A Consideration of Indications for Preoperative Transfusions Based on Analysis of Blood Volumes and Circulating Proteins in Normal and Malnourished Patients With and Without Cancer *

JOSEPH C. PEDEN, JR., M.D., MAYS MAXWELL, M.D., ALEXANDRE OHIN, M.D., CARL A. MOYER, M.D.

From the Department of Surgery, Washington University School of Medicine and the Homer G. Phillips Hospital, St. Louis, Missouri

THE PREOPERATIVE transfusion of blood has been asserted to be beneficial whenever the patient to be operated on has a cancer or is cachectic. This assertion was based on the discovery that the cachectic person usually had a blood volume that was significantly smaller than that which he was estimated to have had during good health.[7, 12]

Keys, *et al.*,[29] have studied the effects of controlled starvation on the volumes of blood and other physiologic parameters of human beings. They found that the volumes of extracellular fluid and plasma change little as the starved person loses weight. However, the mass of red cells in the circulation of the starving individual falls roughly proportionately with the loss of weight. In short, Keys *et al.* found that the starved person possesses a blood volume, relative to body weight, that is equal to or proportionately greater than it was before the weight was lost, and this is due to the failure of the plasma volume to decline as rapidly as the weight of the body does. Calculations of blood volume and total circulating plasma proteins and hemoglobin relative to body weight have been made from data published by others of blood volumes, plasma proteins and hemoglobin concentrations in normal and starved patients (Tables 1–6). These data support the observations of Keys on experimental starvation.

The studies reported here were performed in an attempt to ascertain the degree of concurrence of observations made upon normal and cachectic cancerous and noncancerous patients with those made by Keys *et al.*, on starved young normal men. Measurements of blood volumes, of total circulating plasma proteins, and of hemoglobin concentrations have been made. The effects of giving blood transfusions to cachectic patients have been observed in an attempt to learn more about the peculiarities of the biological reactions to them.

Methods

Plasma volumes were determined with Evans blue dye, using a modification of the method of Gibson and Evelyn,[16] or with radioactive iodinated human serum albumin (RISA). The latter method employed an injection into an anticubital vein of radioactive iodinated albumin containing about eight microcuries. Immediately thereafter the same volume of RISA was injected into a flask containing 2,000 ml. of saline. This solution served as the standard. Fifteen minutes after injecting the RISA a sample

* Submitted for publication June 16, 1959.

This study was supported in part by a grant-in-aid from the United States Public Health Service, CS-9108(C8).

TABLE 1. *Plasma Volume, Red Cell Volume and Total Blood Volume in Normal Patients (in ml./kg. of body weight)*

			PV		RCV		TBV	
Author	Method	No. Pts.	Aver.	Range	Aver.	Range	Aver.	Range
Chang[6]	CO	16					66	
Hopper[24]	CO	9	45		35		80	
Smith[42]	CO	20					71	
Tennant[44]	T-1,824	30 f	40	38–42	28		68	
		30 m	42	40–44	35		77	
Inkley[25]	T-1,824	51	41	31–48	30		71	
Gibson[15]	T-1,824	41 f	41		25		66	
		49 m	43		35		78	
Hardy[21]	T-1,824	8 m	43	28–57				
Hopper[24]	T-1,824	9	45		35		80	
Ling[30]	T-1,824	34	45	32–57	35	22–49	80	58–106
Brady[5]	T-1,824	25	45	32–54	36		81	57–100
Gregersen[19]	T-1,824		45		40		85	
Keys[29]	T-1,824	32	45		40		85	
Reeve[38]	T-1,824	13	47	40–52	35	27–39	82	73–87
Gibson[17]	T-1,824	40 m	48	38–62	35	27–44	83	67–103
Cohn[8]	T-1,824	60 m	48	31–63				54–101
Keith[27]	Vital red	42	50	42–56	35		85	78–97
Smith[42]	Dye	20					93	
Storaasli[43]	RISA	31 m	40	24–62	30		70	
Inkley[25]	RISA	51	41	23–55	32		73	
Brady[5]	RISA	25	44	33–51	33		78	58–97
Erickson[13]	RISA	42		34–60		26–40		60–85
Brady[5]	P^{32}	25	38	38–49	30	22–39	68	49–92
Gibson[17]	Fe^{59}	40 m	40	33–54	30	23–36	70	55–88
Reeve[38]	P^{32}	13	41	34–45	30	26–34	71	63–79
Kelly[28]	P^{32}	11	36		34		70	
Nylin[36]	P^{32}	19			34			
Hevesy[22]	P^{32}	21			39			
Govaerts[18]	P^{32}						74	
Berlin[3]	P^{32}	71 m	39		30		69	
		16 f	37		27		64	
Mean—Dye & RISA methods			43.9 (571 patients)		32.9 (503 patients)		77.1 (523 patients)	
Mean—Tagged red cell methods			38.9 (176 patients)		31.2 (216 patients)		68.9 (176 patients)	

Key: PV—Plasma volume.
RCV—Red cell volume.
TBV—Total blood volume.
CO—Carbon monoxide.
T-1824—Evans Blue Dye.
RISA—Radioactive iodinated serum albumin.

of venous blood was withdrawn into a syringe wet with heparin in saline. The radioactivity in 3.0 ml. of the plasma from this sample was measured using a scintillation counter and a well-type chamber, and the radioactivity of the same volume of the standard was determined immediately thereafter. The plasma volume was readily calculated from this data in the following manner:

$$\text{Plasma volume in ml.} = \left\{ \frac{\text{Radioactive count of standard–background count}}{(\text{Radioactive count of plasma–background count})} \right\} \times 2{,}000$$

TABLE 2. *Total Circulating Plasma Proteins and Hemoglobin in Normal Patients (Gm./kg. of Body Weight)*

Author	Method	No. Cases	TCP Aver.	TCA Aver.	TCH Aver.
Tennant[44]	T-1,824	30 f	2.90		
		30 m	2.95		
Ling[31]	T-1,824	34	3.12		
Keys[29]	T-1,824	32 m	2.99	1.93	12.8

Key: TCP—Total circulating plasma proteins.
TCA—Total circulating albumin.
TCH—Total circulating hemoglobin.

Venous hematocrits were used to calculate the total blood volumes. No correction of red cell volume or total blood volume was made for the known discrepancies between the venous and the total body hematocrits.[20, 33, 34] Measurements of hemoglobin and plasma proteins[39, 45, 46] made simultaneously with the measurements of the plasma volumes permitted the calculation of the total circulating hemoglobins and plasma proteins.

In the transfusion experiments whole blood was given in quantities that seemed clinically appropriate to the patients' hemoglobin concentrations and hematocrits.

Data

The data on blood volume and circulating proteins (Tables 7–12) are divided into the following categories:

1. Normals
   A. Average (men and women)
   B. Fat (men and women)
   C. Lean (men and women)

TABLE 3. *Blood Volume in Malnourished Noncancer Patients (ml./kg of Body Weight)*

Author	Method	Cases	Aver. Body Wt. (kg.)	PV		RCV		TBV	
				Aver.	Range	Aver.	Range	Aver.	Range
Maladie de Famine[32]	Congo red	18	32.2	75		40		114	
Mollison[35]	T-1,824	15	40.2	63	48–85	29	17–46	92	63–125
Seed[41]	RISA	25	59.9	55		35		90	
Keys[29]	T-1,824	32	52.0	64		37		101	
Ling[31]	T-1,824	27	50.8	54	41–72	34	22–46	88	70–114
Mean (117 cases)				61		35		96	

Key: PV—Plasma volume.
RCV—Red cell volume.
TBV—Total vlood volume.
CO—Carbon monoxide.
T-1824—Evans Blue Dye.
RISA—Radioactive iodinated serum albumin.

TABLE 4. *Total Circulating Plasma Proteins and Hemoglobin in Malnourished Noncancer Patients (Gm./Kg. of Body Weight)*

Author	Method	No. Cases	Aver. Body Wt. (kg.)	TCP		TCA		TCH	
				Aver.	Range	Aver.	Range	Aver.	Range
Keys[29]	T-1,824	32	52.0	4.03		2.60		12.0	
Ling[31]	T-1,824	27	50.8	4.03	2.95–5.41			11.5	7.5–15.9

Key: TCP—Total circulating plasma proteins.
TCA—Total circulating albumin.
TCH—Total circulating hemoglobin.

TABLE 5. *Blood Volume in Malnourished Cancer Patients (ml./kg. of Body Weight)*

Author	Method	No. Cases	Aver. Body Wt. (kg.)	PV		RCV		TBV	
				Aver.	Range	Aver.	Range	Aver.	Range
Clark[7]	T-1,824	10 (stomach)	55.8	49	27–70				
		6 (pancreas)	53.0	47	38–54				
Homburger[23]	T-1,824	13	59.4	52	37–54				
Co Tui[10]	T-1,824	26	55.0	62	42–92	39	23–51	96	69–143
Bateman[2]	T-1,824	33	59.0	50	32–77	28	13–49	78	54–117
Mean				54.5 (88 cases)		30.7 (59 cases)		86.0 (59 cases)	
Berlin[4]	P^{32}	66 (cancer)	57.3	37	28–82	26	11–44	63	42–112
		17 (cancer cachexia)	48.9	45	28–82	27	17–44	72	52–112

Key: PV—Plasma volume.
RCV—Red cell volume.
TBV—Total blood volume.

2. Cachectic patients *
   A. Simple malnutrition
   B. Malnutrition complicated by infection, hepatic disease or renal disease
   C. Malnutrition with cancer

The results of blood transfusion in six patients are recorded in Table 13.

1. Normals (Tables 7–9). The "average" normals were persons who were neither exceptionally fat nor exceptionally lean. For this group of 20 persons the mean total blood volumes was 77.5 ml./kg., mean red cell volume 32.5 ml./kg., and mean plasma volume 45 ml./kg. These means are the same, essentially, as the respective means of these parameters reported by other investigators. (Compare Tables 7 and 1.)

The "fat" normals were grossly obese but not ill in any other respect (Table 8). Their total blood, red cell, and plasma volumes per kilogram of weight were significantly smaller than those of the "average" and "lean" normals.

The "lean" normals (Table 9) were persons having very little body fat. It was particularly difficult to find women who fitted this category. This group had total blood, red cell, and plasma volumes per kilo that were insignificantly larger than those of the average normals.

Table 12–A is a summary of the differences in the various parameters of the blood volume and

* Does not include any person with visible loss of blood.

TABLE 6. *Total Circulating Plasma Proteins and Hemoglobin in Malnourished Cancer Patients (Gm./Kg. of Body Weight)*

Author	Method	No. Cases	Aver. Body Wt. (kg.)	TCP		TCA		TCH	
				Aver.	Range	Aver.	Range	Aver.	Range
Homburger[23]	T-1,824	13	59.4	3.08	2.36–3.95	1.36	0.97–1.75		
Co Tui[10]	T-1,824	26	55.0	3.75	2.54–5.00				
Bateman[2]	T-1,824	33	59.0	3.30	2.1–5.4	1.94	1.3–3.3	9.2	3.3–14.0

Key: TCP—Total circulating plasma proteins.
TCA—Total circulating albumin.
TCH—Total circulating hemoglobin.

TABLE 7. *Blood Volume, Total Circulating Plasma Proteins, and Total Circulating Hemoglobin in Normal People*

	Body Wt. (kg.)	PV	RCV	TBV	TCP	TCA	TCH
		Average Normals					
		ml./kg. body weight			Gm./kg. body weight		
				1. Men			
H. D.	80.0	41	26	67	2.75(6.7)	1.76(4.3)	8.50(12.8)
E. J.	76.0	40	26	66	2.71(6.8)	1.63(4.1)	7.24(11.0)
C. B.	59.7	58	46	104	3.58(6.3)	1.94(3.4)	14.83(14.4)
J. G.	61.0	56	40	96	3.21(5.9)	1.69(3.1)	12.22(12.8)
T. E.	65.0	43	40	83	2.72(6.3)	1.82(4.2)	11.80(14.2)
H. P.	51.4	53	43	96	3.28(6.1)	1.70(3.1)	11.92(12.5)
E. B.	55.0	47	40	87	3.16(6.5)	2.09(4.3)	12.19(14.0)
L. F.	60.0	48	36	84	2.69(5.7)	1.55(3.2)	11.75(14.0)
E. C.	58.2	42	38	80	2.64(6.3)	1.34(3.2)	12.50(15.6)
E. I.	71.0	39	34	73	3.54(6.5)	1.48(3.8)	10.10(13.8)
	Mean	47	37	84	2.93	1.70	11.31
	SD	6.54	6.30	12.03	0.31	0.21	1.93
	SE	2.18	2.10	4.01	0.10	0.07	0.64
				2. Women			
R. S.	55.0	43	24	67	2.34(5.4)	1.82(4.2)	8.36(12.5)
B. S.	54.0	40	25	65	2.42(6.0)	1.48(3.7)	8.03(12.4)
P. T.	56.0	41	31	72	2.32(5.6)	1.70(4.1)	9.40(13.1)
E. S.	56.0	48	30	78	2.57(5.4)	1.80(3.8)	9.76(12.6)
S. M.	54.5	33	25	58	1.83(5.5)	1.25(3.7)	7.65(13.2)
S. C.	51.0	53	39	82	3.55(6.0)	1.98(3.4)	11.08(11.9)
B. P.	50.0	40	30	70	2.54(6.3)	1.46(3.6)	9.84(14.0)
P. C.	68.0	44	26	70	2.56(6.0)	1.69(3.8)	7.61(11.0)
R. L.	65.0	40	35	75	2.34(6.2)	1.55(4.1)	7.98(12.5)
E. B.	61.0	47	29	76	2.89(6.1)	1.83(3.9)	8.58(12.0)
	Mean	43	28	71	2.54	1.67	8.83
	SD	5.22	3.23	6.59	0.42	0.18	1.09
	SE	1.74	1.08	2.20	0.14	0.06	0.36

Key: PV—Plasma volume.
RCV—Red cell volume.
TBV—Total blood volume.
TCP—Total circulating plasma proteins.
TCA—Total circulating albumin.
TCH—Total circulating hemoglobin.

(Concentrations in Gm. per cent given in parentheses.)

proteins of the above three groups of persons. The blood volumes and circulating proteins of the lean men and of the lean women are so alike as to permit their combination into one set of data to serve as a basis for comparison of malnourished patients of both sexes.

2. *Cachectic Patients* (Tables 10, 11). This group of patients has been subdivided into three categories: (A) those exhibiting simple malnutrition; (B) those exhibiting malnutrition complicated by infection, renal disease or hepatic disease; and (C) those exhibiting malnutrition with cancer. The latter group consisted of individuals having incurable cancers that were generally wide-spread. All of these patients had experienced significant losses of weight. Persons having had visible loss of blood were not included in these groups. The cancerous cachectic persons were found to have red cell volumes and total circulating hemoglobins that were significantly smaller than those of persons in the "lean normal" group, while their plasma volumes and total circulating plasma proteins did not differ significantly from the "lean normals" (See LN : Ca, Table 12–B). However, variances of these parameters in patients with cancer are so large as to prevent the use of the means as descriptive bases.

Malnutrition complicated by infection, hepatic disease or renal disease is often associated with significantly smaller red cell volumes, total circulating hemoglobins, and plasma proteins than those obtained in the lean normal group while their plasma volumes were the equals of those of lean normal persons (see LN : CC, Table 12–B).

The patients with simple malnutrition were found to possess volumes of blood and plasma and total circulating plasma proteins and hemoglobins that in relation to their weights were significantly larger than those possessed by lean normal persons (see SC : LN of Table 12–B).

3. *The effects of blood transfusions given to malnourished and anemic patients* (Table 13). (A) The first case is that of S. S. He was very cachectic and continuously lost body fluids and protein through decubitus ulcers. He was given transfusions of blood because he would not eat. These affected the changes shown in Table 13. The first transfusion of 1,000 ml. of blood was followed by an increase in his plasma and red cell volumes. However, the administration of another 1,500 ml. of blood effected no change in total blood volume even though the albumin and hemoglobin concentrations were still below normal when these latter three 500-ml. transfusions were given. Subsequent to them his plasma volume decreased by an amount equal to the gain in the red cell mass. Consequently, these latter three transfusions did not change the blood volume at all. However, in this case the total mass of circulating plasma proteins increased after three transfusions. This change is entirely accountable to the increase of the globulin fraction.

(B) The second patient, M. G., had lost much weight, yet he still weighed 85 kg. During three days 1,500 ml. of blood in 500-ml. aliquots were given to him; one day after the last transfusion it was found that a mass of plasma equal to the 900 ml. transfused had escaped from his circulation while practically all of the 600 ml. of red cells administered remained in the circulation.

(C) The response of the third patient, O. P., illustrates one of the dangers of blood transfusions attendant upon the attempted correction of a low hematocrit and low hemoglobin and albumin

TABLE 8. *Blood Volume, Total Circulating Plasma Proteins, and Total Circulating Hemoglobin in Normal People*

	Body Wt. (kg.)	PV	RCV	TBV	TCP	TCA	TCH
		Fat Normals					
		ml./kg. body weight			Gm./kg. body weight		
				1. Men			
C. C.	100	36	30	66	2.02(5.7)	1.54(4.3)	9.97(15.2)
J. W.	84	35	33	68	2.40(6.7)	1.39(3.9)	9.41(13.6)
F. M.	113	31	21	52	1.57(5.1)	1.09(3.5)	6.50(12.5)
J. S.	93	31	23	54	1.51(5.0)	1.00(3.3)	6.78(12.5)
B. P.	80	38	30	68	2.83(7.3)	1.50(3.9)	9.88(14.5)
J. G.	96	32	28	60	2.13(6.6)	1.21(3.7)	9.28(15.2)
T. W.	90	37	25	62	2.62(7.4)	1.42(3.9)	8.83(14.0)
	Mean	34	27	61	2.15	1.31	8.66
	SD	2.52	4.26	6.30	0.48	0.17	1.36
	SE	1.03	1.74	2.57	0.20	0.07	0.55
				2. Women			
L. C.	72	38	24	62	2.46(5.9)	1.38(3.3)	7.65(11.3)
B. W.	120	30	20	50	2.12(7.1)	1.11(3.7)	5.97(12.0)
N. G.	81	44	25	69	—	—	8.23(11.0)
H. C.	136	25	21	46	1.69(6.6)	1.07(4.3)	6.43(14.0)
L. P.	145	35	19	54	1.52(6.3)	1.12(3.5)	5.62(10.5)
E. B.	70	31	25	57	1.97(6.3)	1.07(3.4)	8.00(14.0)
	Mean	34	22	56	1.95	1.15	6.98
	SD	6.28	2.63	7.83	0.34	0.12	1.04
	SE	2.81	1.17	3.50	0.17	0.06	0.47

Key: PV—Plasma volume.
RCV—Red cell volume.
TBV—Total blood volume.
TCP—Total circulating plasma proteins.
TCA—Total circulating albumin.
TCH—Total circulating hemoblogin.

(Concentrations in Gm. per cent given in parentheses.)

TABLE 9. *Blood Volume, Total Circulating Plasma Proteins, and Total Circulating Hemoglobin in Normal People*

	Body Wt. (kg.)	PV	RCV	TBV	TCP	TCA	TCH
		Lean Normals					
		ml./kg. body weight			Gm./kg. body weight		
				1. Men			
A. R.	63.0	51	39	90	2.94(5.7)	2.21(4.3)	11.72(13.0)
T. W.	70.5	54	33	87	2.54(4.7)	1.50(2.8)	10.63(12.2)
A. M.	67.5	50	33	83	2.59(5.2)	1.75(3.5)	9.93(12.0)
T. C.	65.0	54	38	92	2.71(5.0)	1.68(3.1)	12.39(12.5)
R. B.	66.0	51	38	89	2.50(4.9)	1.83(3.6)	10.52(13.0)
F. T.	55.5	45	32	77	2.52(5.7)	1.62(3.7)	10.42(13.6)
L. C.	50.0	50	37	87	3.14(6.3)	1.54(3.1)	11.30(13.0)
W. W.	55.0	51	36	87	3.18(6.3)	2.15(4.1)	10.55(12.2)
F. W.	45.0	44	29	73	3.24(7.6)	1.19(4.6)	9.67(13.0)
	Mean	50	35	85	2.82	1.80	10.79
	SD	3.27	3.20	5.91	0.27	0.23	0.84
	SE	1.15	1.13	2.09	0.09	0.08	0.28
				2. Women			
L. L.	30.0	50	32	82	3.33(6.6)	2.00(4.0)	9.30(11.3)
J. A.	44.0	62	32	94	4.29(7.3)	2.48(4.2)	9.46(10.0)
E. G.	45.0	43	30	73	2.80(6.5)	1.92(4.5)	9.29(13.0)
P. M.	51.0	55	37	92	3.88(5.9)	2.00(4.0)	11.97(13.0)
	Mean	52	33	85	3.57	2.10	10.00
	SD	6.95	2.58	8.41	0.56	0.22	1.18
	SE	4.01	1.49	4.85	0.32	0.13	0.68
				3. Men and Women			
	Mean	51	34	85	3.05	1.89	10.55
	SD	4.52	3.28	6.48	0.53	0.29	0.99
	SE	1.30	0.95	1.87	0.15	0.08	0.29

Key: PV—Plasma volume.
RCV—Red cell volume.
TBC—Total blood volume.
TCP—Total circulating plasma proteins.
TCA—Total circulating albumin.
TCH—Total circulating hemoglobin.

(Concentrations in Gm. per cent given in parentheses.)

concentrations in a cachectic individual. All of the red blood cells and plasma contained in the first 1,000 ml. of blood given at the rate of 500 ml./day were retained in the circulation. However, when an additional 1,500 ml. of blood were given, while the hematocrit was still 26 and the hemoglobin only 9.4 Gm. per cent, the 600 ml. of red cells were retained in the circulation, while the equivalent of the 900 ml. of transfused plasma escaped from it and, in addition, 1,000 ml. of his plasma left the circulation. Concomitantly he developed pulmonary edema and died. In other words, the pulmonary edema developed after the transfusions while his circulating blood volume declined.

(D) The fourth patient, R. C., had a normal blood volume relative to body weight and a definite anemia. He suffered from a wide-spread metastatic carcinoma of undetermined origin that had invaded his bone marrow. He also had had signs of cardiac decompensation and had been taking digitalis. The first 500 ml. of blood given to him were retained without trouble, but two days later, when an additional 500 ml. were given, pulmonary edema developed and he died. When he died his hematocrit and hemoglobin concentrations were still remarkably low, 32 per cent and 9.6 Gm. per cent respectively.

(E) The fifth patient, F. J., was not cachectic. He had had repetitive gastro-intestinal hemorrhages from a gastrojejunal ulcer. However, he was found to have a normal total blood volume relative to body weight, and an essentially normal circulating plasma protein mass, although his hematocrit was only 15 and his hemoglobin concentration was 3.6

Gm. per cent. After the first 1,500 ml. of blood were given to him an inexplicably large increase of red cell volume occurred, while no change in his plasma volume took place. Upon transfusing an additional 1,500 ml. of blood, all of the red cells given in this transfusion were retained in the circulation and a volume of plasma equal to that which had been given left the circulation. This patient developed no circulatory embarrassment or evidence of pulmonary edema, and the transfusions significantly increased his blood volume and red cell volume without reducing his plasma volume significantly.

(F) The sixth patient, F. P., had an anemia of undetermined origin. He also demonstrated the phenomenon of retention of the transfused red cells and rejection of the transfused plasma. He was given 3,000 ml. of whole blood containing about 1,800 ml. of plasma and by the time all of the blood was given, his plasma volume was 600 ml. smaller than it was before the transfusions. This patient retained 26 Gm. of the transfused albumin, or about one-third of the amount given. He was the only person of the six to gain circulating albumin from the blood transfusions.

Discussion

During the last decade and a half many surgeons have looked upon the preoperative transfusion of blood as a very important part of the preoperative care of the cachectic person. In the main this attitude developed because the blood volumes of malnourished individuals were found to be smaller than those of their theoretically normal counterparts. In other words, the cachectic individual has been considered to

TABLE 10. *Blood Volume and Circulating Proteins in Noncancer Cachexia*

Pt.	Body Wt. (kg.)	Diagnosis	PV	RCV	TBV	TCP	TCA	TCH
			ml./kg. body weight			Gm./kg. body weight		
			A. Simple Cachexia					
B. R.	44.5	Concussion	57	39	96	4.38(7.1)	2.47(4.0)	11.65(12.2)
C. H.	44.0	Fr. mandible	75	43	118	4.27(6.4)	2.14(3.2)	11.55(11.0)
J. R.	44.1	Cardiac decomp.	62	43	105	3.74(6.0)	2.27(3.5)	14.16(13.3)
Z.	43.0	Fr. mandible	64	45	109	4.69(7.3)	2.41(4.3)	—
C. G.	58.0	Postop. fistula, small bowel	69	36	105	5.03(7.3)	3.17(4.6)	10.38(9.8)
A. B.	43.0	Chr. leg ulcer, malnutrition	65	42	107	3.54(5.4)	2.16(3.3)	10.87(10.4)
	Mean, 6 patients without infection, renal or liver disease		65	41	106	4.27	2.44	11.72
	SD		5.99	3.41	5.93	0.55	0.32	1.53
	SE		2.68	1.53	2.65	0.25	0.14	0.77
			B. Cachexia Complicated by Other Disease					
S. S.	36.0	Malnutrition; megocolon; decubiti	59	26	85	2.64(4.5)	1.11(1.9)	6.83(8.1)
V. J.	45.0	Pyelonephritis	60	23	83	3.36(5.6)	1.76(2.9)	9.44(11.2)
S. B.	35.7	Senile psychosis and pneumonitis	69	21	90	2.27(3.3)	1.04(1.5)	7.31(8.1)
A. LeF.	35.0	TBC peritonitis	65	31	96	4.48(6.9)	1.89(2.9)	9.17(9.5)
P. B.	45.4	Chr. glomerular nephritis	38	25	63	2.77(7.4)	1.50(4.0)	6.89(11.0)
D. B.	45.0	Cirrhosis of liver	75	17	92	3.91(5.2)	2.33(3.1)	6.00(8.2)
	Mean, 6 patients with infection, renal or liver disease		61	24	85	3.24	1.60	7.61
	SD		11.62	4.35	10.69	0.76	0.45	1.24
	SE		5.30	1.95	4.78	0.34	0.20	0.56

TABLE 11. *Blood Volume and Circulating Proteins in Cancer Cachexia*

Pt.	Body Wt. (kg.)	Diagnosis Carcinoma of:	PV	RCV	TBV	TCP	TCA	TCH
			ml./kg. body weight			Gm./kg. body weight		
J. L.	63.2	Rectum	53	35	88	3.26(6.2)	1.95(3.7)	10.78(12.3)
E. C.	38.2	Esophagus	72	57	129	3.79(5.3)	1.94(2.7)	18.90(14.7)
M. H.	34.6	Cervix	83	32	115	5.02(6.1)	2.22(2.7)	10.29(9.0)
C. M.	31.2	Breast	84	28	112	4.26(5.11)	2.34(2.8)	8.05(7.2)
H. Mc	49.0	Breast	59	23	82	3.34(5.7)	1.63(2.8)	7.34(9.0)
A.	58.0	Lung	58	18	76	3.12(5.4)	1.31(2.1)	—
DeW.	37.0	Esophagus	38	33	71	—	—	—
N. B.	38.0	Esophagus	37	24	61	—	—	—
E. B.	35.0	Stomach	34	37	71	—	—	—
H. D.	43.3	Cervix	65	28	93	4.09(6.3)	2.19(3.5)	7.48(8.1)
M. P.	39.1	Esophagus	38	24	62	2.35(6.1)	1.30(3.4)	—
D. C.	43.6	Esophagus	56	18	74	3.37(6.0)	1.70(3.0)	5.55(7.5)
F. B.	40.0	Esophagus	34	22	56	1.78(6.3)	1.03(3.0)	6.43(11.6)
D. P.	44.0	Esophagus	51	25	76	3.36(6.6)	1.68(3.3)	7.86(10.3)
C. W.	54.0	Larynx	47	26	73	2.65(5.6)	1.52(3.2)	7.50(10.3)
E. H.	45.0	Pharynx	78	31	109	3.11(4.8)	1.89(2.9)	7.66(8.4)
S. S.	37.0	Esophagus	58	25	83	3.62(6.2)	1.86(2.3)	7.67(9.2)
M. W.	27.0	Cervix	81	36	117	4.85(6.0)	2.33(2.9)	11.11(9.5)
E. W.	43.0	Metastatic to rib	51	31	82	1.53(3.0)	1.53(3.0)	7.33(9.0)
O. P.	44.0	Stomach (edema)	72	19	91	3.50(4.9)	1.43(2.0)	6.45(7.1)
L. H.	34.0	Colon	61	45	106	3.74(6.1)	2.03(3.3)	13.55(12.8)
E. W.	58.5	Cervix	64	13	77	4.28(6.7)	2.14(3.4)	3.84(5.0)
G. R.	53.0	Colon	48	20	68	3.47(7.3)	2.04(4.3)	5.85(8.6)
C. B.	45.0	Stomach	61	35	96	3.45(5.7)	1.82(3.0)	11.09(11.6)
K. P.	51.0	Larynx	48	29	77	3.19(6.7)	1.57(3.3)	8.25(11.0)
C. J.	45.0	Breast	60	17	77	4.48(7.5)	2.62(4.4)	5.35(7.0)
H. P.	54.0	G. I.	62	22	84	3.39(5.5)	1.85(3.0)	5.89(7.0)
Q. D.	51.0	Breast (ascites)	41	20	61	3.27(8.1)	1.08(2.7)	5.59(9.2)
	Mean		57	27	84	3.51	1.80	8.25
	SD		14.5	8.99	18.65	0.55	0.39	3.18
	SE		2.80	1.73	3.99	0.11	0.08	0.68

have a deficit of blood volume because measurement of the blood volumes of malnourished patients has shown them to be smaller than those of normal persons of similar stature.

Actually the comparison of the blood volumes of cachectic individuals with those of thin, normal persons, who as a matter of fact have the largest blood volumes per unit of body weight, is more appropriate biologically than comparing them with the blood volumes of the normal, somewhat obese American. However, even when the blood volumes of malnourished patients are compared with those of lean, normal individuals, the cachetic one with but a few exceptions has been found to have a blood volume relative to body mass that is significantly larger than that possessed by lean, normal people. The greater volume of blood per unit of body weight possessed by the cachectic, sick person who does not suffer from chronic infection, hepatic or renal disease, or cancer, is related to the relatively greater size of his plasma volume; his red cell mass relative to his body weight tends to be the same or slightly larger than that of the lean, normal person.

There have also been those who have recommended the transfusion of plasma to the malnourished patient before an operation because it was presumed that he suffered from a plasma protein deficit because the concentrations of protein in the plasma of the malnourished, sick person were often below those characteristic of the plasma of persons in good health. In these studies the total circulating plasma proteins of malnourished patients excepting those having chronic infections, cirrhosis and far advanced renal disease, were found to be normal or increased, relative to their body weights, even though the concentrations of the plasma proteins in their blood were oftimes below normal. The reductions in concentration of plasma proteins that do occur in the malnourished individual are compensated by a concomitant increase in the plasma volume relative to body weight. This compensation is of such magnitude that with but a few exceptions, the total circulating plasma proteins in the malnourished individual are no different than they are in lean, well-nourished persons having normal concentrations. In brief, upon comparing the blood volumes and total circulating plasma proteins of the malnourished ill person with the blood volumes and total circulating proteins of normal *lean* individuals of similar stature, the malnourished ill person is usually found to possess per unit of body mass a blood volume that is slightly larger and a plasma protein mass that is at least the equal of these parameters in the normal lean person.

Obviously, these observations have dis-

TABLE 12–A. *Statistical Analysis of Data in Normal Patients*

	PV	RCV	TBV	TCP	TCA	TCH
ANM:ANF	0	M ≫ F	M ≫ F	M > F	0	M ≫ F
ANM > FNM	A ≫ F	A ≫ F	A ≫ F	A ≫ F	A ≫ F	A ≫ F
ANM = LNM	0	0	0	0	0	0
ANF > FNF	A ≫ F	A ≫ F	A ≫ F	A ≫ F	A ≫ F	A ≫ F
LNF:ANF	L > A	L > A	L ≫ A	L ≫ A	L ≫ A	0
FNM = FNF	0	M > F	0	0	0	M > F
LNM > FNM	L ≫ F	L ≫ F	L ≫ F	L ≫ F	L ≫ F	L ≫ F
LNF > FNF	L ≫ F	L ≫ F	L ≫ F	L ≫ F	L ≫ F	L ≫ F
LNM = LNF	0	0	0	M > F	M > F	0

Key: ANM = Average normal men.
ANF = Average normal women.
FNM = Fat normal men.
FNF = Fat normal women.
LNM = Lean normal men.
LNF = Lean normal women.

$x \gg y$ = x significantly greater than y at 1% probability level.
$x > y$ = x significantly greater than y at 5% probability level.
0 = no significant difference.

TABLE 12–B. *Statistical Analysis of Data in Lean Normals and Cachetic Patients*

	PV	RCV	TBV	TCP	TCA	TCH
SC:CC	0	SC ≫ CC	SC ≫ CC	SC > CC	0	SC ≫ CC
SC:Ca	SC > Ca	SC ≫ Ca	SC ≫ Ca	SC ≫ Ca	SC ≫ Ca	SC ≫ Ca
Ca:CC	0	0	0	0	Ca ≫ CC	0
SC:LN	SC ≫ LN	SC ≫ LN	SC ≫ LN	SC ≫ LN	SC ≫ LN	0
LN:CC	0	LN ≫ CC	0	0	LN ≫ CC	LN ≫ CC
LN:Ca	Ca > LN	LN ≫ Ca	0	Ca > LN	0	LN ≫ Ca

Code: LN = All lean normals (men and women).
SC = Simple cachexia.
CC = Complicated cachexia.
Ca = Cancerous cachexia.

$x \gg y$ = x significantly greater than y at 1% probability level.
$x > y$ = x significantly greater than y at 5% probability level,
0 = no significant difference,

tinct clinical significance. The belief that the malnourished sick person suffers from chronic, oligemic shock must be abandoned, and the transfusion of blood and the transfusion of plasma to correct theoretical deficits in red cell and plasma protein masses in the malnourished sick patient are unwarranted unless a deficit of the red cells or circulating protein relative to body weight exists. The only way to determine surely the need for transfusing blood or plasma preoperatively into persons who have not lost blood *is to measure the total red cell volume and plasma volume with methods that are accurate*. In other words, the indications for the transfusion of blood and plasma preoperatively can only be presumed to exist when the person in question has been found by actual measurement to have a blood volume or a circulating plasma protein mass that is significantly smaller per unit of body weight than that which is characteristic of lean normal individuals. Were it not for the dangers attendant upon the preoperative transfusion of blood into cachectic persons this statement could not be made so dogmatically. However, the troubles associated with the transfusion of blood are rather protean, and we believe that the malnourished patient having hemoglobin and plasma protein concentrations smaller than normal but a blood volume relative to body mass that is larger than normal may be particularly susceptible to transfusional circulatory overloading. In the presence of a reduced red cell volume per unit of body weight or a reduced hemoglobin concentration, the biologic response to the transfusion of blood is determined by the ability of the organism to dispose of plasma and plasma proteins from his vascular system while retaining the red cells in it. Fortunately, the truly anemic individual, when given a blood transfusion, is with but few exceptions capable of making these adjustments. However, at times the transfusion of blood into individuals having blood volumes of 100 ml./kg. or more, or peripheral edema, or incipient cardiac failure, is attended by acute pulmonary edema and death (Cases C and D). In individuals such as these the replenishment of the circulatory red cell mass might be effected more appropriately by administering packed red blood cells.

Cachectic individuals having chronic infections, renal disease, or hepatic disease and those with advanced neoplasia usually possess total red cell volumes that are significantly smaller than those of healthy individuals of similar stature and weight, while they have total blood volumes relative to body weight that are the same as those of lean normal persons. Consequently, one cannot presume without measuring it that a person having cancer, a chronic infection, or renal or hepatic disease and anemia has a blood volume that is small for his weight. This statement is especially applicable to cachectic individuals having cancers because the alterations in the blood volumes found in this group of patients bore no definite relationship to their hemoglobin and plasma protein concentrations. Should an individual fitting this category be found to have a red cell mass per unit of body weight that is significantly below normal, the transfusion of packed red blood cells would be more appropriate biologically than transfusing whole blood.

In brief, these studies contradict the concept that the cachetic individual who has not bled has a significantly reduced blood volume and is benefited by the transfusion of blood preoperatively.

The limited retention of transfused blood in the circulatory systems of the five cachectic ill persons studied who had not lost blood through hemorrhage was to be expected should the physiologic reactions of the cachectic individual to transfusions be those characteristic of normal mammals. Krumbhaar and Chanutin [29] rendered dogs plethoric by the daily transfusion of 25 to 200 ml. of whole blood. They discovered that the dogs' plasma volumes initially de-

TABLE 13. *Changes in Blood Volume and Circulating Proteins After Transfusion*

	TP	A (Gm./100 ml.)	G	TCP	TCA (Gm.)	TCG		Hb(Gm./ 100 ml.)	TCH (Gm.)	PV	RCV (milliliters)	TBV	PV	RC (ml./kg.)	TBV
A. S. S. Marked malnutrition; acquired megacolon; decubitus ulcers. Body weight 36 to 37 kg.															
Initial values	4.5	1.9	2.6	95	40	55	30	8.1	246	2,120	920	3,040	59	26	85
1,000 ml. blood; 4 days later	4.8	2.1	2.7	114	50	64	32	10.2	356	2,380	1,120	3,500	64	31	95
After 500 ml. blood/d ×3	5.2	1.8	3.4	140	36	104	43	13.2	462	2,000	1,500	3,500	54	41	95
Seven days later										2,160	1,320	3,480	59	36	95
B. M. G. Ruptured diverticulum of colon with abscess. Carcinoma hepatic flexure of colon. Body weight 85 kg., 62 years old															
Initial values	5.7	3.3	2.4	161	92	69	38	10.6	467	2,720	1,680	4,400	32	19	51
After 500 ml. blood/d ×3	5.9	2.9	3.0	166	81	85	44	13.6	690	2,820	2,230	5,050	33	26	59
Net change				+5	−11	+16			+223	+100	+550	+650			
C. O. P. Far-advanced carcinoma of the stomach with peripheral edema. Body weight 45 to 46 kg.															
Initial values	4.9	2.0	2.9	154	63	91	21	7.1	284	3,140	840	3,980	72	19	91
Values 4 days after transfusion (1,000 ml.)	4.4	2.7	1.7	155	95	60	26	9.4	447	3,520	1,240	4,760	79	28	107
Immediately after 500 ml. blood/d ×3	4.5	2.1	2.4	112	53	59	45	11.6	530	2,500	2.060	4,560	55	45	100
D. R. C. Metastatic carcinoma of bone, primary unknown. Congestive heart failure. Body weight 38 kg., 69 years old															
Initial values	7.3	3.7	3.6	195	98	97	25	6.8	255	[2,700	900	3,600	71	24	95
After 500 ml. blood/day							27	7.6	340	2,950	1,100	4,050	78	29	107
After 500 ml. blood 2 days later							32	9.6							
Died 10 hours after transfusion with pulmonary edema															
E. F. J. Blood transfusion for intermittent gastro-intestinal bleeding. Man, 56 years old, 3 years after subtotal gastrectomy for duodenal ulcer. Body weight 55 kg.															
Initial values	6.7	4.2	2.5	253	159	94	15	3.6	160	3,775	675	4,450	69	12	81
Values 2 days after 500 ml. blood/d ×3	5.9	3.4	2.5	218	125	93	34	8.6	480	3,680	1,920	5,600	65	33	98
One day after 500 ml. blood per day ×3	6.5	3.7	2.8	234	133	101	36	11.0	616	3,600	2,000	5,600	63	35	98
Net change				−19	−26	+7			+456	−175	+1,325	+1,150			
F. F. P. Anemia of undetermined cause. Man, 51 years old, body weight 60 kg.															
Initial values	5.2	2.3	2.9	206	91	115	23	5.0	259	3,960	1,215	5,175	66	20	86
After 1,500 ml. whole blood	5.7	3.4	2.3	204	122	82	35	8.9	490	3,580	1,920	5,500	59	32	91
After 1,500 ml. additional whole blood	5.7	3.5	2.2	190	117	73	45	12.5	750	3,340	2,660	6,000	56	44	100
Net change				−16	+26	−42			+491	−620	+1,445	+925			

clined, demonstrating that volumes of plasma larger than those given had left the blood stream. At the same time a large part, but not all, of the transfused red blood cells remained in the animals' circulation. Coller and associates[9] corroborated their observations on the dog.

The fact that the response of cachectic individuals to the transfusion of blood was characteristic of that of normal animals supports the assumption that the blood volumes of cachectic persons, though smaller than those of unstarved men of like stature, are physiologically appropriate to them. It also suggests that the most appropriate base for the assessment of the normalcy of a measured volume of blood in any person including an obese one is the relationship of the volume of the person's blood to his *existent* body mass exclusive of edema.

However, granted that relative to body mass oligemia does not exist often in starved persons who have not bled and consequently its spectre cannot be used to justify the giving of blood to cachectic patients preoperatively, cannot the existence of the "anemia" of cachexia justify the preoperative transfusion of blood? Actually, the moderate reduction of the concentrations of hemoglobin and red cells that accompanies cachexia among persons who do not lose blood does not constitute an anemia often; the red cell volumes of the persons usually still bear the same relationship to the individuals' nonedematous weights that they do in lean or normal persons. The hemoglobins and the red cell counts are low because usually the cachectic person's plasma volume per unit of body mass is larger than it is in a well-nourished person. In other words, the cachectic person should not be looked upon as being anemic so long as his red cell mass bears the same relationship to a unit of his weight as does that of a well-nourished person. On the other hand, cachectic patients with wide-spread cancer, chronic infection, and advanced hepatic and renal disease may have a true anemia with reduced red cell volumes but normal total blood volumes relative to body weight. An increase in total blood volume may not be needed, and certainly the degree of anemia which is critical and demands correction is unknown. The decrease in circulation time (increase in rate of flow) which accompanies an anemia is indicative of the compensatory changes in the circulation which provide for the maintenance of a constant supply of oxygen to the tissues in the face of a reduced carrying capacity of the blood. Thus, the effect of an anemia will depend on the circulatory reserve of the individual. It will also depend on the varying needs of the tissues for oxygen, and the effect, if any, of surgical operations on this factor is unknown. If there is no increase in the rate of oxygen consumption during operation over that of the resting state, an already tolerable anemia need not be corrected.

Other reasons that we have repeatedly heard given for transfusing the starved person preoperatively are:

(1) "Give him a transfusion to pick him up a bit." Were the two cachectic individuals (Cases C and D) who died following the transfusions "picked-up"?

(2) "He hasn't been eating—give him some blood, it's a superb food." The caloric equivalent of the proteins (of the red cells and plasma), fat and carbohydrate in a liter of blood is about 900 calories. Two liters of 10 per cent dextrose will provide as much food as a liter of blood does much more quickly, much more cheaply, and with far less risk to the recipient.

(3) "His hemoglobin is low—give him a transfusion so that his wound will heal." Full-thickness burns covering 14 to 20 per cent of rats' bodies heal as rapidly when the animals' red cell concentrations are kept at one-half of their normal values by intermittent hemorrhage as they do when the animals' concentrations of hemoglobin and red blood cells are normal throughout the time the wounds were healing.[26]

(4) "He is starved and won't stand the operation well. I won't operate upon him until he has been transfused." Carefully controlled experiments performed by Pareira *et al.*[37] have demonstrated that starved rats were no more susceptible to trauma, tourniquet shock or proportionate hemorrhage than were the normally fed controls.

The answer to the question, "When should transfusions of blood be given to cachectic persons preoperatively?" is so far as extant evidence goes in no way different from that pertaining to the case of the well-nourished, namely, give blood preoperatively:

(1) During or after the acute loss of blood that is sufficient to produce a physiological significant oligemia.

(2) When there exists an oligemic anemia such as that associated with the chronic loss of blood through various organ-tracts or through large granulating surfaces, and acute and chronic infections.

Excepting that hemorrhage has recently occurred or is in progress, the transfusion of blood preoperatively should be performed rarely without first having ascertained that the patient having a low hemoglobin concentration or red blood cell count has a circulating erythrocytic volume that really is significantly smaller than it should be in relation to his extant nonedematous weight. Transfusing blood preoperatively without doing this is often nothing more than pernicious meddling. This statement also applies to the administration of plasma preoperatively or of serum albumin preoperatively to individuals having reduced serum albumin concentrations. In this study cachectic patients with but few exceptions have been found to have total circulating plasma protein masses that are at least the equal of those of lean normal persons of similar stature.

These studies of the cachectic ill, excepting for a few of those who had cancer, chronic infections, hepatic or renal diseases, are fully corroborative of the observations made by Keys *et al.*[29] upon slowly starving young men.

Summary

1. Wide variations in blood volume relative to body weight are found in normal individuals, in great part related to variances of their body fat.

2. Cachectic individuals without advanced cancer, renal disease, hepatic disease, or chronic infection have normal or super-normal blood volumes relative to the blood volumes of lean normal persons.

3. A super-normal plasma volume associated with subnormal hematocrit and hemoglobin concentrations characterizes simple malnutrition. Actual blood loss and conditions which interfere with the maintenance of red cell volume, such as chronic infections, renal disease, hepatic disease, and wide-spread cancers, are accompanied by larger decrements in hematocrit and hemoglobin concentrations than those attendant upon the high plasma volumes accompanying simple malnutrition.

4. In the absence of acute blood loss, blood transfusion should not be given to correct deficits in blood volume which have not been demonstrated by accurate measurements.

5. Correction of anemia by blood transfusion in the presence of normal or super-normal blood volumes may be hazardous, for pulmonary edema and death may result. The indications for the need for correction of anemia in preparation for operation have not been defined.

Bibliography

1. Aust, J. B., S. N. Chou, J. F. Marvin, E. L. Brackney and G. E. Moore: A Rapid Method for Clinical Total Blood Volume Determination Using Radioactive Iodinated Human Serum Albumin (RIHSA). Proc. Soc. Exper. Biol. & Med., 77:519, 1951.
2. Bateman, Jeanne C.: A Study of Blood Volume and Anemia in Cancer Patients. Blood, 6:639, 1951.

3. Berlin, N. I., Grace M. Hyde, R. J. Parsons and J. H. Lawrence: The Blood Volume in Various Medical and Surgical Conditions. New England J. Med., **247**:675, 1952.
4. Berlin, N. I., R. J. Parsons and I. H. Lawrence: The Blood Volume in Cancer. Cancer, **8**:796, 1955.
5. Brady, L. W., D. Y. Cooper, M. Colodzin, J. E. McClenalhan, E. R. King and R. Williams: Blood Volume Studies in Normal Humans. Surg., Gynec. & Obst., **97**:25, 1953.
6. Chang, H. C. and G. A. Harrop, Jr.: The Determination of the Circulating Blood Volume with Carbon Monoxide. J. Clin. Invest., **5**:393, 1927–28.
7. Clark, J. H., W. Nelson, C. Lyons, H. S. Mayerson and P. DeCamp: Chronic Shock. The Problem of Reduced Blood Volume in the Chronically Ill Patient. Ann. Surg., **125**: 618, 1947.
8. Cohn, J. E. and N. W. Shock: Blood Volume Studies in Middle Aged and Elderly Males. Amer. J. Med. Sc., **217**:388, 1949.
9. Coller, Frederick, *et al.*: Personal communication.
10. CoTui, N. H. Kuo, M. Chuachiaco, R. Rosh and J. H. Mulholland: Protein Nutrition in Cancer. Surg. Clin. of North America, **29**: 449, 1949.
11. Crispell, K. R., B. Porter and R. T. Nieset: Studies of Plasma Volume Using Human Serum Albumin Tagged with Radioactive Iodine. J. Clin. Invest., **29**:513, 1950.
12. Ellison, E. H., R. M. Zollinger, N. Cedars and C. I. Britt: Value of Blood Volume Determinations in Gastrointestinal Disease. A. M. A. Arch. Surg., **66**:869, 1953.
13. Erickson, J. R., J. B. McCormick and L. Seed: An Improved Method for the Determination of Blood Volume Using Radioactive Iodinated Human Serum Albumin. Science, **118**:595, 1953.
14. Fretheim, B.: The Total Circulating Serum Proteins in Patients with Gastric Cancer. Acta Chir. Scand., **108**:125, 1954.
15. Gibson, J. G. II and W. A. Evans, Jr.: Clinical Studies of Blood Volume. II. The Relation of Plasma and Total Blood Volume to the Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans. J. Clin. Invest., **16**:317, 1937.
16. Gibson, J. G. and K. A. Evelyn: Clinical Studies of the Blood Volume. IV. Adaptation of the Method to the Photoelectric Microcolorimeter. J. Clin. Invest., **17**:153, 1938.
17. Gibson, J. G., II, W. C. Peacock, A. M. Seligmann and T. Sack: Circulating Red Cell Volume Measured Simultaneously by the Radioactive Iron and Dye Methods. J. Clin. Invest., **25**:838, 1946.
18. Govaerts, J. and A. Lambrechts: Etude sur le volume sanguin: Methode de mesure du volume chez l'homme et le chien a l'aide du radiopyosphore. Acta Biol. Belg., **11**:425, 1942.
19. Gregersen, M. I.: A Practical Method for the Determination of Blood Volume with the Dye T-1824. J. Lab. & Clin. Med., **29**:1266, 1944.
20. Gregersen, M. I.: Effect of Circulatory States on Determinations of Blood Volume. Amer. J. Med., **11**:785, 1953.
21. Hardy, J. D., P. K. Sen and D. Drabkin: The Relation of Body Fluid Compartments to Body Fat. Surg., Gynec. & Obst., **93**:103, 1951.
22. Hevesy, G., R. H. Koster, G. Sorensen, E. Warburg and K. Zerahn: The Red Corpuscle Content of the Circulating Blood Determined by Labelling the Erythrocytes With Radiophosphorus. Acta Med. Scand., **116**:561, 1955.
23. Homburger, F. and N. F. Young: Studies on Hypoproteinemia. I. Hypoproteinemia in Patients with Gastric Cancer; Its Persistence After Operation in the Presence of Body Tissue Repletion. Blood, **3**:1460, 1948.
24. Hopper, J., Jr., H. Tabor and A. W.Winkler: Simultaneous Measurements of the Blood Volume in Man and Dog by Means of Evans Blus Dye, T-1824, and by Means of Carbon Monoxdie. I. Normal Subjects. J. Clin. Invest., **23**:628, 1944.
25. Inkley, Scott R., L. Brooks and H. Krieger: A Study of Methods for the Prediction of Plasma Volume. J. Lab. & Clin. Med., **45**: 841, 1955.
26. Jurkiewicz, Maurice: Personal communication.
27. Keith, N. M., L. G. Rowntree and J. I. Geraghty: A Method for the Determination of Plasma and Blood Volume. Arch. Int. Med., **16**:547, 1915.
28. Kelly, F. J., D. H. Simonsen and R. Elman: Blood Volume Determination in the Human With Red Cells Containing Radioactive Phosphorus (P^{32}) and with Pure Human Albumin. J. Clin. Invest., **27**:795, 1948.
29. Keys, A., J. Brozek, A. Henschel, O. Mickelsen and H. L. Taylor: The Biology of Human Starvation. The University of Minnesota Press, Minneapolis, 1950.

30. Krumbhaar, E. B. and A. Chanutin: Studies on Experimental Plethora in Dogs and Rabbits. J. Exp. Med., **35**:847, 1922.
31. Ling, W. S. M. and H. Sprinz: Blood Volume Changes and Available (Thiocyanate) Fluid Space in Soldiers With Chronic Wound Infections and Associated Nutritional Depletion. Amer. J. Med. Sc., **215**:554, 1948.
32. Maladie de Famine. Recherches Cliniques sur la Famine Executees dans le Ghetto de Varsovie en 1942. Varsovie, 1946. American Joint Distribution Committee.
33. Mayerson, H. S., C. Lyons, W. Parson, R. J. Nieset and W. V. Trautman, Jr.: Comparison of Results of Measurement of Red Blood Cell Volume by Direct and Indirect Technics. Am. J. Physiol., **155**:232, 1948.
34. Mensely, G. R., E. B. Wells and P. F. Hahn: Application of the Radioactive Red Cell Method for Determination of Blood Volume in Humans. Am. J. Physiol., **148**:531, 1947.
35. Mollison, P. L.: Observations on Cases of Starvation at Belsen. Brit. Med. J., **1**:4, 1946.
36. Nylin, G. and S. Hedlund: Weight of the RBC in Heart Failure Determined With Labelled RBC During and After Decompensation. Am. Heart J., **33**:770, 1947.
37. Pareira, M. D., N. Sicher and S. Lang: Survival of the Undernourished Organism. I. Following Surgical Trauma. Ann. Surg., **147**: 51, 1958.
38. Reeve, E. B. and N. Veall: A Simplified Method for the Determination of Circulating Red Cell Volume with Radioactive Phosphorus. J. Physiol., **108**:12, 1949.
39. Sanford, A. H. and C. Sheard: The Determination of Hemoglobin with the Photoelectrometer. J. Lab. & Clin. Med., **15**:483, 1930.
40. Schultz, A. L., J. T. Hammarsten. B. I. Hetter and R. V. Ebert: A Critical Comparison of the T-1824 Dye and Iodinated Albumin Methods for Plasma Volume Measurement. J. Clin. Invest., **32**:107, 1953.
41. Seed, L., E. Kaplan and R. G. Eggen: Blood Volume Studies with I^{131} Tagged Albumin. Am. Surg., **21**:533, 1955.
42. Smith, H. P., H. R. Arnold and G. H. Whipple: Blood Volume Studies. VII. Comparative Values of Welcker, Carbon Monoxide and Dye Methods for Blood Volume Determinations. Accurate Estimations of Absolute Blood Volume. Amer. J. Physiol., **56**: 336, 1921.
43. Storaasli, J. P., H. Krieger, H. L. Friedell and W. D. Holden: The Use of Rardioactive Iodinated Plasma Protein in the Study of Blood Volume. Surg., Gynec. & Obst., **91**: 458, 1950.
44. Tennant, R., L. Adelson, G. McAdams and R. Davis: The Use of Blood Volume Studies as a Clinical Aid in Intravenous Therapy. Yale J. Biol. & Med., **23**:735, 1950.
45. Weichselbaum, T. E.: An Accurate and Rapid Method for the Determination of Proteins in Small Amounts of Blood Serum and Plasma. Am. J. Clin. Path. Tech. Supp., **10**:40, 1946.
46. Wintrobe, M. M.: The Size and Hemoglobin Content of the Erythrocyte. J. La. & Clin. Med., **17**:899, 1932.