel that found after severe hemorrhage.[16] The last case, with a relatively high hemoglobin and high count of red corpuscles, has a plasma volume of 5.1 per cent., or $1/19.4$ of the body weight. It is apparent, therefore, that but little variation occurs in the plasma volume in primary anemia. The reduction in the total volume of blood in cases with hemoglobin above 30 per cent. is due entirely to the low content of corpuscles. The average volume of corpuscles is $1/5$ of that found for normals and $1/13$ of the number in polycythemia. A total mass of 270 c.c. of corpuscles, as in Case 8, contrasts greatly with the usual quantity of about 2,000 c.c. found in the normal.

RESULTS IN MISCELLANEOUS CASES

The group of miscellaneous cases includes one case (Case 22) of cardiac failure of the congestion type, with anasarca, and two cases (Cases 16 and 17) of chronic nephritis with extensive edema. The average results presented in Table 4 show, so far as the plasma is concerned, a remarkably small deviation from the normal. The average plasma value is 4.9 per cent., or $1/20.3$ of the body weight.

16. Robertson, O. H., and Bock, A. V.: J. Exper. M. **29**:139, 1919.

TABLE 1.—Data for Five Normal Individuals *

Case No.	Sex*	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
1	♂	63	57	91	3,628	1/17.3	5.7	2,130	5,758	1/10.9	9.1	1,372	128	4.8	27.6
2	♂	82	46	76	3,731	1/21.9	4.5	2,487	6,218	1/13.1	7.6	1,442	122	4.8	30.0
3	♀	55	54	83	2,990	1/18.4	5.4	1,610	4,600	1/11.9	8.3	901	108	4.0	18.4
4	♂	67	50	82	3,343	1/20	5.0	2,137	5,480	1/12.2	8.2	1,205	119	5.2	28.6
5	♂	69	49	77	3,380	1/20	5.0	1,901	5,281	1/13	7.7	.....	...	5.0	26.4
Average		67	51	81	3,414	1/19.6	5.1	2,053	5,467	1/12.2	8.2	.....	119	4.8	26.2

* In this and the following tables, ♂ indicates male and ♀ female.

TABLE 2.—Data for Three Cases of Polycythemia

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
6	♂	60.5	47	123	2,820	1/21.4	4.7	5,725	8,545	1/7	14.3	2,851	180	8.8	75.1
7	♂	54	47	134	2,570	1/21	4.8	4,772	7,342	1/7.3	13.7	2,934	198	10.3	75.6
8	♀	49	61	128	3,013	1/16.2	6.1	3,264	6,277	1/7.8	12.8	1,299	112	8.3	51.9
Average		54.5	51.6	128	2,824	1/19.3	5.1	4,587	7,388	1/7.3	13.7	2,364	163	9.1	67.6

TABLE 3.—Data for Seven Cases of Pernicious Anemia

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
9	♀	43.5	59	70	2,597	1/17.2	5.9	468	3,055	1/14.2	7.0	284	50	1.7	5.1
10	♀	43	54	64	2,329	1/18.3	5.4	411	2,740	1/15.7	6.3	300	59	1.8	4.9
11	♀	45	48	54	2,189	1/20.5	4.9	270	2,459	1/18.2	5.4	197	43	1.2	3.0
12	♂	50	54	61	2,729	1/18.3	5.4	337	3,066	1/16.3	6.1	266	46	1.3	4.0
13	♀	55	38	44	2,136	1/25.7	3.8	264	2,400	1/23	4.3	125	28	1.1	2.7
14	♂	71	41	44	2,933	1/24.2	4.1	221	3,154	1/22.5	4.4	139	24	0.67	2.1
15	♂	59	51.5	72.5	3,040	1/19.4	5.1	1,241	4,281	1/13.7	7.3	583	73	3.2	13.9
Average		52.3	49.3	58.5	2,555	1/20.4	4.9	459	3,022	1/17.3	5.7	270	47	1.6	5.1

Consideration of the fact that the method used in determining the plasma volume and the complex nature of the problem itself leads to the conclusion that the results in these cases are quite identical with those found in the normal. It is to be noted again that the smaller total volume of 7.1 per cent., or $\frac{1}{14}$ of the body weight, is due to the diminished volume of corpuscles associated with the anemia present in some of the cases.

RESULTS IN DIABETES MELLITUS

Eight cases of diabetes mellitus afford an interesting study which will be made the subject of a later report. For the purpose of this paper it is important, only, to point to the average results as shown in Table 5. The average plasma value per kilo is 48 c.c., 4.8 per cent., or $\frac{1}{20.8}$ of the body weight. The variations of plasma volume in individual cases are greater than were found in other conditions, but the general average for the plasma volume in diabetes is close to the normal. Notwithstanding this fact, the problem of the plasma volume in diabetes, particularly during the stage of severe acidosis, remains to be worked out.

THE EFFECT OF EDEMA ON THE PLASMA VOLUME

It is the prevailing view in the literature that rapid alterations in body weight due to the water content of the body are associated with changes in the blood volume. With sudden increase in weight of the body the blood is said to become hydremic and with sudden losses it becomes more concentrated.[17] For example, Krehl [18] states that there is no reason why the blood should not become edematous as well as other tissues. He believes that a real hydremic plethora accompanies cardiac and renal diseases, and thinks there is no reason a priori why an increase in the total quantity of blood should not take place. Von Noorden,[19] on the other hand, after reviewing similar considerations, concludes that one cannot be certain of such a plethora because of the little certain knowledge of the watery content of the blood.

While it is possible that hydremia or hydremic plethora, as it is usually called, may be present in some conditions, it certainly is not found in the usual course of events, and its occurrence must be regarded as infrequent except possibly as a terminal affair. In Table 6 is presented evidence in three cases of edema to show that the relation of the blood plasma to the body weight remains undisturbed in such conditions. In Case 16, a chronic glomerulonephritis in a girl,

17. Barker, L. F.: Monographic Medicine **1**:561, 1916.
18. Krehl, L.: Clinical Pathology, Ed. 2. 1907, p. 172.
19. Von Noorden, C.: Metabolism and Practical Medicine **2**: 1907.

TABLE 4.—Data for Seven Miscellaneous Cases

Case No.	Sex	Diagnosis	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
16	♀	Chronic nephritis	54.5	40	47	2,200	1/24.7	4.0	387	2,587	1/21	4.7	217	45	2.0	5.7
17	♀	Chronic nephritis	40	57	76	2,291	1/17	6.0	764	3,055	1/33	7.7	360	63	3.3	10.0
18	♂	Chronic nephritis	65	47	67.5	3,117	1/20.8	4.8	1,273	4,390	1/14.8	6.7	758	98	4.7	20.5
19	♂	Myasthenia gravis	63	46.6	78	2,933	1/21.5	4.6	2,038	4,971	1/12.7	7.8	1,144	123	5.3	26.6
20	♀	Secondary anemia	60.5	56	74	3,400	1/17.8	5.6	1,073	4,473	1/13.5	7.4	476	57	4.4	19.6
21	♀	Secondary anemia	53.5	53.4	72	2,860	1/18.7	5.3	953	3,813	1/14	7.1	368	52	4.0	15.5
22	♂	Cardiac failure	72.2	46	81	3,333	1/21.6	4.6	2,514	5,847	1/12.3	8.2	1,231	114	5.0	29.2
Average..................			58.4	49.4	70.7	2,876	1/20.3	4.9	1,183	4,162	1/14	7.1	670	79	3.9	18.3

TABLE 5.—Data for Eight Cases of Diabetes

Case No.	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions	Per Cent. Plasma Sugar
23	41.5	57	91	2,366	1/17.5	5.7	1,419	3,784	1/11.2	8.9	770	110	4.6	18.4	0.22
24	54.5	40	62	2,200	1/24.7	4.0	1,163	3,363	1/16.2	6.1	723	116	4.6	15.7	0.38
25	62	40	61	2,841	1/26.6	3.7	1,278	3,759	1/16.5	6.0	969	139	3.7	13.9	0.24
26	35.5	62	82.5	2,200	1/16	6.2	733	2,933	1/12.1	8.2	475	87	3.3	9.7	0.39
27	47	53	85	2,500	1/18.8	5.3	1,530	4,030	1/11.6	8.7	790	110	4.1	16.6	0.19
28	50	42.5	66.5	2,136	1/23.4	4.2	1,201	3,337	1/14.9	6.7	860	139	6.0	20.0	0.26
29	70	42.7	66.7	2,988	1/23.4	4.2	1,700	4,688	1/14.9	6.7	1,096	126	5.12	24.0	0.36
30	43	56.8	90	2,444	1/17.6	5.6	1,435	3,879	1/11.9	8.3	....	...	4.5	17.6	0.22
Average	50.4	48	75.5	2,414	1/20.8	4.8	1,308	.....	1/13.5	7.3	812	118	4.6	17.0	

aged 16, after a loss of 13.5 kg. in weight and disappearance of all visible edema, the plasma volume per kilogram of body weight remained unchanged. No attempt is made to explain the relatively low plasma volume in this patient, who also suffered from a severe anemia. In Case 28, diabetes mellitus in a boy, aged 17, after the addition of 4 kg. in weight while on a forced fluid and increased salt intake, there was essentially no alteration in the plasma volume per kilogram of weight. In Case 22, a man, aged 75, with cardiac failure of the congestion type, and with anasarca at the time of the first observation, the figures show an apparent change in plasma volume, which, however, is only 8 per cent. and is within the margin of error. Keith, Rowntree and Geraghty [2] found similar results in a case of nephritis with edema.

Boycott [20] found that the edema which may be brought about by the administration of water to animals with uranium nephritis involved the blood as well as the rest of the tissues. The blood dilution, determined by changes in hemoglobin, in such animals was associated with fluid in the pleural and peritoneal cavities and with edema of the loose connective tissue in general. The effect on the blood volume of intravenous injection of dextrose and of sodium chlorid was found to be more prolonged in nephritic than in normal rabbits.[21] It is possible that in man the edema associated with acute nephritis might be reflected for a time in dilution of the blood plasma, but in subacute and chronic conditions the body adjustments seem to compensate for the disturbance in fluid balance, and the blood does not share in the general edema of the tissues.

A recent theory by McLean [22] concerning the mechanism of edema is worthy of note in the present discussion. The usual idea of edema is that the excess fluid represents an accumulation of fluid in the body, a process static in nature. McLean points out that the condition cannot be static in nature but that there must be a constant interchange of fluid and dissolved substances in edema as well as under normal conditions between the blood, tissue fluids, and contents of lymph channels in order to maintain cellular life. The condition must be regarded as an equilibrium, as Meltzer has also suggested. As the plasma volume determinations in cases of edema presented above have indicated, there is no shift of increased fluid into the blood in edema, but the balance between plasma and tissue fluids is maintained through such an interchange of fluid and dissolved substances as to maintain the fluid phase of the blood at about its normal level.

A summary of the above data is presented in Table 7.

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20. Boycott, A. E.: J. Path. & Bacteriol. **18**:11, 1913.
21. Boycott, A. E., and Douglas, C. G.: J. Path. & Bacteriol. **19**:221, 1914.
22. McLean, F. C.: Personal communication.

TABLE 6.—DATA SHOWING INFLUENCE OF EDEMA ON BLOOD PLASMA

Case No.	Sex	Date	Diagnosis	Weight in Kilos	Edema	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
16	♀	Jan. 9	Chronic nephritis	54.5	+++	40	47	2,200	1/24.7	4.0	387	2,587	1/21	4.7	217	45.2	2.0	5.7
16	♀	Jan. 24	Chronic nephritis	46	++	41	50	1,900	1/24.2	4.1	417	2,317	1/19.8	5.0	262	60.6	2.5	5.9
16	♀	Feb. 3	Chronic nephritis	41	0	41	48	1,690	1/24.2	4.1	275	1,965	1/20.8	4.8	223	61.5	2.4	4.7
28	♂	Jan. 23	Diabetes	50	0	42.5	66.5	2,136	1/23.4	4.2	1,201	3,337	1/15	6.6	861	139.0	6.0	20.0
28	♂	Jan. 27	Diabetes	54	±	44	66.5	2,376	1/22.7	4.4	1,221	3,592	1/15	6.6	736	111.0	5.0	17.8
22	♂	Apr. 16	Cardiac failure	72.2	+++	46	81	3,333	1/21.6	4.6	2,514	5,847	1/12.3	8.1	1,231	114.0	5.0	29.2
22	♂	Apr. 20	Cardiac failure	61.3	±	51.6	91	3,170	1/19.3	5.1	2,112	5,582	1/10.9	9.1	1,271	112.7	5.0	27.9

TABLE 7.—AVERAGE RESULTS

No. of Cases	Diagnosis	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Cent. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O_2 Capacity in C.c.	Per Cent. Hb. Calculated from O_2 Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Trillions
5	Normal..............	67	51	81	3,414	1/19.6	5.1	2,053	5,467	1/12.2	8.2	1,230	119	4.8	26.2
3	Polycythemia.........	54.5	51.6	128	2,824	1/19.3	5.1	4,587	7,388	1/ 7.3	13.7	2,364	163	9.1	67.6
7	Pernicious anemia....	52.3	49.3	58.5	2,555	1/20.4	4.9	459	3,022	1/17.3	5.7	270	47	1.6	5.1
7	Miscellaneous.........	58.4	49.4	70.7	2,876	1/20.3	4.9	1,183	4,162	1/14	7.1	670	79	3.9	18.3
8	Diabetes.............	50.4	48	75.5	2,414	1/20.8	4.8	1,308	3,721	1/13.5	7.3	812	118	4.6	17.0

THE EFFECT OF HEMORRHAGE ON THE PLASMA VOLUME

Acute hemorrhage results in an immediate mechanical reduction of the total blood volume. If the hemorrhage is not too great, and if a reserve supply of tissue fluids is available, a flow of fluids from the tissue spaces into the circulation occurs during the process of hemorrhage so that the blood plasma may be diluted to its normal level as rapidly as possible. In a case of controlled hemorrhage four conditions may prevent a return of the plasma volume to normal: (1) lack of adequate fluid reserve in the tissues, as was found frequently

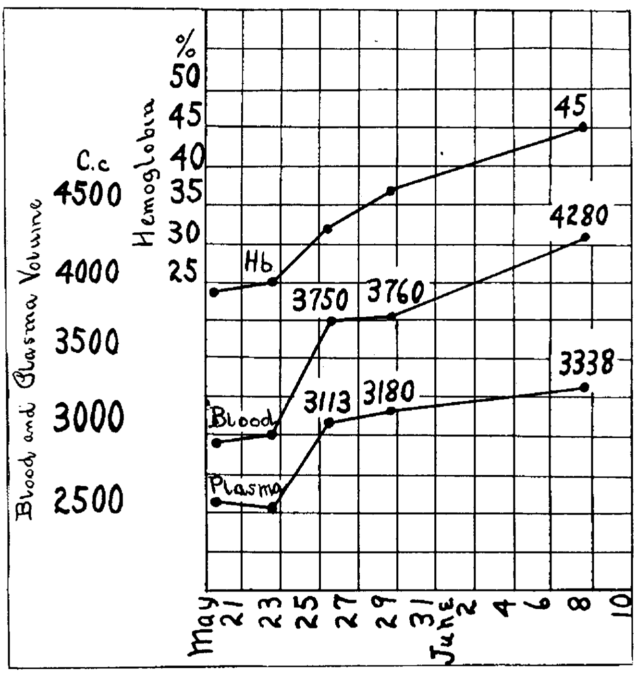

Fig. 1.—This chart is constructed from data published by Robertson and Bock, their Case 4, to show the rapid recovery of the plasma volume to normal after hemorrhage, and the gradual restoration of the total blood volume.

in soldiers wounded in action; (2) lack of adequate fluid intake by the alimentary tract; (3) a state of shock which in some degree always accompanies moderate and severe hemorrhage and in which the regulation of fluid balance between the blood and tissue fluids is disturbed; (4) a reduction in total hemoglobin below 25 per cent., as was shown by Robertson and Bock.[16] In the last condition, as long as the hemoglobin remains at or below 25 per cent., the plasma volume will remain below normal and no known measures can change this condition except the addition of more hemoglobin. If none of the four conditions above named are present, the plasma tends to assume normal proportions in a comparatively short time and will then remain at the level normal for the given individual. The total blood volume, however, will remain below normal until the processes of blood regeneration have restored the normal quantity of corpuscles. Figure 1, constructed from Case 4, of Robertson and Bock, illustrates this mechanism of recovery in a case of severe hemorrhage. With a hemoglobin value of 24 per cent., the plasma remained at 2,600 c.c. Accompanying a rise in hemoglobin to 33 per cent. the plasma increased to 3,113 c.c. Two days later the hemoglobin was 38 per cent. and the plasma 3,180 c.c. Nine days later, when the hemoglobin had reached 45 per cent., the

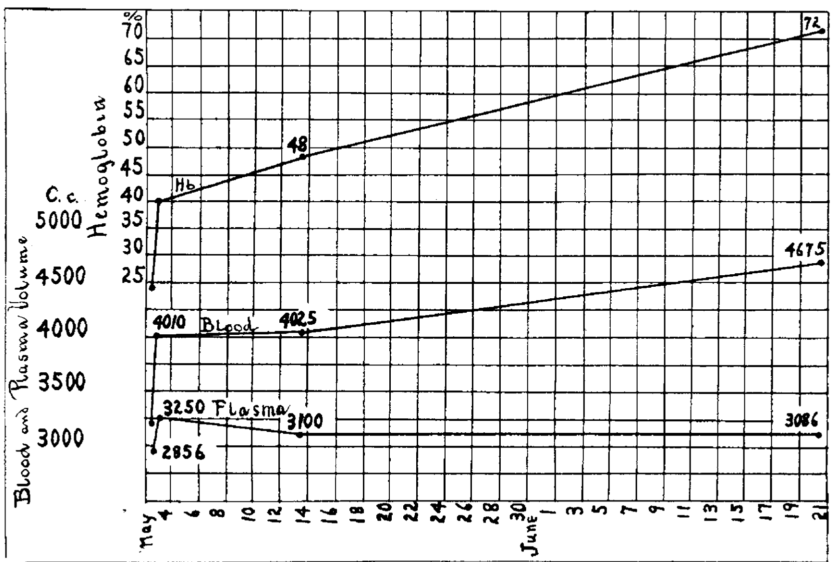

Fig. 2.—Also from Robertson and Bock, their Case 5, showing the constant level of the plasma volume as the total volume increases by the addition of red corpuscles.

plasma was 3,338 c.c. and the total volume had increased 1,300 c.c. since the original observation. Figure 2, Case 5, also from the same authors, shows a reduced plasma of 2,856 c.c. as a result of a hemorrhage which was brought up to normal by transfusion. Subsequent determinations show approximately no change in the figures. The total volume increased 650 c.c.

Figure 3 is the record of a case showing reaction following hemorrhage from a gastric ulcer. The first observation was made approximately twelve hours from the time hemorrhage apparently stopped. The plasma curve as represented shows the plasma reduction at once after hemorrhage, and after dilution to the usual level for this patient.

No further change in plasma volume occurred although the total blood volume steadily increased by reason of the addition of new red corpuscles.

Figure 4 represents the findings in another case of gastric ulcer, the observations beginning three days after hemorrhage had ceased and at a time when the plasma had already reached a normal level by dilution. The patient was transfused because of the low hemoglobin figure of 32 per cent. The plasma volume prior to transfusion was 2,685 c.c., and subsequent determinations showed very little change from this figure.

As a result of experimental hemorrhage in animals, it has frequently been reported that overdilution of the blood occurs by absorp-

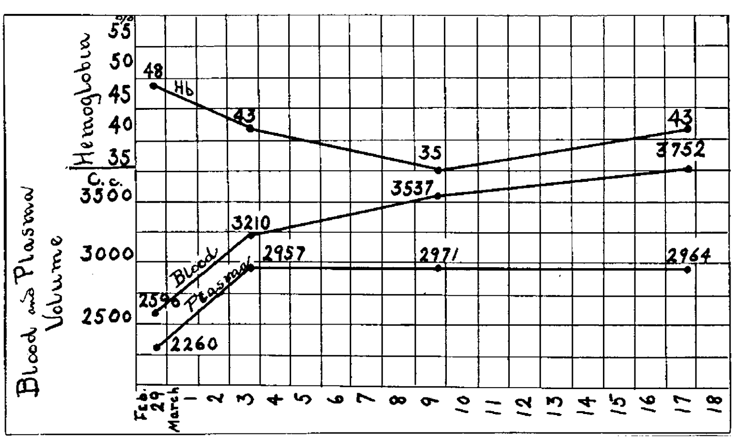

Fig. 3.—Showing the reaction of the blood following hemorrhage from a gastric ulcer, observations beginning twelve hours after the hemorrhage stopped. The plasma volume after dilution to normal, remains constant. Incidentally, this case illustrates a falling color index often seen in blood regeneration after hemorrhage.

tion of fluid from the tissues with the result that the total volume immediately subsequent to the absorption period is greater than before the hemorrhage occurred. For a discussion of this question reference may be made to the work of Boycott and Douglas.[23] Observation of the reaction from hemorrhage in man has failed to show that overdilution takes place and it may be said that this condition does not occur under the conditions which usually obtain. It should be understood that the blood volume determinations referred to in the work of Boycott and Douglas are "relative blood volumes" in the sense

23. Boycott, A. E., and Douglas, C. G.: J. Path. & Bacteriol. **13**:256, 1908.

that they are calculated from changes in the hemoglobin. Actual blood volume determinations made under the same experimental conditions employed by these authors would be interesting.

CHANGES IN THE PLASMA VOLUME IN CERTAIN CLINICAL CONDITIONS

While increase or reduction in the plasma volume does not occur in disease to any great degree, certain conditions are associated with concentration or loss of blood which remain to be mentioned, since they constitute exceptions to the general rule. The exceptions are

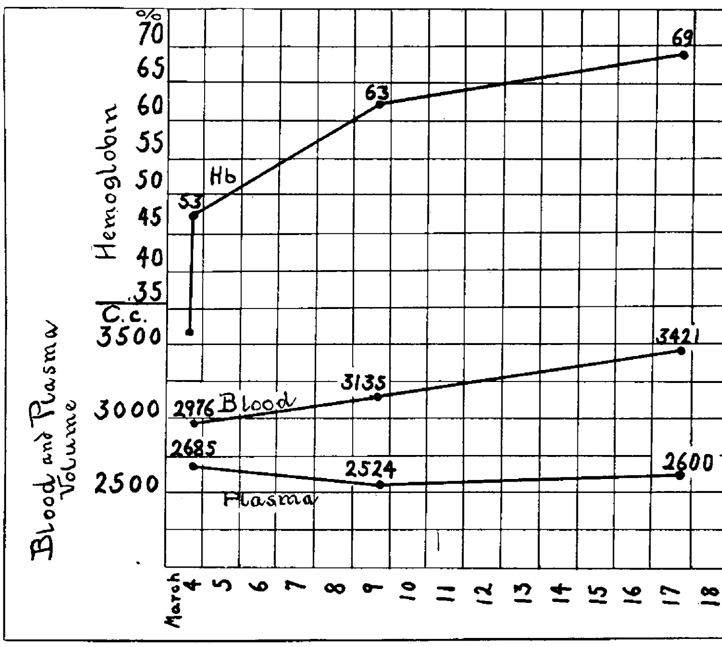

Fig. 4.—Observations begun three days after hemorrhage from gastric ulcer. Initial dilution of plasma to normal had already occurred. The effect of transfusion in this case on the plasma volume is negative, whereas the hemoglobin increased from 32 to 53 per cent.

concerned with conditions in which there is great fluid loss either directly from the circulation or through a more gradual loss of the body reserve fluid. Aside from acute hemorrhage and shock already mentioned, such conditions as acute edema of the lungs, excessive sweating, and diarrhea of severe type as seen in infants and in Asiatic cholera are outstanding examples. Cunningham[24] observed a patient having edema of the lungs, in whom the oxygen capacity of

24. Cunningham, T. D.: Personal communication.

the blood at the height of the attack was 25 volumes per cent. as compared to the man's normal oxygen capacity of 19 volumes per cent. Such a change in the oxygen capacity per unit volume of blood, occurring in a short time, suggests extensive contraction of the plasma volume. This finding is in agreement with experimental work on the effects of poison gas in rabbits by Haldane, Meakins and Priestley.[25] They found, at necropsy, extensive edema of the lungs which was believed to be associated with a corresponding depletion of the blood plasma.

Many observers have reported changes in the peripheral blood indicating concentration as a result of great sweating incident to work and exercise. No blood volume determinations are reported in such conditions except by Schneider and Havens.[26] These workers found the usual changes in the peripheral blood, notable increase in the percentage of hemoglobin, red corpuscle count and rise in specific gravity, which have been observed by others repeatedly. They also found, however, that abdominal massage for a brief period increased the number of red blood cells in the peripheral blood in about the same proportions as occurred after vigorous exercise. The logical deduction that they make is that a reserve store of corpuscles is present in the splanchnic area during comparative inaction which is called into the circulation by exercise. They found no alteration in the blood volume by the carbon monoxid method. Some doubt may, therefore, be entertained concerning fluctuations of the plasma volume under conditions of work and exercise.

The dehydration of the body fluids as a result of diarrhea and cholera is well known to clinicians. Marriott[27] has recently called attention to a condition in infants in which he described changes in the blood which simulate those found in hemorrhage and shock. The thickness of the blood in cholera requires little comment. In this condition dehydration of the tissues proceeds to an extreme state in an effort to meet the requirements of the blood plasma but concentration of the blood inevitably occurs.

The effect of altitude on the total blood volume has also been studied in both man and animals. The results in man indicate that the final alterations consist in a variable increase of red corpuscles and a slight increase in the total blood volume. Douglas, Haldane, Henderson and Schneider[7] report an additional increase in the blood volume after descent from Pike's Peak, and offer as an explanation

25. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: Personal communication from J. C. Meakins.

26. Schneider, E. C., and Havens, L. C.: Am. J. Physiol. **36**:239, 1915.

27. Marriott, W. McK.: Paper read before Am. Soc. for Clin. Investigation, 1919.

a probable dilution of the blood plasma in order to decrease the viscosity of blood in which polycythemia had occurred as a result of residence at the summit of Pike's Peak. Such an interpretation does not coincide with present findings in cases of polycythemia vera in which the problem of viscosity is not adjusted by an increase in the plasma volume. Whatever the mechanism of adjustment may be, it is certain that such changes in volume are temporary in persons who have resumed residence at the usual altitudes.

In the present discussion may be included a condition of another type, namely obesity, in which there is known to be a reduction in the total blood volume. Haldane and Smith[6] report one case of extreme obesity having a volume of $\frac{1}{30}$ of the body weight. Keith, Rowntree and Geraghty[2] present six cases having an average plasma volume of 37.1 c.c. per kilogram, or 3.8 per cent. of the body weight. There is no evidence that fluctuations in the plasma volume occur in this condition.

DISCUSSION

In relation to the present series of cases, certain additional results in the work of Keith, Rowntree and Geraghty[2] should be mentioned. They found an increased blood volume in the latter months of pregnancy in twelve cases. The average blood volume was 9.56 per cent. and the average plasma volume 5.7 per cent. After labor the blood volume was 9 per cent. and the plasma volume 4.9 per cent. of the body weight. Such results are in accord with volume findings in pregnancy in animals, but the increase found in women cannot be considered very great and Williams[28] has attached very little significance to it.

With respect to anemia, in ten cases they found three with abnormally high plasma volumes and in six the plasma values were considered slightly higher than normal. The average in eight cases was 56 c.c. per kilogram of body weight. Of three cases of pernicious anemia, two were found to have normal plasma values, 54 c.c. and 53 c.c. per kilogram, while the third had 72 c.c. It is difficult to harmonize the finding of such a high plasma volume in anemia. At variance also with the results obtained in anemia in the present series is the work of Lorrain Smith,[9] who found that in chlorosis and in pernicious anemia the blood volume is greatly increased. For a patient with chlorosis weighing 44.5 kg. the volume found was 6,181 c.c., or 139 c.c. per kilogram of body weight. In a case of pernicious anemia the total volume found was 6,500 c.c., or 112 c.c. per kilogram.

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28. Williams, J. W.: Contributions to Medical and Biological Research. Dedicated to Sir William Osler, **2**:1238, 1919.

In each instance the volume is comparable only to that found in polycythemia. In the case of chlorosis the total oxygen capacity was 418 c.c., which is not unlike that of Case 20 of the present series, a patient having secondary anemia of chlorotic type, whose oxygen capacity was 476 c.c. and whose total volume was 4,473 c.c., or 74 c.c. per kilogram. Likewise the case of pernicious anemia reported by Smith, with a total oxygen capacity of 195 c.c., may be compared to Case 12 of the present series, in which the total oxygen capacity was 266.4 c.c. and the total volume was 3,066 c.c., or 61 c.c. per kilogram. The results of the present investigation indicate that the blood volume is diminished in anemia in direct proportion to the decrease in corpuscles.

Of the other conditions reported by Keith, Rowntree and Geraghty, plasma values on the lower limit of normal were found as an average result in thirteen cases of chronic nephritis and hypertension, the average plasma volume being 42.8 c.c. per kilogram. In scattered cases of diabetes emaciation, myocardial insufficiency, aneurysm of the arch, chronic bronchitis, neurasthenia, and so forth, the plasma values were within the normal range.

It is important to remember that in conditions of chronic anemia, for example, no device exists for increasing the fluid volume of the blood beyond the level already attained by the patient, providing a normal tissue fluid reserve is present. Every such patient who has even a moderate fluid intake daily will have an optimum total blood plasma. Lindeman[29] supposed that by forcing food and fluids in cases of pernicious anemia the blood volume was thereby increased. He wrote that a patient with a large blood volume will bear a greater degree of anemia without experiencing palpitation of the heart or roaring in the ears. When the blood volume is small he thought that a less degree of anemia would produce a greater degree of exhaustion. These assumptions have not been confirmed. When symptoms are present in such cases the need is for more hemoglobin, which is the only factor that will bring relief.

Finally, a suggestion may be made concerning the relative values of blood volume methods. There is a belief that dilution of the blood as shown by changes in the hemoglobin percentage is a reliable method of studying blood volume changes. Bogert, Underhill and Mendel[15] recently emphasized the constancy of the hemoglobin per unit of circulating blood, and Scott[30] concluded that large masses of corpuscles are not held in the capillaries of any organ. The work of

29. Lindeman, E.: J. A. M. A. **70**:1292 (May 4) 1918.
30. Scott, F. H.: J. Physiol. **50**:157, 1916.

Schneider and Havens[26] and of Lamson,[31] however, indicates that such a storage of large numbers of red cells does occur in the body and that they may readily be shifted into the peripheral circulation as, for example, by exercise or by administration of epinephrin. Clinical observation has shown that great shifts may occur in the red corpuscle count in diabetics in short periods of time. It seems, therefore, in view of the present uncertain status of our knowledge with respect to the existence of red corpuscle reservoirs, that methods for the determination of blood volume which depend on dilution of whole blood, as well as any other methods employing the red corpuscles primarily, are not theoretically sound. And when one reviews the possible variations in the total corpuscle content of the body, which in this series ranged from two trillions to seventy-five trillions, the possibility for error in such methods is obvious. On the other hand, the plasma volume is relatively a fixed constant, its fluctuations must be limited to a very narrow range and, therefore, methods by which the plasma volume can be directly determined seem to be subject to the smallest number of discrepancies and afford the most accurate results.

Theoretically, there is a mass of data, chiefly physicochemical in nature, that suggests the necessity for a stable plasma volume. The physicochemical relations existing between the blood and tissues of the body form a series of complex phenomena that is disturbed only with difficulty; the effort of the organism, as a whole, is to seek an equilibrium between plasma and cells, although, as Henderson[32] pointed out, equilibrium is never actually attained within the organism. It seems reasonable to suggest that the plasma volume must be free from great alterations from the normal, in quantity, if cellular activity is to proceed at an optimum rate. While absolute fixation of the plasma volume cannot occur in the nature of things, the considerations reviewed above indicate only a narrow range for the volume changes which may occur.

SUMMARY

Plasma and total blood volume determinations have been made by the vital red method in a series of thirty cases. The conditions represented in these patients include extremes of total corpuscle content, a very wide range in total blood volumes, and instances of edema and anasarca. It has been shown that in all of these conditions, so long as the hemoglobin is above 30 per cent., there is a constancy of plasma volume comparable to the normal. The significance of this phenom-

31. Lamson, P.: J. Pharmacol. & Exper. Therap. **7**:169, 1915.
32. Henderson, L. J.: Nat. Acad. Sc. **2**: 1916.

enon is great, since it shows that variations in the total blood volume, per kilogram of body weight, depend on the corpuscle content, except in patients with very low hemoglobin values in whom there is also a corresponding reduction of the plasma volume. Thus it happens that in a case of polycythemia with a total corpuscle content of seventy-five trillion there may be the same plasma volume per kilogram as is found in a case of pernicious anemia with a total corpuscle content of three trillion cells. In this connection attention has been called to the universally accepted high figures for blood volume in pernicious anemia and chlorosis, which vary greatly from present known and theoretical considerations.

After acute hemorrhage it has been shown that, ordinarily, rapid dilution of the plasma volume to its former normal level occurs and that it remains constant thereafter, even though the total blood volume may be much reduced by reason of loss of red corpuscles.

Certain exceptions to the general proposition of a constant plasma volume have been cited, such as hemorrhage and shock, edema of the lungs, excessive sweating and diarrhea of severe type, including cholera. Brief mention has also been made of alterations in blood volume incident to changes in altitude.

Emphasis has been placed on the necessity for a normal tissue fluid reserve. When such a reserve is present the blood plasma volume tends to remain at a normal physiologic level.

Finally, a note has been made suggesting a source of error in methods for blood volume determinations that depend on dilutions of whole blood, or primarily upon the corpuscle content. Methods by which the more fixed plasma volume may be directly determined seem to offer the most accurate results.

CONCLUSIONS

1. The constancy of the plasma volume in terms of body weight in health has been demonstrated by previous work and is verified in five cases of the present series. The value is $\frac{1}{19.6}$, or 5.1 per cent. of body weight.

2. The constancy of the plasma volume found in twenty-five cases of widely varying conditions with respect to the circulation, including edema, is a striking fact. The value for this series is $\frac{1}{20}$, or 5 per cent. of the body weight.

3. Variations in the total blood volume per kilogram of body weight are due for the most part to changes in the corpuscle content of the blood.

4. Previous figures quoted in the literature for the blood volume in pernicious anemia and chlorosis are too high.

5. In edema associated with cardiac and renal disease the blood plasma retains its normal value per kilogram of body weight.

6. Recovery after hemorrhage is associated with rapid restoration of plasma to the normal plasma level provided the tissue fluid reserve is adequate. Complete restoration of the total blood volume is dependent on increase in the number of corpuscles. Overdilution of the plasma after hemorrhage has not been encountered.