THE EFFECTS ON THE CARDIOVASCULAR SYSTEM OF FLUIDS ADMINISTERED INTRAVENOUSLY IN MAN. I. STUDIES OF THE AMOUNT AND DURATION OF CHANGES IN BLOOD VOLUME

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The injection of fluids intravenously to combat dehydration, maintain nutrition and to treat shock has increased considerably during the past few years. Although the benefits from this procedure are generally striking, clinical experience has shown that untoward effects occur under certain circumstances. Until knowledge of the physiological effects of intravenous fluids is more adequate, the causes of the untoward effects cannot be fully understood. Studies have been designed to learn the amount and duration of changes in blood volume, and the resulting effects on the dynamics of the circulation after the injection of fluids intravenously in man.

The present communication reports our studies of the changes in blood volume after intravenous injections of varying amounts of isotonic or slightly hypertonic solutions at various rates. A subsequent paper (30) will report the effect of these injections on arterial and venous pressures, the work of the heart, and related aspects of the circulation.

LITERATURE

Several early physiologists demonstrated that the injection of large volumes of fluids intravenously caused diminution of the concentration of red cells and the percentage of hemoglobin of the blood. In fact, Kottmann in 1906 (1) and Plesch in 1909 (2) utilized the magnitude of change in the hematocrit (1) and in the percentage of hemoglobin (2) following known volumes of isotonic saline intravenously to estimate blood volume.

After injection of hypertonic glucose in dogs, other more recent investigators have found decrease in the red cell count, hematocrit, and hemoglobin concentration of whole blood (3, 4, 5), decrease in protein concentration of the serum (3, 4, 5) and decrease in serum specific gravity (6). After varying quantities of isotonic glucose or of physiological saline intravenously, dilutions of the cellular elements of the blood, of the hemoglobin and of the serum protein concentration in dogs and in rabbits have also been observed (3, 5, 6, 7, 8, 9, 10, 11).

Experimental attempts to demonstrate increase in blood volume after intravenous fluids by methods dependent on the introduction of dyes into the circulation have given variable and contradictory results. Miller and Poindexter (7), after injecting intravenously in dogs volumes of physiological saline sufficient to cause marked decreases in red cell count, hematocrit, and serum protein, were not able to show an increase in blood volume by the brilliant vital red method as described by Hooper, Smith, Belt and Whipple (12). Lamson and Rosenthal (3), using the method of Keith, Rowntree and Geraghty (13), likewise were unable to demonstrate increase in blood volume of dogs which received physiological saline or hypertonic glucose in sufficient amounts to produce marked reduction in the hemoglobin percentage of the blood. Smith (4), on the other hand, did demonstrate increase in blood volume after hypertonic glucose by using his modification of the vital red method (14) which permitted repeated measurements of blood volume in the same animal. The increases in blood volume as calculated by the dye method in these experiments averaged 50 per cent as great as the increases calculated from the hematocrit and hemoglobin changes (4).

Blalock, Beard and Thuss (5), after injections of solutions of various concentrations of saline and of glucose in dogs with normal blood pressures, found increases in blood volume, as calculated from the control blood volume and the hemoglobin and hematocrit changes.

Reports of reliable studies of blood dilution and of changes in blood volume in man following intravenous fluid therapy are few. Yesko, Passalacqua and Judd (15) have reported decreased blood hemoglobin and red cell concentrations after the injection of 1000 cc. of 10 per cent glucose in 1 per cent saline in five patients. Jones and Eaton (16) have suggested that the continuous administration of fluids intravenously may have played an important rôle in the causation of the low concentrations of serum protein found in certain of their patients postoperatively. Gibson and Evans (17), using the dye "Evans Blue" and the "indirect method" of measurement of blood volume (17), found an increase of approximately 200 cc. in the plasma volume of one patient five minutes after the intravenous injection of 50 cc. of 50 per cent glucose in physiological saline solution.

From the hitherto published data on studies in animals and man, it appears that in the absence of shock the concentration of blood cellular elements and of plasma protein may remain appreciably decreased for from approximately a half hour to several hours after the injection of solutions of crystalloids intravenously

(5, 6, 9, 11, 15, 16). When equivalent volumes of solutions of colloids, such as gum acacia or whole blood, are injected in animals, the increases in blood volume are greater and more sustained (5, 9, 18). The presence of shock markedly diminishes the effectiveness of solutions of both colloids and crystalloids in producing and maintaining increase in the blood volume level (18, 19, 20).

MATERIAL AND METHODS

The fluids have been administered to patients after surgical procedures and to patients on the medical wards; the compositions of the fluids and the amounts and rates of injection (Table I) include those frequently used in various clinics (21). The ages of the subjects were from seventeen to seventy-one years; 24 were males, 10 females. Thirty of the subjects showed no evidences of renal or cardiac insufficiency; two patients had uremia, one angina pectoris and another compensated rheumatic heart disease. None of the patients had lowered blood pressure or any evidences of shock. The unoperated patients received no food or fluid for fourteen hours before the test; the surgical cases received usual preoperative care for scheduled morning operations, and the effects of fluids intravenously were studied from one to four hours after the operation. To gain information on the state of the blood volume at the time of fluid administration in the operated cases, studies of the concentration of serum protein and of the hematocrit were made in eight patients four hours after lunch on the afternoon before the operation, and the results compared with observations made postoperatively just prior to fluid injection.

The fluids were warmed before injection and administered through the antecubital vein. In some instances blood samples for protein, hematocrit and other measurements were obtained by means of a three-way stopcock attached to the needle through which the fluid was administered; in other cases the samples were drawn from the opposite arm. Before a blood sample was drawn after fluid injection, three to five minutes was allowed for

TABLE I

*Changes in the hematocrit readings, serum protein concentrations, and plasma and blood volumes following fluids, administered intravenously**

Case	Ward†	Sex	Age	Body surface area	Fluid injected		Hematocrit		Serum protein		Control blood volume	Plasma volume increase	Blood volume increase	Remarks
					Amount	Rate	Before injection	After injection	Before injection	After injection				
			years	*square meters*	*cc.*	*cc. per minute*			*grams per 100 cc.*	*grams per 100 cc.*	*cc.*	*cc.*	*cc.*	
5 PER CENT GLUCOSE IN 0.85 PER CENT SALINE														
I. F.	M.	M.	27	1.74	450	37	47.0	42.6	6.27	5.36	4320‡	380	370	
L. C.	S.	F.	39	1.88	500	6	46.0	43.5	6.69	6.38	4220	110	10	
S. G.	M.	M.	17	1.66	500	9	44.2	41.8	7.10	6.40	4800	290	290	
L. P.	M.	M.	32	1.49	500	9	46.8	43.8	6.82	6.00	4020	300	320	
T. A.	M.	M.	38	1.77	500	50	42.9	37.8	6.49	5.22	5420‡	750	750	
O. G.	S.	M.	64	1.85	550	55	50.0	43.5	6.88	5.88	5520	470	200	
J. M.	S.	M.	41	1.66	600	23	40.5		7.73	6.60	4800	490		
M. B.	S.	F.	44	1.55	600	24	27.3	23.6	6.50	5.72	4000	390	320	Study made one day after operation
E. S.	S.	F.	48	1.77	600	24	37.8		8.25	6.80	4200	560		
H. F.	M.	M.	20	1.79	600	27	44.4	40.0	6.05	5.24	5350	460	390	
R. G.	M.	F.	52	1.41	600	30	41.9	35.8	6.08	4.85	3600	530	480	
A. F.	S.	F.	35	1.59	600	40	47.6	39.2	7.56	5.32	4030	890	910	
D. L.	S.	M.	44	1.89	600	60	44.5§		6.59	5.56	5660	570		
A. S.	S.	F.	43	1.81	700	64	46.1	39.0	7.37	5.66	4200	680	620	
F. N.	S.	F.	38	1.67	950	22	39.9	34.1	6.96	5.90	4180	450	320	Compensated rheumatic heart disease
L. P.	M.	M.	32	1.49	1000	9	46.8	43.0	6.82	6.00	4020	330	320	Study after 1st 500 cc. given above¶
S. G.	M.	M.	17	1.66	1000	11	44.2	40.2	7.10	6.00	4800	490	500	Study after 1st 500 cc. given above¶
W. S.	M.	M.	71	1.57	1000	17	39.6	33.6	5.93	4.59	4400	770	780	
H. S.	S.	M.	52	1.83	1000	32	35.9	30.9	6.86	5.58	5460	810	770	
G. H.	M.	M.	22	1.77	1000	36	45.6	39.7	7.19	6.06	5210	530	330	
I. F.	M.	M.	27	1.74	1000	36	47.0	40.6	6.27	4.95	4320‡	610	600	Study after 1st 450 cc. given above¶
I. O.	S.	M.	17	1.66	1000	38	47.7	40.3	7.24	5.44	4800	840	810	
J. Mo.	S.	M.	22	1.82	1000	40	46.4	38.2	7.15	5.34	5400	990	900	
J. S.	S.	M.	25	1.90	1000	43	48.4	43.2	7.47	6.25	5700	560	470	
T. A.	M.	M.	33	1.77	1000	43	42.9	36.6	6.49	5.04	5420‡	890	880	Study after 1st 500 cc. given above¶
M. A.	S.	M.	28	1.72	1000	71	48.0	40.0	7.61	5.59	5060	950	910	
W. S.	M.	M.	71	1.57	1500	16	40.3	35.0	6.03	4.25	4400	1100	1320	This study 2 days after previous one in this case

TABLE I—*Continued*

Case	Ward†	Sex	Age	Body surface area	Fluid injected		Hematocrit		Serum protein		Control blood volume	Plasma volume increase	Blood volume increase	Remarks
					Amount	Rate	Before injection	After injection	Before injection	After injection				
			years	*square meters*	*cc.*	*cc. per minute*			*grams per 100 cc.*	*grams per 100 cc.*	*cc.*	*cc.*	*cc.*	
0.85 PER CENT SALINE														
B. S.	M.	M.	18	1.72	500	55	46.3	41.5	6.77	5.51	5030	610	580	
L. M.	M.	M.	57	1.72	1000	28	24.3	22.5	5.55	5.47	5060	70	−40	Uremia
S. J.	M.	M.	46	1.60	1000	29	30.5	27.8	6.52	5.86	4580	350	320	
R. S.	M.	M.	58	1.95	1000	29	43.2		6.72	5.95	5850	430		Angina pectoris
T. L.	S.	F.	44	1.62	1000	32	38.2	32.2	6.86	5.81	4100	460	320	
B. G.	S.	F.	42	1.89	1000	33			7.26	6.62	4230			
R. C.	M.	M.	37	1.52	1000	35	44.9	40.8	6.98	6.43	4000‡	190	60	
B. C.	S.	F.	57	1.47	1000	37	40.4	34.4	6.79	5.07	3800	770	830	
B. S.	M.	M.	18	1.72	1000	59	46.3	39.8	6.77	5.17	5030	840	830	Study after 1st 500 cc. given above¶
A. So.	M.	M.	52	1.67	1000	67	40.5	35.8	6.39	5.70	4820	340	170	
B. S.	M.	M.	18	1.72	1500	58	46.3	37.9	6.77	4.96	5030	980	880	Studies after 1st 500 and 1000 cc. given above¶
5 PER CENT GLUCOSE														
J. Mc.	M.	M.	45	2.08	1000	53	22.5	19.6	7.18	5.98	6300	980	990	Uremia
A. R.	M.	M.	25	1.76	1000	69	48.1	42.8	7.40	5.83	5200	730	790	
A. R.	M.	M.	25	1.76	1500	61	48.1	41.1	7.40	5.38	5200	1020	1090	Study after 1st 1000 cc. given above¶
3 PER CENT SALINE														
G. Hy.	M.	M.	25	1.83	500	21	40.3	36.3	6.94	5.96	5460	520	480	Buerger's disease, involving one foot

* Plasma and blood volume changes have been calculated from protein and hematocrit findings and control blood volume (Method A).

† Cases designated "S" are surgical patients on whom operations were performed within four hours preceding fluid therapy; cases designated "M" are cases on which no recent operations had been performed and are, for the most part, medical ward cases.

‡ Control blood volume actually measured by "Evans Blue" dye method.

§ Hematocrit estimated from preoperative studies.

¶ In each of these instances two or more studies of the blood changes were made during the continuous injection of a given total volume of fluid.

mixing of the injected fluid. When the blood was drawn through a three-way stopcock, the needle and stopcock were rinsed by withdrawing and re-injecting a few cubic centimeters of blood. In several instances further blood specimens have been obtained from twenty minutes to two and one-half hours after the end of injection. Stasis was avoided in all blood sampling.

The degree of dilution of the blood by the injected fluids has been ascertained by several methods in each subject and the results compared. The concentrations of serum protein before and after injection have been studied in every instance; hematocrits have been measured in almost every instance; red cell counts and hemoglobin measurements have been performed in some cases.

The changes in plasma and blood volume after fluids have been calculated from the control blood volume and the protein and hematocrit findings before and after injection (Method A). In five instances in three patients the blood volume method which employs the azo dye " Evans Blue," as described by Gregerson, Gibson and Stead (22), and modified by Gibson and Evans (17), has been utilized (Method B). The validity of estimations of changes in blood volume obtained by calculation from the control blood volume and the hematocrit readings alone (Method C) has been tested.

Method A. The calculations utilized to obtain the changes in plasma and blood volume from the concentrations of plasma protein and the hematocrits before and after injection were as follows.

1. From the surface area, computed according to DuBois, and the sex of the subject, the control total blood volume was estimated from the chart of normal values of Gibson and Evans (23). In those instances where blood volume was measured by the Gibson and Evans method, the control blood volume obtained from the actual measurement was utilized.

2. The control plasma volume was calculated from the formula:

$$\text{Control plasma volume} = \text{Control total blood volume} \times \frac{\text{Per cent of plasma}}{100}.$$

3. The plasma volume after injection was calculated thus:

$$\text{Final plasma volume} = \text{Control plasma volume} \times \frac{\text{Control protein (grams per 100 cc. serum)}}{\text{Final protein (grams per 100 cc. serum)}}$$

The increase in plasma volume was obtained by subtracting the control from the final plasma volume.

4. The final total blood volume was calculated from the final plasma volume and the final hematocrit thus:

$$\text{Final total blood volume} = \text{Final plasma volume} \times \frac{100}{100\text{–hematocrit}}.$$

The increase in total blood volume was obtained by subtracting the control blood volume from the final blood volume.

Method B. In the experiments where measurements of blood volume by the dye method were performed, the dye injection and samplings were done according to the short "indirect method" described by Gibson and Evans (17). Dr. Gibson kindly coöperated by making the spectrophotometric readings of the concentration of "Evans Blue," and the calculations of volume changes therefrom.

Method C. The total blood volume change was also calculated independently from the initial and final hematocrit readings.

1. The increase in volume of 100 cc. of initially undiluted blood was obtained from the formula:

$$x = 100\frac{C_1}{C_2} - 100$$

where x is the gain in volume per 100 cc. of blood and C_1 and C_2 the percentile cell volumes of the initial and diluted bloods respectively (24).

2. The total original blood volume was obtained as above described.

3. The following formula was then utilized to estimate the total fluid gain to the blood (y):

$$y = \frac{\text{total blood volume}}{100} \times \text{gain in volume per 100 cc. of blood.}$$

The possibility of shrinkage of the cells after injection of hypertonic solution (5 per cent glucose in physiological saline) was investigated by comparing the hematocrit changes with changes in red cell count and hemoglobin in several instances.

Protein concentrations of sera were measured in duplicate by the macro-Kjeldahl method (25), nonprotein nitrogen being subtracted from the total nitrogen. The hematocrit readings of heparinized blood samples were made as described by Rourke and Ernstene (26) and in duplicate. In patients in whom measurements of blood volume were made by the dye method, hematocrit readings represent total cell percentages. Hemoglobin concentrations were measured using the Evelyn microphoto colorimeter (27). Red cell counts were made in duplicate.

RESULTS

The injection of fluids intravenously under the conditions of this study invariably caused lowering of the hematocrit and decrease in the concentration of the serum protein (Table I). When the larger volumes of fluid were injected these changes were at times great, serum protein values frequently decreasing as much as 1.5 to 2.0 grams per cent.

Calculations from the values for protein, hematocrit and blood volume before injection and the protein and hematocrit values immediately after injection (Method A) showed increases in plasma volume in every instance (Table I). The increases in total blood volume were in many cases practically identical with those in plasma volume, but in several instances were somewhat less (Table I).

The average increase in blood volume in 7 cases at the end of injection of a liter of physiological saline solution at the average rate of 41 cc. per minute was 360 cc. The average increase in 11 cases after a liter of 5 per cent glucose in physiological saline at an average injection rate of 34 cc. per minute was 660 cc. Although in general the physiological saline produced a lesser change in blood volume than did the hypertonic solution of 5 per cent glucose in physiological saline, there was considerable overlapping of values in individual instances (Table I).

No exact relationship obtains between increase in blood volume and rate of injection of given volumes of fluid of the same composition in different subjects over the range of rates employed (Table I). However, the fastest rates of injection generally produced the greatest increases in blood volume and the slower rates the smaller increases (Table I, Figure 1).

After the injection of from 450 to 600 cc. of the various solutions at rates above 20 cc. per minute the increases in plasma and blood volume closely approximated the volumes of fluid injected. In two patients in whom 500 cc. (T. A.) and 600 cc.

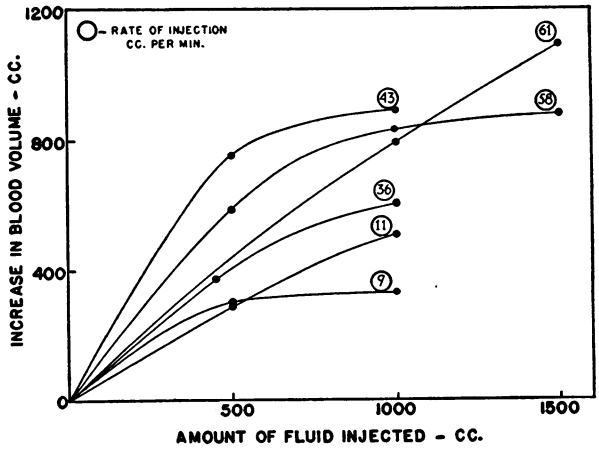

FIG. 1. RELATIONSHIP BETWEEN INCREASES IN BLOOD VOLUME, AS CALCULATED BY METHOD A, AND AMOUNTS OF FLUID INJECTED, IN SIX PATIENTS FROM WHOM SAMPLES OF BLOOD WERE DRAWN AT INTERVALS DURING FLUID INJECTIONS MADE AT RATES OF 9 TO 61 CC. PER MINUTE

Five per cent glucose solution was injected in Case A. R. (61 cc. per minute), 0.85 per cent saline in Case B. S. (58 cc. per minute) and 5 per cent glucose in 0.85 per cent saline in the remaining four cases.

(A. F.) of 5 per cent glucose in 0.85 per cent saline solution were injected at rates of 50 and 40 cc. respectively, the blood volume increases exceeded considerably the amounts of fluid injected (Table I). When 1000 to 1500 cc. of fluid were injected, the blood volume increases were generally considerably less than the amount of fluid injected. This trend of change in blood volume is shown graphically in Figure 1, where data obtained after injection of progressively greater amounts of fluid in six cases have been plotted.

The duration of increased blood volume was investigated in thirteen subjects (Table II) from whom samples of blood for measurements of protein and hematocrit were drawn from twenty minutes to two and one-half hours after the end of fluid injection. These data show considerably elevated blood volumes thirty minutes after injection and appreciable elevations up to about two hours after the end of injection.

In the surgical cases of this study, the immediate effect of intravenous fluid injections on the blood volume and the duration of the changes were similar to the findings in the unoperated cases. The following data and discussion show that most of the operated patients were not markedly dehydrated at the time fluids were administered. Serum protein and hematocrit studies were made in eight patients on the afternoon be-

TABLE II

*Duration of blood volume changes after intravenous injection of fluids**

Case	Fluid injected			Time after end of injection	Serum protein	Hematocrit	Plasma volume increase	Blood volume increase
	Composition	Amount	Time consumed					
		cc.	*minutes*	*minutes*	*grams per 100 cc.*		*cc.*	*cc.*
T.A.†	5 per cent glucose in 0.85 per cent saline solution	1000	23	30	5.77	39.7	380	360
I.F.†		1000	28	30	5.57	43.1	290	240
A.S.		700	11	60		44.2‡		
J.S.		1000	23	60		46.0‡		
J.Mo.		1000	25	90	6.58	43.6	250	200
I.O.		1000	26	90	6.48	44.2	300	250
G.H.†		1000	28	90		45.6‡		
M.A.		1000	15	105	6.81	45.0	300	270
B.S.†	0.85 per cent saline solution	1000	26	20	5.41	40.0	660	560
R.C.		1000	28	120	6.85	43.0	40	−50
T.L.		1000	32	150	6.35	34.5	200	70
S.J.†		1000	34	150	6.33	30.0	100	120
A.R.†	5 per cent glucose	1500	25	30	6.44	46.1	410	560

* Plasma and blood volume changes calculated, by Method A, from control data before fluid injection and data presented here. Values for protein and hematocrit before and at end of injection and for plasma and blood volume increases at end of injection in these cases are available in Table I.

† Unoperated cases.

‡ Because protein concentrations were not measured, changes in plasma and blood volumes could not be calculated in these cases. Blood dilution at the time of these hematocrit studies is evident from comparison of results with the hematocrit readings before injection, namely: A.S., 46.1 per cent; J.S., 48.4 per cent; G.H., 45.6 per cent.

TABLE III

*Changes in concentration of serum protein and in hematocrit following operation**

Case	Period of observation	Serum protein	Hematocrit	Description of operation	Duration of operation	Anesthesia
		grams per cent			*minutes*	
I.O.	Preoperative	7.2	48.0	Appendectomy	35	Gas, oxygen
	Postoperative	7.2	47.7			
E.S.	Preoperative	8.3	38.0	Vulvectomy	60	Ether
	Postoperative	8.3	37.8			
R.F.	Preoperative		39.8	Exploratory laparotomy, appendectomy, suspension of uterus	75	Ether
	Postoperative		40.5			
D.L.	Preoperative	6.4	43.8	Right inguinal herniorrhaphy	50	Spinal
	Postoperative	6.6				
M.A.	Preoperative	7.3	44.0	Incisional herniorrhaphy	60	Spinal
	Postoperative	7.6	48.0			
M.B.	Preoperative	7.1	26.8	Bilateral salpingectomy, hysterectomy, appendectomy, left oophorectomy	120	Ether
	Postoperative	7.5	33.8			
A.S.	Preoperative	6.9	42.7	Repair of large umbilical hernia	50	Local
	Postoperative	7.4	46.1			
A.F.	Preoperative	6.9	42.5	Bilateral salpingectomy, hysterectomy, appendectomy, bilateral oophorectomy	130	Ether
	Postoperative	7.6	47.6			

* Postoperative blood studies were made at variable times up to three and one-half hours after operation. No fluids were administered parenterally prior to the studies; no significant amounts of fluids were taken orally.

fore operation and again at some time during the first three and one-half hours after operation (Table III). The similarity of values before and after operation in the first four cases of Table III, in which the duration of operation was from thirty-five to seventy-five minutes, speaks against any considerable blood loss or dehydration during or immediately following operation; the results in the last four cases, in two of which the operations were relatively extensive and time-consuming, indicate appreciable dehydration at the time of postoperative study. The operations in the remaining surgical cases of Table I were for the most part uncomplicated appendectomies, simple herniorrhaphies or pelvic repairs; presumably then, most of these cases were not appreciably dehydrated prior to fluid injection.

A comparison of the changes in plasma and blood volume as calculated from serum protein and hematocrit findings (Method A) and as obtained by the "Evans Blue" dye method after intravenous fluid administration, in five measurements in three cases, is presented in Table IV. The results are in good accord.

When calculations of blood volume changes from the hematocrit readings alone (Method C) were attempted, many of the results were in satisfactory accord with those obtained in the same experiments by calculation from the protein and hematocrit findings (Method A) and by the "Evans Blue" method. In several instances, however, the increases in blood volume when calculated by Method A were significantly higher than those obtained by the other methods; these instances are represented by those cases of Tables I and IV which show greater increases in plasma volume than in blood volume. In these latter instances, therefore, the decrease in hematocrit was somewhat greater than could be accounted for by the plasma dilution as measured by changes in protein and dye. These discrepancies occurred both in cases receiving isotonic saline and in those receiving hypertonic solution of 5 per cent glucose in physiological saline.[1]

Simultaneous studies of red cell count and hematocrit in three cases and of hemoglobin and hematocrit in two cases failed to reveal shrinkage of the cells after fluid injections (Table V).

[1] Five per cent glucose in physiological saline solution has approximately two times the osmotic pressure of isotonic saline alone.

TABLE IV

*Comparison of increases in plasma and blood volumes after intravenous fluids, as calculated from serum protein and hematocrit findings (Method A) and as found by the "Evans Blue" dye method**

Case	Composition of fluid injected	Amount injected	Increase in plasma volume		Increase in blood volume	
			Calculated from protein and hematocrit findings	Found by dye method	Calculated from protein and hematocrit findings	Found by dye method
		cc.	*cc.*	*cc.*	*cc.*	*cc.*
I.F.	5 per cent glucose in 0.85 per cent saline	450	380	330	370	240
		1000	610	650	600	650
T.A.	5 per cent glucose in 0.85 per cent saline	500	750	620	750	560
		1000	890	660	880	520
R.C.	0.85 per cent saline	1000	190	260	60	170

* Control blood volume as actually measured by dye method used for both calculations. Blood samples were divided for protein, dye and hematocrit measurements.

TABLE V

Comparison of changes in red blood cell count and hemoglobin, with changes in hematocrit after injection of fluids intravenously

Case	Amount of fluid injected*	Plasma† volume increase	Blood volume increase	Hematocrit		Red blood cell count		Mean corpuscular volume	
				Before injection	After injection	Before injection	After injection	Before injection	After injection
	cc.	*cc.*	*cc.*			*per cu. mm.*	*per cu. mm.*	*cu. μ*	*cu. μ*
G.H.	1000	530	330	45.6	39.7	5.17	4.27	0.88	0.93
J.Mo.	1000	990	900	46.4	38.2	5.56	4.61	0.84	0.83
M.A.	1000	950	910	48.0	40.0	5.28	4.74	0.91	0.85
						Hemoglobin		$\frac{\text{Hemoglobin}}{\text{Hematocrit}}$	
						Before injection	After injection	Before	After
						per cent	*per cent*		
I.F.	450	380	370	47.0	42.6	100	90	2.13	2.11
	1000	610	600	47.0	40.6	100	83	2.13	2.04
T.A.	500	750	750	42.9	37.8	96	84	2.24	2.22
	1000	890	880	42.9	36.6	96	81	2.24	2.21

* Composition of fluid injected was 5 per cent glucose in 0.85 per cent saline.
† The plasma and blood volume increases were calculated by Method A.

DISCUSSION

The close correspondence of the changes in blood volume, as estimated by the "Evans Blue" method and by calculation from the serum protein and hematocrit changes (Method A), after intravenous fluids supports the validity of the application of either of these methods to this study. The latter method has been utilized, except for reasons of comparison, because of its relative simplicity; we believe this method to be at least as accurate as the dye method under the conditions of our experiments. Obviously, it would be inadvisable to attempt to utilize the change in protein concentration as a measure of plasma volume increase under conditions other than relatively acute experiments, or under any circumstances which could conceivably cause protein to leave or enter the blood stream. Blalock, Beard, and Thuss (5), by comparing the change in hemoglobin concentration with that in plasma protein concentration, concluded that the total amount of protein of the plasma remained the same after injection of iso-

tonic solutions of crystalloids in dogs with normal blood pressures; the similarity of the percentage decreases in the concentration of albumin and of globulin after the fluid injections in these experiments further indicates no loss or gain of plasma protein. However, in animals with low blood pressure, protein may be washed out of the circulation by intravenous injections of fluids (5).

The apparent small decrease in the total volume of circulating blood cells (inferred from the relatively greater change in hematocrit values than in protein and dye concentrations) in some cases following intravenous fluids as administered in these studies, is of interest. There is no available evidence suggesting that red cells are destroyed by intravenous injections of isotonic or slightly hypertonic solutions. The results of experiments designed to show appreciable shrinkage of the erythrocytes following fluids were negative (Table V). Data of Blalock, Beard and Thuss (5) likewise reveal no significant shrinkage of red blood cells after isotonic or slightly hypertonic solutions of crystalloids in dogs; on the other hand, definite cell shrinkage has been observed after intravenous injections of approximately 40 per cent glucose solutions in dogs (4). From these considerations, it seems probable that at times some cells must leave the circulation under the stimulus of increased blood volume following intravenous fluids; the volume of cells which apparently leaves the circulation is indicated by the degree to which the plasma volume increase exceeds the total blood volume increase in some cases of Table I. Such cell storage when the blood volume is increased is opposite to the release of cells into the circulation observed when the blood volume is lowered by shock or hemorrhage. From this discussion, it appears that a study of the changes in hematocrit, or in hemoglobin alone, after intravenous fluids, may afford only a rough approximation of changes in blood volume after intravenous fluids, even when the solutions injected are isotonic.

The tendency of the curve of blood volume increase to become flat when the blood volume has been elevated approximately 20 per cent by injection of fluids at rapid rates (Figure 1) suggests that the forces which operate to remove fluid from the blood stream are, under the conditions of rational fluid therapy, capable of resisting appreciable further change in blood volume. That increases of blood volume of this order are produced at times in the clinic follows from the fact that single injections of 1000 cc. of isotonic or of somewhat hypertonic solutions (5 or 10 per cent glucose in physiological saline) are, for purposes of simplicity and comfort to the patient, administered frequently at rates of 20 cc. per minute or faster. The cumulative effect of larger volumes of fluids administered at slower rates (Figure 1) (16, 28) suggests that blood volume changes of this magnitude may also obtain in patients receiving continuous drip therapy.

The effects of intravenous administration of isotonic solutions of crystalloids on the blood volume in patients and animals with severe shock are quite different from those observed in the subjects of this study. Cannon has repeatedly stressed the inadequacy of isotonic saline and of Ringer's solution in increasing blood volume in shock (19). It has further been demonstrated experimentally, in dogs in which shock has been induced by continuous intestinal trauma, that not only may the plasma volume fail to increase during intravenous injections of solutions of crystalloids but that an actual decrease in plasma volume may occur and that an additional loss of the plasma protein to the tissue spaces may result (20). The failure of the blood vessel walls to maintain the normal relationship of distribution of plasma and tissue protein in shock is probably the most important single causal factor in the abnormal response to intravenous fluid administration. The rather widespread opinion, which is not compatible with the facts presented in this paper, that, in general, injections of crystalloid solutions intravenously do not cause appreciable changes in blood volume may have arisen from inferences based on findings in shock. It would appear from the data here presented that if intravenous injections of crystalloid solutions must be given in shock, because blood transfusions are not immediately available, the solutions should be hypertonic and administered rapidly in large volume.

The development of edema following repeated intravenous injections of large volumes of saline solutions in surgical patients is not uncommon (16, 29). That the excess volume of fluid in the vascular system following intravenous injections would tend to be transferred to the tissue spaces,

at least temporarily, is understandable. On the basis of available knowledge, the flow of fluid from the blood is enhanced by decrease in the colloid osmotic pressure of the plasma and by increase in venous pressure. That a considerable or, under certain circumstances, a marked decrease in plasma protein concentration occurs after fluids intravenously is evident from the data of this study; that intravenous fluid administration tends to increase venous pressure, at times greatly, is demonstrated by the data of Altschule and Gilligan (30). Both of these factors, together with an increase in the area of filtering surface due to vasodilatation (30), tend toward transfer of fluid to the tissues. Jones and Eaton (16) and Jones, Eaton and White (28) have pointed out that edema following continued intravenous saline therapy is particularly frequent and extensive in patients who have a lowered concentration of plasma protein, due to any cause, before fluid therapy is started. The length of time during which fluids will remain in the tissues after transfer from the blood depends to a large extent on the composition of the fluid injected. The tendency of the body to retain ingested or parenterally administered fluids containing sodium chloride has been stressed repeatedly (29, 31, 32).

Further clinical applications of knowledge gained from the blood volume studies of this report will be discussed in connection with our simultaneous studies of the dynamics of the circulation, in a report to follow (30). On the basis of the blood volume studies alone it may be inferred that in cardiac, elderly, and debilitated patients, intravenous fluids, if not administered slowly and in isotonic solution in barely necessary amounts, may lead to congestion of the lungs and other viscera because of increased blood volume.

SUMMARY AND CONCLUSIONS

1. The effects on the hematocrit, concentration of plasma protein, and blood volume of fluids injected intravenously have been studied in 42 instances in patients not suffering from shock, most of whom showed no evidences of dehydration, or cardiac or renal insufficiency. The compositions of the fluids injected, namely 0.85 per cent saline, 5 per cent glucose, or 5 per cent glucose in physiological saline, and the rates of injection included those utilized routinely in most clinics.

2. The hematocrit and the concentration of serum protein have always been found lowered after the injection intravenously of from 450 to 1500 cc. of fluid.

3. Plasma and blood volume changes have been estimated by three methods: *A*—by calculation from the control blood volume and the protein and hematocrit findings before and after injection, *B*—directly by the "Evans Blue" dye method, and *C*—by calculations from the control blood volume and the hematocrit findings alone. The reliability and the relative merits of these methods have been discussed.

4. Plasma and blood volumes were found increased immediately after the end of injection. In cases receiving a given volume of solution of given composition the greatest increases in blood volume were usually obtained after the faster rates of injection and the lesser increases at the slower rates of injection.

5. The average increases in plasma and blood volume were somewhat greater when the hypertonic solution of 5 per cent glucose in physiological saline was given than after plain physiological saline solution.

6. The per cent of the injected fluid present in the circulation decreased as the volume of fluid injected increased. The data indicate that, after intravenous fluids, the forces which govern the escape of fluid from the circulation normally act to resist increases in blood volume of over approximately 20 per cent.

7. The plasma and blood volumes have been found appreciably increased up to approximately two hours after injections of 1000 cc. of 0.85 per cent saline or of 5 per cent glucose in 0.85 per cent saline at rates of 30 cc. per minute or greater.

8. Operations of the order of uncomplicated appendectomies or inguinal herniorrhaphies do not cause appreciable reduction in blood volume as evidenced by the absence of change in hematocrit and concentration of serum protein after operation; the increase in blood volume after injection of fluids intravenously was not influenced by such operations.

9. The importance of the lowered plasma protein concentration, together with the increased venous pressure and vasodilatation accompanying the elevated blood volume, is discussed in reference to the occurrence of edema following intravenous fluid therapy.

10. It is suggested that pulmonary congestion which occasionally occurs after intravenous fluid injections may result from the rapid increase in blood volume.

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