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Research Article

BLOOD VOLUME PRECEDING AND FOLLOWING SPLENECTOMY IN HEMOLYTIC ICTERUS AND SPLENIC ANEMIA[1]

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Very little investigative work has been published concerning the relationship of the spleen to blood volume. Barcroft, Harris, Orahovats, and Weiss allot to the spleen a function that correlates well with its anatomic structure. They demonstrated that the spleen acts as a reservoir in the normal resting animal, and that blood is expressed into the general circulation as a result of stimulation to a need for oxygen. The presence of a storage function is further demonstrated by the observation that carboxyhemoglobin disappears less rapidly from the spleen than from the general circulation, indicating that hemoglobin is, under normal conditions, stored in the spleen. These workers demonstrated the greater susceptibility of the splenectomized animal to carbon monoxide intoxication. Cruickshank's experiments on the cat indicate that the capacity of the spleen is from 2 to 5 per cent of the blood volume when calculated by fluctuations in hemoglobin and in changes in the volume of the spleen.

Observations concerning the spleen and splenectomy in relation to blood volume in man have not been found in the literature. The studies carried out previously have dealt largely with variations in the concentration of the erythrocytes and the hemoglobin, the morphology, and the chemistry of the blood. We know that splenectomy is curative in certain diseases and markedly beneficial in others, and definitely untoward effects attributable to splenectomy have not been observed in man, although there has been some question as to whether a factor of safety is removed by this operation.

[1] Read by title at the meeting of the American Society for Clinical Investigation, Washington, D. C., April 28, 1928.

Our study was undertaken to determine: (1) the blood volume and plasma volume in patients suffering from certain diseases associated with splenomegaly, (2) the effects of splenectomy on the blood and plasma volume, and (3) whether in certain forms of splenomegaly the anemia is apparent rather than actual. The cases selected for this study fall into four groups:

	number of cases
1. Normal subjects	74
2. Primary splenomegaly without anemia:	
Preceding splenectomy	5
Following splenectomy	4
3. Hemolytic icterus:	
Preceding splenectomy	11
Following splenectomy	9
4. Splenic anemia:	
Preceding splenectomy	18
Following splenectomy	7

The dye method was used to determine the blood volume and plasma volume. Congo-red was employed and three to four minutes allowed for the mixing time. Determinations were made under resting conditions without breakfast (8).

It has been shown in anemia that with a decrease in the hemoglobin and cell volume there is usually an increase in plasma volume. This is doubtless a compensatory phenomenon designed to maintain an adequate volume of circulating blood. The increase of plasma varies in different forms of anemia; according to Rowntree and Brown, it is absent or slight in the anemia of glomerulonephritis with edema and in the anemia associated with myxedema and Addison's disease. In this connection we have employed the term "replacement index" to represent the ratio of the percentage increase in plasma to the percentage decrease in cell volume.

For example, if the plasma volume is 61 cc. for each kilogram (normal 51.2 cc.) there would be an increase of 9.8 cc. (19 per cent). If the cell volume is 21 cc. for each kilogram (normal 36.5 cc.) there would be a decrease of 15.5 cc. (42 per cent). The ratio is $\frac{19}{42} = 0.45$; the replacement index is 45. This indicates roughly that for every 100 cc. loss in cell volume there is approximately an increase of 45 cc. in plasma.

NORMAL SUBJECTS

Dreyer and Ray have maintained that blood volume is a function of surface area rather than of body weight. We have, therefore, expressed our data according to both surface area and body weight and the statistical treatment of these data has shown a slightly higher correlation of volume to surface area then to body weight in normally built subjects.

The results obtained in seventy-four normal adult subjects (forty-nine males and twenty-five females) have been reported by Rowntree and Brown. The ages varied from seventeen to sixty-three years. The mean weight was 65.9 kgm. The mean value for the blood volume for each kilogram of body weight was 87.7 cc. (with a range of from 70 to 100 cc. in 98 per cent of the cases). The mean value for the plasma volume was 51.2 cc. (with a range of from 42 to 60 cc.). The mean value for the cell volume was 36.5 cc. for each kilogram. The mean value for the blood volume for each square meter of surface area was 3278 cc. For the plasma volume it was 1920 cc. for each square meter of surface area. The mean value for circulating hemoglobin was 13.8 grams for each kilogram of body weight, or 508 grams for each square meter of surface area. The cells by hematocrit were 41 per cent[2] by the dry oxalate method, and the hemoglobin for each 100 cc. was 15.7 grams. These values closely approximate those obtained by Keith, Rowntree and Geraghty in their original report based on eighteen subjects. Many of the normal subjects varied considerably from the accepted average weight for height and age, but could not be classified as underweight or obese. When a classification of this group was made on the basis of a 10 per cent variation above or below the average standard for height and age, the mean values for the blood volume and plasma volume were only slightly different.

PRIMARY SPLENOMEGALY WITHOUT ANEMIA

Cases of primary splenomegaly without anemia, when all etiologic factors have been excluded, such as syphilis, malaria, hemolytic icterus,

[2] In subsequent work it has been found that hematocrit values obtained by the dry oxalate method should be corrected by the addition of 3.4 per cent. Therefore, 41 per cent, as used here, should read 44.4 per cent.

TABLE 1

Splenomegaly without definite anemia: blood volume preceding and following splenectomy

Case	Sex	Age	Date	Weight	Surface areas	Hemoglobin	Erythrocytes	Cells by hematocrit	Blood: Volume	Blood: Cubic centimeters for each kilogram	Blood: Cubic centimeters for each square meter	Plasma: Volume	Plasma: Cubic centimeter for each kilogram	Plasma: Cubic centimeter for each square meter	Cells: Volume	Cells: Cubic centimeter for each kilogram	Cells: Cubic centimeter for each square meter	Hemoglobin: Volume	Hemoglobin: Grams for each kilogram	Hemoglobin: Grams for each square meter	Weight of spleen
				kgm.	*sq. m.*	*grams in each 100 cc.*	*millions in each cu. mm.*	*per cent*	*cc.*			*cc.*			*cc.*			*grams*			*grams*
1	M.	49	November 23, 1922	76	1.83	13.9	4.66	42	7,480	98	4,090	4,340	57	2,370	3,140	41	1,720	1,020	13.4	557	
2*	M.	25	May 25, 1923	60	1.74	15.6	5.10	41	6,330	105	3,745	3,740	62	2,210	2,590	43	1,535	987	13.1	568	
			February 22, 1925	55	1.65	16.8	3.90	46	6,870	124	4,240	3,710	67	2,290	3,160	57	1,950	1,154	20.9	700	920
3	M.	36	February 2, 1926	58	1.70	15.4	5.24	45	6,290	108	3,700	3,460	60	2,040	2,830	48	1,660	969	16.6	570	
4*	M.	43	June 2, 1925	62	1.68	15.0	3.82	38	5,520	89	3,260	3,430	55	2,040	2,090	34	1,220	828	13.3	493	
			June 12, 1925	62	1.68	15.0	3.93	36	5,310	85	3,150	3,395	54	2,015	1,915	31	1,135	796	12.8	475	720
5*	M.	42	April 5, 1927	70	1.82	11.0	4.57	49	7,390	105	4,040	4,500	64	2,460	2,890	41	1,580	813	11.6	446	
			April 15, 1927	65	1.79	11.0	4.15	34	5,845	90	3,265	3,865	59	2,160	1,980	31	1,105	643	9.9	359	464
6*	F.	26	July 22, 1927	60	1.65	15.4	3.88	43	6,390	106	3,740	3,640	60	2,170	2,750	46	1,570	984	16.4	596	800
Average values:																					
Preceding......................				65.2	1.75	14.2	4.68	41.0	6,602	101	3,767	3,894	59.6	2,224	2,708	41	1,543	923.4	13.6	526.8	
Following......................				60.5	1.69	14.5	3.96	39.7	6,103	101	3,598	3,652	60.0	2,158	2,451	41	1,440	894.0	15.0	532.5	

* Cases in which estimations were made following splenectomy. In case 6 the estimation was not made preceding splenectomy, and in cases 1 and 3 estimations were made preceding splenectomy only.

chronic infectious splenomegaly and various blood dyscrasias, have ordinarily been regarded as potential splenic anemia in the pre-anemic stage, and the splenic enlargement has been the outstanding clinical feature.

There were six cases in this group. Three were studied both before and after splenectomy. Two cases were studied preceding splenectomy and one case only after the operation. The results of these studies are shown in table 1.

Comment. The blood volume preceding splenectomy was 101 cc. and the plasma volume was 59.6 cc. These values are high. While the ratio of cell to plasma volume, as denoted by the hematocrit value of 41 per cent, was normal. This state has also been disclosed in cases of chronic passive congestion and in arteriovenous fistula, conditions in which a compensatory increase in the volume of circulating blood seems to be necessary for circulatory efficiency. This leads to the possibility that in primary splenomegaly without anemia, the increased circulatory bed due to the splenomegaly and enlarged blood vessels necessitates a larger blood volume for circulatory needs.

The comparison of the average values of the two groups of cases before splenectomy and after splenectomy does not show significant change in blood volume, plasma volume or in the percentage of cells by hematocrit. In case 5, with an interval of nine days, there was a decrease of 20 per cent in total blood volume and of 3 per cent in plasma volume. Since the weight decreased 5 kgm., the changes in volume for each kilogram were not so marked. This could be ascribed to operation and loss of blood. The large blood volumes in the cases with long intervals, one year and one and a half years after splenectomy, are probably more significant; these patients have a large volume of normal blood, an unusual condition in subjects of normal build.

HEMOLYTIC ICTERUS

The clinical features of hemolytic icterus are well known. The fundamental process is abnormally active hemolysis and the pathologic basis is probably chiefly concerned with increased fragility of the erythrocytes and microcytosis (Giffin). In the diagnosis of hemolytic icterus care must be taken to exclude cirrhosis of the liver with

TABLE 2

Hemolytic icterus: blood volume preceding and following splenectomy

Case	Sex	Age	Date	Weight	Surface area	Hemoglobin	Erythrocytes	Cells by hematocrit	Blood			Plasma			Cells			Hemoglobin			Weight of spleen
									Volume	Cubic centimeter for each kilogram	Cubic centimeter for each square meter	Volume	Cubic centimeter for each kilogram	Cubic centimeter for each square meter	Volume	Cubic centimeter for each kilogram	Cubic centimeter for each square meter	Volume	Grams for each kilogram	Grams for each square meter	
				kgm.	*sq. m.*	*gm. in each 100 cc.*	*millions in each cu. mm.*	*per cent*	*cc.*			*cc.*			*cc.*			*grams*			*grams*
1	F.	57	May 21, 1925	45	1.45	8.1	2.33	18	4,480	100	3,090	3,680	82	2,540	800	18	550	363	8.0	250	
			June 2, 1925	45	1.45	8.2	3.72	24	3,510	77	2,420	2,660	59	1,840	850	19	580	288	6.4	199	800
2	M.	31	June 24, 1925	67	1.87	12.4	3.54	28	4,950	74	2,650	3,550	53	1,900	1,390	20	750	614	9.1	328	
			July 4, 1925	62	1.80	13.6	3.84	35	6,920	109	3,840	4,500	71	2,500	2,420	40	1,340	941	15.0	522	1,450
3	F.	35	November 24, 1925	50	1.50	8.6	3.60	23	4,350	87	2,900	3,360	67	2,240	990	19	660	374	7.5	249	
			December 8, 1925	45	1.41	12.5	4.16	33	5,160	120	3,660	3,460	80	2,450	1,700	38	1,210	644	14.3	457	820
4	F.	43	November 24, 1925	61	1.70	8.1	3.74	20	4,240	70	2,490	3,390	55	1,995	850	14	495	343	5.6	202	
			December 8, 1925	54	1.61	11.7	3.74	35	5,360	99	3,330	2,950	54	1,830	2,410	44	1,500	627	11.6	389	945
5*	F.	22	September 15, 1925	52	1.46	6.7	3.02	20	4,320	83	2,940	3,450	66	2,350	870	17	590	289	5.6	198	1,640
6	F.	6.5	May 24, 1926	20	0.83	8.3	2.84	19	3,060	153	3,690	2,470	123	2,975	590	30	715	254	12.0	306	
			June 3, 1926	20	0.83	12.1	3.80	30	2,570	125	3,130	1,800	90	2,190	870	43	940	311	15.0	375	500
7	F.	4	July 31, 1925	18	0.77	8.9	3.69	24	1,560	87	2,025	1,190	66	1,545	370	20	480	139	7.7	180	
			August 14, 1925	18	0.77	14.1	4.21	34	1,580	87	2,100	1,050	58	1,400	530	29	700	223	13.0	290	203
8	M.	9	July 27, 1926	23	1.00	6.8	2.57	16	2,050	89	2,050	1,720	75	1,720	330	14	330	139	6.0	139	
			August 14, 1926	23	1.00	12.9	3.88	30	2,090	82	2,480	1,460	58	1,740	630	28	740	410	18.0	410	550

9*	F.	22	January 13, 1927	54	1.60	7.7	2.24	24	5,210	97	3,250	3,960	73	2,475	1,250	24	775	411	7.6	257	
10	M.	14	February 24, 1926	32	1.16	10.3	3.65	20	2,670	83	2,300	2,140	67	1,860	530	17	440	275	8.6	237	
			March 11, 1926	31	1.16	11.2	4.24	30	3,370	109	2,900	2,360	76	2,000	1,010	32	900	377	12.0	325	784
11	M.	27	May 12, 1925	54	1.60	11.4	2.93	25	4,950	92	3,090	3,710	69	2,320	1,240	23	770	564	10.5	353	
			May 20, 1925	50	1.52	10.2	3.93	33	6,190	123	4,020	4,140	82	2,630	2,050	40	1,390	631	12.0	415	1,500
Mean values†				42.7	1.38	8.86	3.10	22.3	3,795	93.2	2,791	2,932	73.1	2,200	836.4	21.7	597.7	359	8.1	247.7	950

* In cases 5 and 9 blood volume was not estimated after splenectomy.

† Mean values estimated on data preceding splenectomy only.

secondary hemolytic characteristics. Splenectomy is a curative measure. Following operation the jaundice disappears, the excessive hemolysis ceases and, in some instances at least, the erythrocytes become less fragile. As Moynihan stated: "The spleen, if not the exclusive cause or seat of the disease, exerts the profoundest influence on its pathogeny."

Preceding splenectomy. Eleven cases of hemolytic icterus were studied (table 2). The body build in this group was subject to wide variation; none of the patients were overweight, but the younger patients were underweight. Studies of the blood volume were made one or two days preceding operation, and from nine to seventeen days following operation. Anemia was present in all of the cases. The patient with a blood volume of 153 cc. was the only one with a volume above the upper range of normal; she was an emaciated girl aged six and a half years, and according to surface area the blood volume was less than the normal mean. According to surface area the mean plasma volume for the entire group was 2200 cc. for each square meter, about 15 per cent higher than the normal mean.

That anemia was actually present is shown by the amount of circulating hemoglobin. The mean value for hemoglobin was 8.1 grams for each kilogram of body weight (normal 13.8 grams). The mean value for the cell volume was 21.7 cc. for each kilogram (normal 36.5 cc.), a decrease of 14.8 cc. (45 per cent). The mean value for the plasma volume was 73.1 cc. (normal 51.2 cc.), an increase of 21.9 cc. (43 per cent). The ratio was, therefore, $\frac{43}{45} = 0.95$. This replacement index of 95 is high, almost twice that seen in primary and simple secondary anemia.

The hemoglobin in grams and the blood volume when separately plotted against the weight of the spleen did not correlate. The cell volume calculated for each kilogram of body weight plotted against the weight of the spleen did not show definite correlation. There was a fairly high correlation of 0.87 between plasma volume and weight of the spleen.

Following splenectomy. Estimations were made from nine to seventeen days following splenectomy in nine of the eleven cases (table 2). The plasma volume according to body weight and surface area showed a smaller percentage variation since the body weight decreased after operation. The total hemoglobin volume increased in all but one case, the range of increase being from 57 to 327 grams, averaging

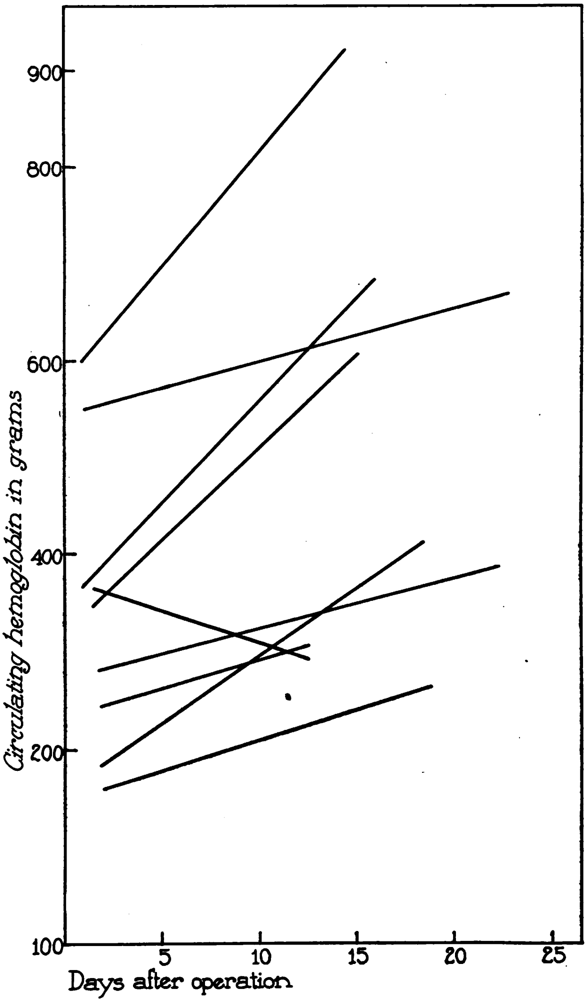

FIG. 1. CHANGES IN THE CIRCULATING HEMOGLOBIN IN CASES FOLLOWING SPLENECTOMY FOR HEMOLYTIC JAUNDICE

183 grams (fig. 1). The percentage of cells by hematocrit and the number of erythrocytes increased in every case, and the hemoglobin in grams for each 100 cc. showed a significant increase in all but two cases.

Comment. The status of the blood volume in hemolytic icterus, according to mean values, is that of decreased cell volume with normal blood volume. The cell volumes and the hemoglobin volumes according to body weight and surface area were decreased, which is indicative of the existence of an actual rather than an apparent anemia. With the exception of one case, that of a child, the blood volume conformed closely to the normal range, which is 70 to 100 cc. for each kilogram. The plasma volume, however, was greatly increased, the increase amounting to a mean of 21.9 cc., 43 per cent for each kilogram above the normal mean. The replacement index was high, 95; in other words, when compared to normal values the increase of plasma to replace the decrease in cells was almost complete. This indicates that in hemolytic icterus the replacement of the diminished cell volume by plasma is effective and adequate, much more so, in fact, than in primary anemia and simple secondary anemia without splenomegaly.

The increase in the blood volume and cell volume following splenectomy in cases of hemolytic icterus is most striking and correlates well with the clinical improvement following operation. In every case but one the cell volume increased significantly within three weeks and the actual volume of hemoglobin showed comparable changes, the increase averaging 183 grams. In case 2 (table 2) the increase in the blood volume was more than a third of the preoperative value, and the actual increase of hemoglobin was 327 grams in ten days, or over 30 grams a day. This increase of hemoglobin represents only the demonstrable increase of pigment and does not include the amount necessary to compensate for that which is normally destroyed. Figures for the normal amount of hemoglobin formed daily in man are not available. Whipple, Robscheit and Hooper have shown that in the dog after unit hemorrhages, the amount of hemoglobin regenerated depends largely on the type of diet. In one experiment with beef heart diet, 43 grams of hemoglobin were formed daily over a seven-day period.

The rate of recovery from anemia after splenectomy is not correctly shown in the concentration values for hemoglobin and erythrocytes. For example, in case 2 (table 2) following operation there was an increase of about 9 per cent in the grams of hemoglobin in each 100 cc. and a questionable increase in the number of erythrocytes. The increase in the blood volume, however, was 1970 cc. (40 per cent) half of which was cells. The increase in the actual volume of hemoglobin was 327 grams, or about 50 per cent. The plasma volume increased 940 cc. while the cell volume increased 1030 cc., that is, cells increased in greater proportion than plasma, thus affecting the ratio of cells to plasma.

Hooper, Robscheit and Whipple have shown that in the recovery from experimental anemia, the increased plasma volume caused by the anemia gradually disappears with the regeneration of cells. In the recovery from anemia in hemolytic icterus, the plasma volume decreased in five cases with the increase of cells, and increased in four cases.

The status of the blood volume as indicated by the mean value in a series of eleven cases of hemolytic icterus preceding splenectomy is that of decreased cells with normal volume. The anemia of hemolytic icterus is an actual rather than an apparent anemia and as the plasma volume increases to cause a slightly high blood volume a small amount of dilution occurs. The blood volume is maintained within a normal range since the replacement of cell volume by plasma is almost complete, as shown by a replacement index of 95. Following splenectomy there is an immediate rapid increase in the cell volume and hemoglobin volume which is not adequately demonstrated by the ordinary clinical estimations for determining the concentration of hemoglobin and erythrocytes.

SPLENIC ANEMIA

Splenic anemia is a useful term to indicate a poorly defined clinical syndrome rather than a disease entity, and the diagnosis is chiefly made by exclusion. Cases included in this group have two features in common: primary splenomegaly, and a secondary type of anemia. Cases of questionable diagnosis are always present in a group of cases classified as splenic anemia, and the difficulties of arriving at conclusions concerning observations on the blood volume are correspondingly increased, especially in those cases in which secondary hepatic cirrhosis is present.

Preceding splenectomy. Estimations of blood volume were made preceding splenectomy in eighteen cases classified as splenic anemia,

TABLE 3

Splenic anemia: blood volume preceding and following splenectomy*

Case	Sex	Age	Date	Weight	Surface area	Hemoglobin	Erythrocytes	Cells by hematocrit	Blood: Volume	Blood: Cubic centimeters for each kilogram	Blood: Cubic centimeters for each square meter	Plasma: Volume	Plasma: Cubic centimeters for each kilogram.	Plasma: Cubic centimeters for each square meter	Cells: Volume	Cells: Cubic centimeters for each kilogram	Cells: Cubic centimeters for each square meter	Hemoglobin: Volume	Hemoglobin: Grams for each kilogram	Hemoglobin: Grams for each square meter	Weight of spleen
				kgm.	*sq. m.*	*grams in each 100 cc.*	*millions in each cu. mm.*	*per cent*	*cc.*			*cc.*			*cc.*			*grams*			*grams*
1	F.	43	November 2, 1923	53	1.70	11.8	3.50	29	5,780	109	3,610	4,100	77	2,560	1,680	31	982	681	13.0	400	
2†	M.	41	December 11, 1926	74	1.96	8.3	4.34	30	8,300	112	4,230	5,800	78	2,960	2,500	34	1,288	688	9.0	352	300
3	F.	31	July 17, 1925	69	1.77	7.6	3.50	26	4,630	67	2,620	3,430	50	1,940	1,200	17	677	338	5.0	190	400
4†	M.	47	January 27, 1926	80	1.93	9.2	3.33	26	8,510	107	4,410	6,320	79	3,270	2,190	27	1,135	783	9.7	405	
			February 20, 1926	70	1.82	11.2	3.00	25	7,280	104	4,000	5,450	77	2,950	1,830	26	1,010	815	11.6	448	1,460
5	F.	23	June 23, 1926	44	1.30	8.5	3.43	32	4,720	107	3,630	3,210	73	2,470	1,510	34	1,160	401	9.0	308	
			January 21, 1927	40	1.31	9.5	3.70	26	3,955	98	3,020	2,930	73	2,235	1,025	25	788	375	9.3	286	700
6†	M.	30	October 14, 1926	87	2.02	10.9	3.96	29	7,460	86	3,690	5,300	61	2,630	2,160	24	1,040	804	9.2	398	
			November 4, 1926	72	1.92	10.7	3.70	30	7,345	102	3,845	5,140	71	2,680	2,205	30	1,160	786	10.9	410	1,440
7†	M.	35	May 31, 1927	72	1.87	7.9	4.32	30	7,350	102	3,910	5,140	71	2,750	2,210	31	1,181	580	8.0	310	1,160
8†	F.	28	July 21, 1927	62	1.65	11.6	4.29	34	6,380	103	3,870	4,210	68	2,550	2,170	35	1,321	741	12.0	450	
			August 12, 1927	57	1.59	12.1	4.32	35	5,780	101	3,635	3,710	65	2,330	2,070	36	1,380	699	12.0	439	1,140
9	F.	29	September 4, 1927	49	1.46	7.6	3.18	25	4,750	97	3,250	3,560	73	2,440	1,190	24	815	362	7.3	247	
			September 19, 1927	45	1.42	6.6		27	4,570	101	3,220	3,330	74	2,345	1,240	27	885	302	6.7	213	1,000
10	F.	34	June 3, 1927	59	1.65	12.8	4.04	42	6,400	108	3,850	3,710	63	2,240	2,690	45	1,670	819	14.0	511	
			June 20, 1927	53	1.60	12.6	3.42	37	5,665	106	3,545	3,565	67	2,225	2,100	40	1,400	714	13.4	446	986

11	F.	40	May 10, 1927	56	1.62	11.1	3.69	37	5,860	104	3,620	3,690	66	2,270	2,170	38	1,340	650	12.0	401	1,000
12	F.	42	September 14, 1927	53	1.59	12.0	3.96	32	6,010	113	3,780	4,090	77	2,570	1,920	36	1,207	721	13.0	453	
13†	M.	49	September 22, 1927	85	2.00	5.6	2.71	21	7,120	84	3,560	5,620	66	2,800	1,500	18	750	399	5.0	197	800
14	M.	55	February 28, 1928	70	1.76	7.5	2.79	23	6,500	93	3,700	5,000	71	2,840	1,500	22	860	486	7.0	276	
			March 15, 1928	63	1.69	9.3	3.42	26	5,530	88	3,270	4,090	65	2,420	1,440	23	850	514	8.2	304	1,480
15†	F.	18	December 8, 1926	60	1.65	10.0	3.86	31	5,930	99	3,590	4,090	68	2,480	1,840	30	1,115	593	9.9	359	1,800
16	F.	55	March 26, 1925	54	1.49	14.1	3.62	33	4,030	75	2,710	2,700	50	1,810	1,330	25	900	568	10.5	381	
17	F.	59	June 21, 1927	51	1.49	8.1	3.41	26	5,750	112	3,860	4,250	83	2,840	1,500	30	1,006	466	9.0	312	
18	M.	26	October 22, 1925	73	1.92	11.2	3.68	32	5,760	79	3,000	3,920	53	2,040	1,840	25	958	645	8.8	335	1,170
Mean values‡				64.2	1.72	9.8	3.70	30.3	6,194.5	97.5	3,600	4,888	68.6	2,512	1,855	30	1,078	594.4	9.7	355.6	
Average values§				57.1	1.62	10.3	3.59	29.4	5,732.0	100.0	3,505	4,031	70.3	2,455	1,701	30	1,068	600.7	10.3	363.7	

* In cases for which only one row of values is given, estimations were made preceding splenectomy only.

† Banti's disease.

‡ Mean values estimated on data preceding splenectomy only.

§ Average values estimated on data following splenectomy only (cases 4, 5, 6, 8, 9, 10, and 14).

seven of the Banti type (table 3). It will be noted in table 3 that in the seven cases of the Banti type there was approximately the same high blood volume as that in the cases without advanced hepatic cirrhosis.

The body build of this group of patients was fairly uniform. None was obese or emaciated. The mean figure for body weight was 64.2 kgm.

Following splenectomy. In seven of the cases observations were made both before and after splenectomy. Estimations of blood volume were made from two to three weeks after operation (table 3).

Comment. The mean value for the blood volume according to the body weight and surface area is increased in splenic anemia approximately 10 per cent above the normal. This increase is largely due to plasma volume since the cell volume is reduced 18 per cent. The mean value for the plasma volume according to weight and area is approximately 30 per cent above normal. The plasma volume is much higher in splenic anemia than in the chronic secondary types of anemia and in pernicious anemia with comparable hemoglobin and cell values. This fact suggests the question whether the anemia is actual or whether dilution factors play a rôle causing apparent anemia. The circulating hemoglobin in grams for each kilogram preceding splenectomy was 9.7 grams, or for each square meter of surface area 355.6 grams compared with a normal of 13.8 grams and 508 grams, respectively. This would indicate that actual anemia exists which is diluted by the abnormally high plasma volume. The anemia is due both to dilution and to actual loss of hemoglobin. The plasma not only replaces the lost cell volume but increases to a point beyond the original blood volume. The replacement index is very high, as is demonstrated by the following calculation: A mean cell volume of 30 cc. for each kilogram, compared with a normal of 36.5 cc., is 6.5 cc., 17.8 per cent, less than normal; the mean value for the plasma volume of 68.6 cc. (normal 51.2 cc.) is 17.4 cc., 34 per cent, above normal. The replacement index would then be 191 ($\frac{34}{17.8} = 1.91$). The replacement index as demonstrated in sixteen cases of secondary anemia was 42 and in ten cases of pernicious anemia was 30.

The reason for the increase in plasma volume in cases of splenic anemia is not clear although there is a close correlation between the plasma volume and the weight of the spleen. It has been suggested that in the cases of enlarged spleen and a presumably active reticulo-endothelial system the dye is removed from the blood with abnormal rapidity. Information on this point has been obtained by the following experiments:

1. In two cases of hemolytic icterus volume determinations were made on the operating table just prior to removal of the spleen. Twenty to thirty minutes after the injection of the dye, samples of blood were taken from the splenic artery, splenic vein and spleen pulp. It was found that the concentration of the dye in the three samples was exactly the same. These experiments seem to demonstrate that the dye is not abnormally removed by the cells of the spleen in hemolytic icterus.

TABLE 4

Percentage of variation in the plasma volume within six minutes after injection of the dye

Case	Time after injection			
	2 minutes*	3 minutes	4 minutes	6 minutes
1	100	100	100	100
2		100	101	107
3	100	100	101	102
4	100	100	100	104
5	100	99	100	96
6	100	97	100	100

* The two-minute determination is taken as 100 per cent.

2. The rate of disappearance of the dye from the blood was ascertained by determining the plasma volume at periods of two, three, four and six minutes in a large series of normal subjects and in six cases of splenic anemia (table 4), demonstrates that an increased or abnormal rate of disappearance of the dye was not present in the cases of splenic anemia. Moreover, dye was not excreted in the urine within one hour after injection, as has been demonstrated in certain cases of nephrosis.

The effect of anemia on the increase in plasma volume was considered. Only rarely in cases of secondary anemia were high plasma volumes found. In thirty cases of primary and secondary anemia there was a moderate increase in the relative volume of plasma with mean values of 60 and 58 cc., respectively. This would indicate that the anemia is probably not the sole factor in the production of the high plasma volume in splenic anemia. It was demonstrated in the series of cases reported in the first portion of this paper that cases of splenomegaly without anemia also show a high plasma volume. It is possible, then, that a high plasma volume may be one of the fundamental changes in cases of splenic anemia, and that it may precede the development of anemia.

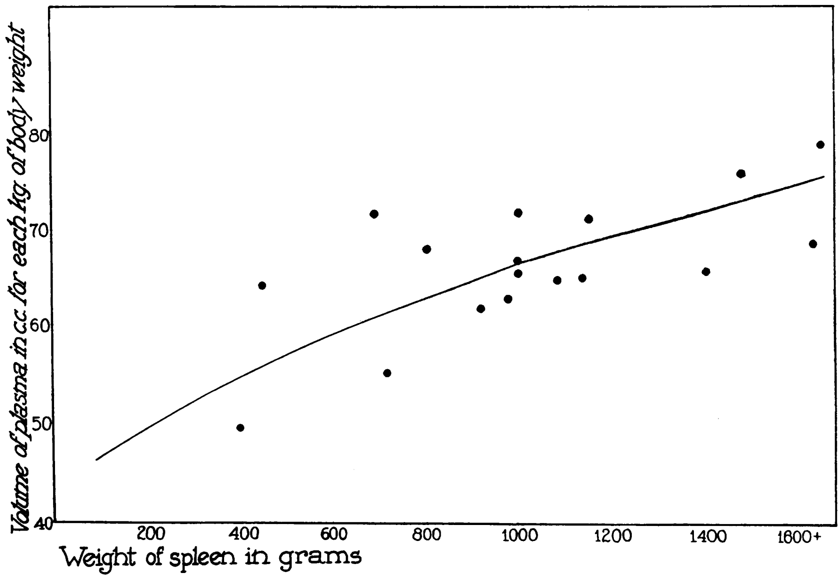

FIG. 2. PLASMA VOLUME AND WEIGHT OF SPLEEN IN SPLENIC ANEMIA

Following splenectomy a decrease in the total volume of the circulating blood occurred in every case. This decrease was slight in one instance but definite in all the others. The maximal decrease was 1230 cc. and the average was 656 cc. The decrease in the total blood volume was more constant and márked than that occurring in the relative blood volume for each kilogram because of variations in body weight. On the basis of surface area a decrease occurred in all but one case. The plasma volume likewise decreased in every instance, with a range of decrease from 145 to 910 cc., the average decrease being

442 cc. Slight increases and decreases occurred according to body weight. The cell volume decreased in five of the seven cases, but was significant in only three cases. In only two cases did the cell volume show an increase. The total amount of circulating hemoglobin in grams showed a decrease in five of the seven cases, averaging 50 grams.

The total blood volume for each kilogram of body weight was charted against the weight of the removed spleen. The curve shows a rough correlation between these factors. It is apparent that larger volumes of blood occurred in the cases in which the spleen was largest. A closer correlation is brought out when the plasma volume for each kilogram is plotted against the weight of the spleen. The curve approximates a straight line (fig. 2). Between the cell volume and the weight of the spleen definite correlation could not be demonstrated.

The moderate reduction in the blood volume after splenectomy in cases of splenic anemia would, at first thought, be attributed to loss of blood. The studies in these cases were made two and three weeks following operation; this interval would ordinarily be regarded as sufficient for adequate blood regeneration. There is great variation in the amount of blood lost at operation; in some cases it is negligible and in others large. There does not seem to be any correlation between the amount lost at operation and the decrease in blood volume. Likewise, the drop in the volume of blood after operation consists largely of plasma, indicating a readjustment following splenectomy. A relationship could not be established between the reduction in blood volume and plasma volume and the weight of the spleen; in fact, the patient (case 5, table 3) with the smallest spleen, showed the greatest decrease in blood volume. Surprisingly small amounts of blood were recovered from the enlarged spleens; the amount ranged from 100 to 500 cc. Either the contraction of the spleen eliminates much of the blood before it is removed, or its actual capacity is reduced, possibly because of fibrosis. One would infer from these observations that loss of blood due to removal of the spleen, although it may affect the results to a certain degree, does not account for all of the reduction in volume of blood, nor could it account for the disproportionate loss in the plasma volume and the relatively high plasma volumes remaining after splenectomy.

Summarizing these results in connection with splenic anemia, it has apparently been shown: (1) the plasma volume, and therefore the total blood volume, is high according to body weight in spite of a decreased volume of cells; (2) the increased plasma volume estimation is not due to an abnormal affinity of the cells of the spleen for the dye, to loss of the dye in the urine, or to an abnormally rapid rate of disappearance from the blood; (3) while the existence of anemia is usually a significant factor in the production of the high plasma volume, it is not the important or sole factor as it seems to be in cases of secondary anemia and pernicious anemia; (4) the enlarged spleen is probably an additional factor in the increase of plasma volume and total blood volume; even in splenomegaly without anemia the plasma volume is slightly increased, and (5) a fairly high correlation exists between the weight of the spleen and the plasma volume for each kilogram.

SUMMARY

The figures obtained in blood volume studies in seventy-four normal adult subjects reported elsewhere by Rowntree and Brown are approximately as follows: for both sexes, mean value for the blood volume for each kilogram of body weight, 87.7 cc.; plasma volume for each kilogram, 51.2 cc.; cell volume, 36.5 cc.; circulating hemoglobin for each kilogram of body weight, 13.8 grams, and for each square meter of surface area, 508 grams; hemoglobin for each 100 cc., 15.7 grams, and cells by hematocrit, 41 per cent. On the basis of each square meter of surface area the values are approximately as follows: volume of blood, 3278 cc.; volume of plasma, 1920 cc., and volume of cells, 1358 cc.

In cases of primary splenomegaly without anemia the mean value for the blood volume was increased to 101 cc, for each kilogram, the plasma volume was increased to 59.6 cc., and the ratio of the cells to plasma was normal. After splenectomy there was no significant change in the blood volume or in plasma volume, the values still remaining above normal.

In hemolytic icterus the blood volume was normal and the cell volume decreased; the replacement of the diminished cell volume by plasma was complete. After splenectomy there was an increase in blood volume and a very striking increase in the volume of cells and hemoglobin. These increases were much greater than were indicated by the ordinary estimations of hemoglobin and erythrocytes.

In splenic anemia blood volume was increased and cell volume decreased. An increase in the plasma volume was found which could not be accounted for solely on the basis of anemia. The anemia was due both to dilution and actual loss of hemoglobin. Following splenectomy a moderate decrease, which was largely in the plasma volume, occurred in the total blood volume, yet the increased plasma volume persisted. A high correlation has been demonstrated for the relative plasma volume and the weight of the removed spleen.

Most of these observations were made within three weeks of the time of operation. The number of observations made at longer intervals subsequent to splenectomy have been too few to warrant discussion.

BIBLIOGRAPHY

1. Barcroft, J., Harris, H. A., Orahovats, D., and Weiss, R., J. Physiol., 1925, lx, 443. A contribution to the physiology of the spleen.
2. Cruickshank, E. W. H., J. Physiol., 1926, lxi, 455. On the output of haemoglobin and blood by the spleen.
3. Dreyer, G., and Ray, W., Proc. Roy. Soc. Lond., 1910, Series B, lxxxii, 545. 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.
4. Giffin, H. Z., Surg., Gynec., and Obstet., 1917, xxv, 152. Hemolytic jaundice; a review of seventeen cases.
5. Hooper, C. W., Robscheit, F. S., and Whipple, G. H., Am. J. Physiol., 1920, liii, 263. Blood regeneration following simple anemia. V. The influence of Blaud's pills and hemoglobin.
6. Keith, N. M., Rowntree, L. G., and Geraghty, J. T., Arch. Int. Med., 1915, xvi, 547. A method for the determination of plasma and blood volume.
7. Moynihan, Berkeley, G. A., The spleen and some of its diseases. Philadelphia, W. B. Saunders Co., 1921.
8. Rowntree, L. G., and Brown, G. E., Blood volume in health and disease. (In press.)
9. Whipple, G. H., Robscheit, F. S., and Hooper, C. W., Am. J. Physiol., 1920, liii, 236. Blood regeneration following simple anemia. IV. Influences of meat, liver and various extractives alone or combined with standard diets.