CHEMICAL, CLINICAL, AND IMMUNOLOGICAL STUDIES ON THE PRODUCTS OF HUMAN PLASMA FRACTIONATION.

VIII. CLINICAL USE OF CONCENTRATED HUMAN SERUM ALBUMIN IN SHOCK, AND COMPARISON WITH WHOLE BLOOD AND WITH RAPID SALINE INFUSION [1,2]

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The present report is concerned primarily with the use of concentrated human albumin solutions, produced from pooled normal human plasma by the method of Cohn and co-workers, (1), in the treatment of shock in man.[3] This work represents a part of a more general study (3) of the circulation in human cases of shock, which has been in progress at Bellevue Hospital, New York City, during the past two years.

In addition, the therapeutic effects of concentrated human albumin will be compared with the effects of whole blood, and of rapid intravenous saline infusion.

Before presenting the results of this investigation, it may be well to define briefly two separate aspects of shock therapy, since the differentiation of these provides the basis of our comparison of the three types of treatment used.

For successful treatment of clinical shock, two things are essential; first, to restore the failing circulation; second, to restore the failing (anoxic) tissues. The circulation can be restored, in most instances, by replacing the deficit in blood volume. The tissues, however, can be restored only by abundant oxygen supply and carbon dioxide removal. For this purpose, the blood must contain adequate amounts of hemoglobin.

To put the matter in its simplest terms, the heart could pump plasma, or even salt solution around the circulation, but neither saline nor plasma will keep tissues alive.

If the blood is anemic, oxygen will be adequately supplied to the tissues only if the cardiac output or total blood flow is proportionately increased above normal. For quantitative discussion of this, we have added the concept of arterial oxygen transport, derived from a scheme presented some years ago by Murray and Morgan (4). This will be considered further below.

MATERIAL

Concentrated human albumin therapy has been given in 12 cases of severe bodily injury, which may be classified as follows:

- 3 cases of multiple compound fractures.
- 1 case of fracture of the pelvis and rupture of the spleen.
- 3 cases of profuse external hemorrhage.
- 2 cases of intra-abdominal injury: one with strangulated hernia, and one with perforation of the duodenum.
- 3 cases of severe burn.

The product used was a solution of human albumin, 25 grams in 100 cc. In 9 instances, the preparation was albumin in saline (both 0.15 and 0.3 molar NaCl); in 3, albumin in 0.3 molar solution of sodium chloride and sodium acetate; in 1 case, both types of preparation were administered.

[1] The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University, with the collaboration of New York University. Additional support for the research was provided by the Commonwealth Fund and the Josiah Macy, Jr. Foundation.

[2] The products of plasma fractionation employed in this work were developed from blood, collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

[3] This study was carried out in order to provide more detailed information on the mechanism of the action of albumin in shock than was possible in the original clinical appraisal (2).

METHODS

The methods of measurement of the circulation, as described in a previous report (3), were used. The following measurements were taken before and at various intervals after injection of the concentrated albumin: (*1*) plasma volume, hematocrit, and serum protein concentration; (*2*) tracings of the pressure contours in the femoral artery; (*3*) right auricular blood pressure, through a long catheter introduced via brachial vein into the right heart; (*4*) simultaneous carbon dioxide content, oxygen content and capacity and pH_s in the arterial blood, and in the mixed venous blood (sampled from the right auricle); (*5*) oxygen consumption and pulmonary ventilation; (*6*) blood lactate. From these measurements, the following data were obtained by calculation: (*1*) total blood volume; (*2*) mean arterial blood pressure; (*3*) oxygen arterio-venous difference; (*4*) cardiac output and stroke volume; (*5*) peripheral vascular resistance; (*6*) pCO_2 and pH_s arterio-venous differences; (*7*) alkali reserve (T40); (*8*) effective arterial oxygen transport to the tissues. In 2 cases, renal circulation was studied by clearance methods.

Because of their particular importance in this study, methods used in determining plasma volume changes and total blood volume changes, and in calculating the amount of albumin retained in the circulation will be briefly outlined.

Plasma volume was measured before and at suitable intervals after injection of the albumin, by the dye dilution method with T-1824 (3), the initial concentration of the dye being obtained by extrapolation of a time-log concentration curve. The corresponding total blood volumes were calculated directly from the arterial hematocrit

TABLE I

Effects of concentrated human albumin injection upon blood volumes in 12 cases of shock

Patient	Type of injury	Hemorrhage between determinations	Albumin: Variety	Albumin: Injected	Albumin: Retained	Albumin: Time after injection	Total crystalloid solutions	Serum protein concentration: Before	Serum protein concentration: After	Hematocrit: Before	Hematocrit: After	Plasma volume: Initial total	Plasma volume: Observed increase†	Plasma volume: Increase per gram of albumin retained
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
				grams	*grams*	*hours*	*cc.*	*grams per cent*	*grams per cent*	*per cent cells*	*per cent cells*	*cc.*	*cc.*	*cc.*
S. H.*	Bilat. frac. tibiae	+	S	34	19	2:45	795	6.3	6.1	37	28	2210	460	24.2
					23	5:15	300		6.1		28		535	23.2
W. C.	Fr. humerus, ribs, pelvis, tibia, pnx.	+	S	63	35	1:45	1150	4.5	5.2	34	27	2070	400	11.4
						5:15	345		5.4		28		370	
H. S.	Fr. pelvis, ankles, bilateral fr. os calci	+	A	50	34	1:30	350	5.0	5.3	32	20	1390	640	18.8
		+	A	46	27	2:15	365	5.3	5.6	20	15	1940	410	15.2
T. L.	Rupt. spleen, fr. pelvis	++	S	66	8	3:15	1285	6.0	5.8	41	27	1700	400	50.0
B. S.*	Lacer. of neck, wrist	0		47	41	3:15	1355	6.8	6.1	38	29	2160	1075	26.2
			S			8:30	750		6.1		29		1185	
					25	36:00	0		5.7		30		835	33.4
S. C.*	Rupt. varicose veins	0	S	70	62	3:15	1150	5.1	5.4	36	26	1960	1140	18.4
					68	25:15	0		5.2		23		1380	20.3
W. K.	Lacer. of radial artery	0	A	46	36	1:00	310	5.3	5.7	36	31	3010	480	13.3
M. C.	Perforated peptic ulcer	0	S+A	72	38	2:30	440	6.0	5.8	64	48	1330	760	20.0
M. G.	Strangulated hernia	0	S	20	9	1:00	655	9.0	8.5	48	43	2160	300	33.4
J. O.*	2nd degree burns, 20 per cent B.S.	0	S	95	73	2:15	2235	6.5	6.3	60	45	1510	1290	17.7
					24	12:15	300		5.7		52		750	31.2
L. V.	2nd, 3rd degree burns, 20 per cent B.S.	0	S	44	19	3:30	835	4.9	4.7	45	34	1560	635	33.4
J. C.*	2nd degree burn, 20 per cent B.S.	0	S	46	31	6:00	185	5.4	5.7	47	39	1610	480	15.5

* Determination by Howe-Kjeldahl method.

† After correction for blood sampling between determinations.

readings. It should be noted that the total blood volume so calculated assumes that the hematocrit in large and small blood vessels is the same. In calculating plasma volume and total blood volume changes, figures were corrected for blood samples taken in the interval. Serum protein concentrations were calculated from the serum specific gravity, obtained by the falling drop method. The total circulating protein was calculated as the product of plasma volume times the serum protein concentration. Protein loss due to sampling and in some instances to bleeding, was calculated according to a method described elsewhere (3). The net protein increase between the initial and any subsequent measurements was then assumed to measure the amount of albumin retained. To test the validity of this assumption, in 5 of the 12 cases studied, the total protein nitrogen and albumin/globulin ratio were determined by the combined Kjeldahl and Howe technics before and after injection of a known quantity of concentrated albumin. It was found in each instance that the increase in total circulating protein was entirely accounted for by the increase in the albumin fraction; the total circulating globulin remained constant, although its concentration decreased. It has been assumed that each 100 cc. of concentrated albumin solution contained 25 grams of albumin.

RESULTS

I. Influence of concentrated human albumin therapy upon plasma volume, hematocrit, and serum protein

Table I summarizes the results of the 12 cases reported. In the first 2 columns, they are classified according to type of injury. Under the third column, note is made whether or not further blood loss occurred, during albumin therapy. This was in all instances confirmed by operation, autopsy findings, or development of a visible hematoma. In the next columns (4, 5, 6, 7, 8) are tabulated the variety of preparation used, amount of albumin injected, amount of albumin retained, amount of crystalloid solution introduced intravenously between blood volume determinations, and interval of time between studies. A double entry is made of Patient H. S., who received albumin in 2 separate doses and was thus studied twice.

In columns (9, 10) under serum protein concentration, the figures entered were obtained at the time of dye injection. In the column (14) "observed increase" in plasma volume, the figures are net changes, from direct reading, after allowance was made for intervening blood samplings.

The data reported in Table I may be summarized as follows:

In the cases of skeletal trauma and hemorrhage with evidence of further bleeding after albumin therapy had been started, there was a sizeable loss of albumin. In cases of burns and peritonitis, with exudation of protein-rich fluid, there was also considerable loss of albumin.

On the other hand, in the 3 cases (B. S., S. C., W. K.,) where there had been no further blood loss and no protein-rich exudation, the several determinations in the table suggest that the albumin was almost wholly retained, and later disappeared slowly from the circulation. On the basis of available data, there appeared to be no difference between the "saline-treated" (S) and "acetate-treated" (A) albumin from the point of view of the retention in the blood stream.

In general, the serum protein concentrations tended to remain about the same before and after albumin administration (Figure 1). Since the average serum protein concentration before treatment was less than normal, this suggests that the blood was diluted, by fluid retention or absorption from tissues, to this previously existing level. In the individual case, however, there was no constant correlation between the initial level of serum protein and the degree of dilution per unit dose of albumin. The amounts of intravenous saline may have contributed to this dilution. But here again there was no correlation between degree of blood hydration following treatment, and the amount of saline that had been given. The smallest volumes of saline given were 185 cc. in a case of burn, and 310 cc. in a case of hemorrhage. There was no seriously dehydrated patient, so that our series of cases probably did not test the limiting capacity of the concentrated albumin to draw fluid from tissues into the blood stream.

The average amount of blood volume increase per gram of albumin *retained* was 23 cc. This compares with 17.4 cc. per gram of albumin *given*, for the series of normal subjects reported by Heyl, Gibson, and Janeway (5) and with 18 cc. per gram obtained by Scatchard, Batchelder and Brown (6) by *in vitro* measurement of osmotic pressure.

In the cases showing hemodilution, the total

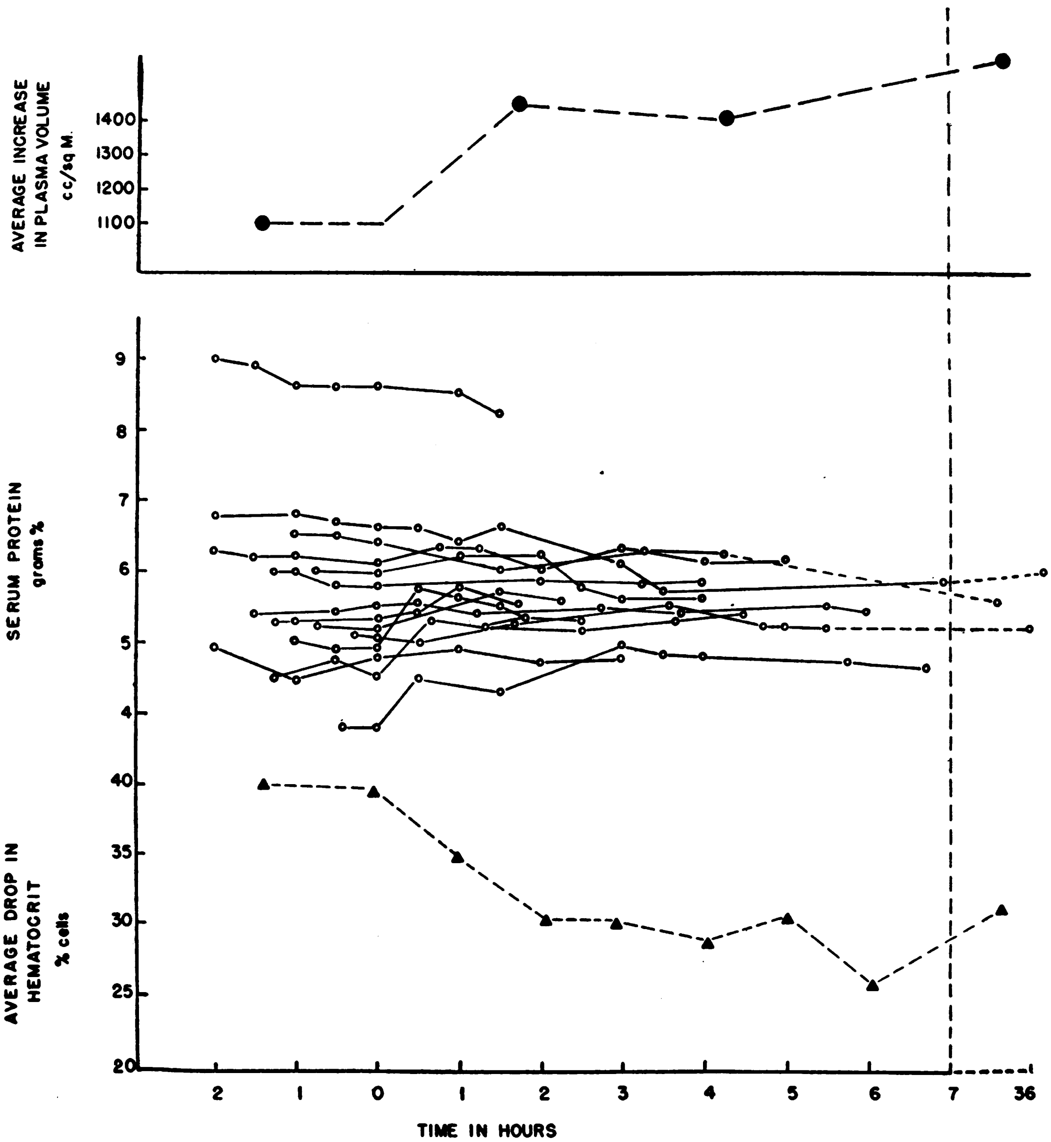

FIG. 1. PLASMA VOLUME, SERUM PROTEIN CONCENTRATION AND HEMATOCRIT VALUES IN 12 CASES OF INJURY WITH SHOCK, BEFORE AND AFTER TREATMENT WITH CONCENTRATED HUMAN ALBUMIN

The albumin was given at zero time on the horizontal scale.

blood volume calculations before and after treatment accounted very satisfactorily for the total red cell volumes. Calculation in the 3 cases of external hemorrhage, for example, gave nearly the same red cell volumes before and after albumin therapy; in the 3 cases that had hemoconcentration, however, there were considerable discrepancies, apparent losses of 160 cc., 180 cc., and 280 cc. of red cells per square meter of body surface being calculated after treatment, when there had been no evidence of further hemorrhage. This discrepancy has been encountered before in the presence of hemoconcentration and is being studied further. It should also be noted that 2 cases (W. C. and B. S.) received small amounts of whole blood during the time of initial study, since the condition of the patient was poor and it was felt that it was necessary to give some immediate therapy to sustain the circulation at this time.

The increase in blood volume brought about by the albumin injected was still maintained at the end of the period of observation, usually 6 hours; the plasma protein concentrations showing little change. This is well illustrated in Figure 1.

II. Effect of concentrated human albumin therapy upon the dynamics of the circulation and arterial oxygen transport

In appraising various treatments of peripheral circulatory failure, recent emphasis has rightly shifted from improvement in arterial blood pressure, to the restoration of blood volume, thereby improving auricular pressure (an approximate index of venous return) and cardiac output.

For relief of tissue anoxia, however, the essential requirement is an increase in the amount of oxygen supplied to the tissues. The "arterial oxygen transport," or cardiac output times oxygen content of arterial blood, expresses this function (4). Murray and Morgan used for this function the term "oxyhemoglobin flow."

In Table II are given individual measurements of the circulation and of arterial oxygen transport in 11 cases, before and after albumin treatment. With 2 exceptions, these cases presented evidence of severe peripheral circulatory failure, before treatment.

In 9 of the 11 cases, significant amounts of albumin were retained in the circulation following injection, with an associated increase in plasma volume. In all these cases, there were: (*1*) a rise in auricular pressure; (*2*) considerable increase in cardiac output; (*3*) increase (though

TABLE II

Measurements of the circulation and of oxygen transport in 11 cases before and after treatment with concentrated human albumin

Patient (body surface)	Diagnosis	Degree of shock	Fluid replacement		Blood volume			Auricular pressure	Cardiac output	Arterial mean press.	Peripheral resistance	Arterial oxygen transport	O_2 consumption
			Albumin retained	Crystalloid solution	Plasma*	Total	Hemat.						
Normal values			0	0	600	2800	43	35	3.2	95	1300	550	150
			grams	*cc.*	*cc. per sq. M.*		*per cent*	*mm. H_2O*	*L. per minute per sq. M.*	*mm. Hg*	*dynes cm.$^{-5}$ second*	*cc. per minute per sq. M.*	
S. H. (1.70)	Bilat. fract. tibiae	+	19	795	ā 1300 p̄ 1510	2060 2100	37 28	+10 +27	3.13 4.21	80 77	1160 810	429 493	146 177
W. C. (1.75)	Fract. humerus, ribs, pelvis, tibia, pnx.	+++	35	1150	ā 1180 p̄ 1440	1800 1990	34 28	+2 +6	2.17 4.29	59 66	1240 700	245 408	187 274
H. S. (1.63)	Fract. pelvis, ankles, bilateral fr. os calci	+++	61	350	ā 850 p̄ 1400	1260 1670	32 16	−3 +17	1.24 4.24	38 88	1500 1020	146 271	114 131
T. L. (1.80)	Rupt. spleen, fract. pelvis	+++	8	1285	ā 950 p̄ 1090	1600 1490	41 27	−4 +1	1.97 2.36	52 64	1170 1205	294 252	177 168
B. S. (1.60)	Lacer. of neck, wrist	+	43	1355	ā 1350 p̄ 1970	2170 2740	38 29	−26 −8	2.69 4.33	100 100	1840 1160	342 459	137 160
S. C. (2.00)	Rupt. varicose veins	++	62	1150	ā 980 p̄ 1500	1530 2030	36 26	+4 +59	2.00 4.50	74 91	1420 810	270 491	164 212
W. K. (1.84)	Lacer. of radial artery	++	36	310	ā 1690 p̄ 1870	2560 2710	37 31	+20 +46	2.40 3.31	39 45	710 590	353 427	175 179
M. C. (1.69)	Perforated peptic ulcer	+++	38	440	ā 790 p̄ 1210	2180 2320	64 48	−18 +65	1.33 2.73	90 106	3200 1830	298 470	152 139
M. G. (1.56)	Strangulated hernia	+++	9	655	ā 1440 p̄ 1600	2830 2810	49 43	+24 +22	1.65 1.87	79 91	2450 2490	312 326	165 170
J. O. (1.81)	2nd, 3rd degree burns, 20 per cent B.S.	++	73	2235	ā 840 p̄ 1500	1990 2740	58 44	+5 +105	2.00 6.85	90 104	1910 620	417 1110	119 205
L. V. (1.67)	2nd, 3rd degree burns, 20 per cent B.S.	++	18	835	ā 930 p̄ 1180	1700 1790	45 34	−5 +14	1.83 4.24	79 65	2070 734	322 560	152 165

* As calculated directly from optical density readings.

less consistent) in arterial blood pressure; and (4) decrease in peripheral vascular resistance. These changes were associated with marked clinical improvement. No unfavorable side-effects were noted.

In 2 cases, T. L., who continued to bleed profusely, and M. G., who lost plasma protein into peritoneal exudate, there was no appreciable retention of albumin in the circulation and no increase in blood volume, in auricular pressure, or in cardiac output. Clinically, these patients were not improved.

One statistical value in this series is of interest. The coefficient of correlation between the amount of albumin retained in the circulation, and the increase in cardiac output, had the extraordinarily high value of $r = +0.928$ ($P < 0.0004$).

So far as oxygen supply to the tissues is concerned, it will be seen from the last 2 columns in Table II, that in all cases which improved, both an increase in oxygen consumption and an effective increase in arterial oxygen transport were found. However, it will also be noted that the cardiac output, in 7 of the 9 cases, was actually increased above normal values.

III. Description of individual cases

This first patient, with extremely severe skeletal trauma, in profound shock, received very large amounts of concentrated human albumin.

Case 1. H. S., a 48-year-old white female, jumped from a third story window, and sustained bilateral fractures of os calci, fracture of the ankles, of the pelvis through the sacrum and of the transverse processes of several lumbar vertebrae. She was first admitted to the psychopathic ward and one hour later was transferred to the emergency ward.

The first series of measurements was completed 3½ hours after injury. The patient was mentally depressed, answering questions clearly, however, and complaining of thirst. There was marked pallor of the skin, and coolness of the extremities. Sweating of the forehead and cyanosis of the lips and ears were noted. Peripheral veins were collapsed, and upon exposure the median basilic vein was found in a state of active constriction. As seen in Figure 2, the arterial blood pressure, which was low on admission, remained unchanged. There was marked reduction in the blood volume to about 50 per cent of normal, with a hematocrit of 32 per cent, and plasma protein level of 5 grams per cent. Other hemodynamic findings were: low auricular pressure, and a very low cardiac index and stroke volume, respectively reduced to 1.24 liters per minute per square meter of body surface, and 18 cc. per beat. The oxygen arterio-venous difference of 96 cc. per liter of blood circulating was high and the oxygen consumption, low. As observed in other cases studied relatively soon after injury, the arterial blood pH_s was only moderately decreased, to 7.32, but the pH_s arterio-venous difference of 0.06 was abnormally large. Ventilation was slightly elevated, the pCO_2 arterio-venous difference was 9 mm. Hg. Blood lactate was 23 mgm. per cent. The arterial blood oxygen saturation was normal. There was complete anuria, suggesting greatly reduced renal circulation (3).

Two 100 cc. ampules (50 grams) of concentrated human albumin in saline-sodium-acetate solution and an additional 150 cc. of an isotonic saline solution were injected in the next half hour. Although pallor and coolness of extremities still persisted, the general appearance was then somewhat improved. A second series of measurements, completed about 2 hours after the first, showed: (*a*) a rise in arterial blood pressure and (*b*) an increase of plasma volume of 340 cc. per square meter of body surface, with a significant reduction in total red cell volume; as previously discussed, there was indication that active bleeding was still taking place. The total blood volume had increased by about 20 per cent over the first measurement. The hematocrit was down to 20 per cent; the plasma protein had increased slightly (see Table I). There was significant increase in auricular pressure and an increase in cardiac index to 2.20 liters per minute per square meter of body surface. The oxygen consumption was still low, but the oxygen arterio-venous difference had diminished to 51 cc. per liter of circulating blood. With the improvement of circulation, arterial pH_s returned to the normal figure of 7.39 and the blood lactate decreased to 13.5 mgm. per cent. Urine flow began but measured only 0.06 cc. per minute, indicating some increase in renal blood flow and filtration, although if one may judge from a previous study on correlation between urine flow and clearance (3), the renal circulation must still have been small.

During the next hour, 2 more ampules (50 grams) of concentrated human albumin and 180 cc. of isotonic crystalloid solution were injected. The general appearance improved considerably, although pallor of the skin was still present. A hemic murmur became audible, loudest at the pulmonic area. After an interval of 1 hour, a third series of measurements was taken. The mean arterial blood pressure had increased to 88. The plasma volume was almost back to normal. No further bleeding had apparently taken place (see Table I), but because of the previous loss of red blood cells the total blood volume was still low. The hematocrit had reached the very low level of 16 per cent; the plasma protein had increased very slightly (see Table I). Obviously, a large amount of fluid had been shifted from the extravascular compartment into the circulating blood. Auricular pressure was maintained at an almost normal level and the cardiac index had increased to 4.24 liters per minute per square meter of body surface, a value appreciably above normal. The oxygen arterio-venous difference was low at 31 cc. per liter of blood and the oxygen consumption had increased by about 15 per cent. The alkali reserve (T40), slightly diminished at the time of the first studies, was now somewhat above the upper

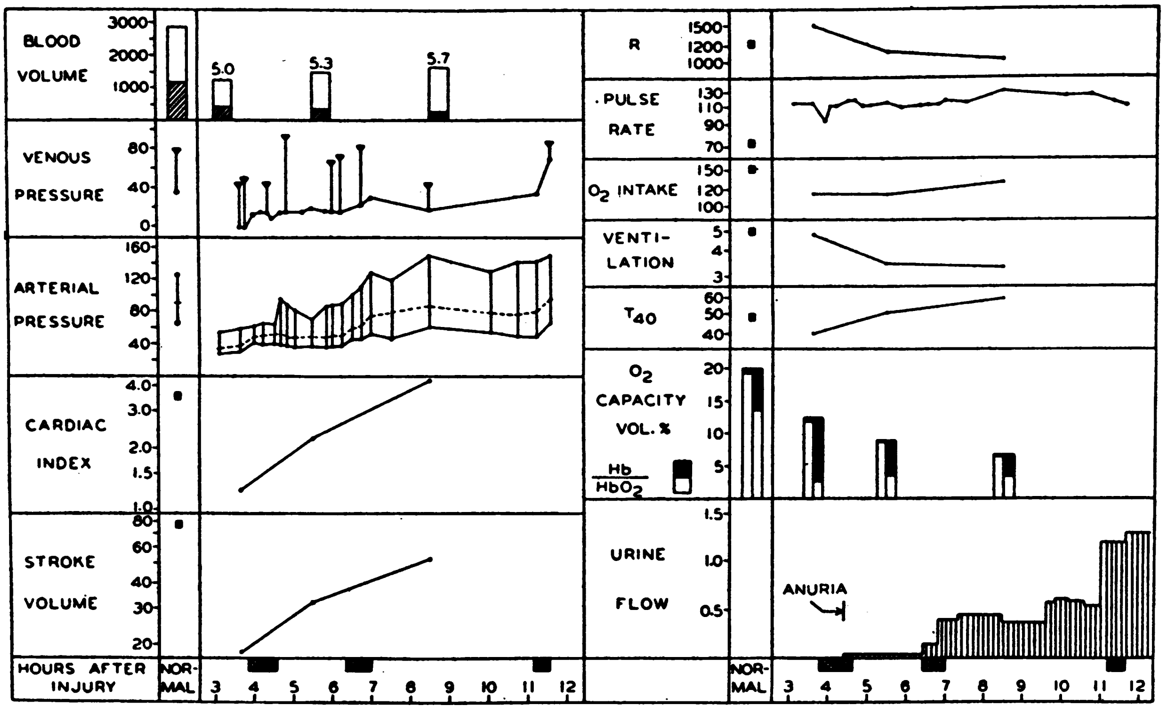

FIG. 2. MEASUREMENTS OF THE CIRCULATION IN THE COURSE OF TREATMENT OF H. S., A CASE OF SEVERE SHOCK DUE TO MULTIPLE FRACTURES

In blood volume section, unshaded blocks = plasma volume cc. per sq. M. of body surface; shaded blocks = red cell volume; figures at top of columns = serum protein per cent. In venous pressure section, triangles = arm venous pressure, mm. of H_2O; solid dots = right auricular pressures. Arterial pressures are recorded as systolic, diastolic, and mean. Cardiac index = cardiac output as liters per minute per sq. M. of body surface. R = peripheral resistance. O_2 intake = oxygen consumption in cc. per minute per sq. M. of body surface. Ventilation = pulmonary ventilation in liters per minute per sq. M. of body surface. T40 = whole blood CO_2 content at 40 mm. CO_2 tension. The double columns in the O_2 capacity section represent: on the left, arterial blood, with solid block indicating reduced hemoglobin, unshaded block oxygenated hemoglobin as cc. oxygen per 100 cc. blood; the right half-column indicates similar values for mixed venous blood.

The symbols nearest the scales are normal values, for comparison. At the bottom is a time scale indicating hours after injury. The cross hatched blocks at the bottom are the times when albumin was administered; the solid block, whole blood transfusion.

level of normal range. Following the second dose of albumin, the urine flow increased to 0.4 cc. per minute, parallel to the improvement in general circulation during this time. About 1½ hours after the third series of general measurements, inulin and p-aminohippurate clearances were measured and found to average about 75 cc. and 500 cc. per minute, respectively, at a time when the mean arterial pressure was 78 mm. Hg. These are approximately 65 per cent and 80 per cent, respectively, of normal.

Because of the very low hematocrit, 500 cc. of blood were transfused before transferring the patient to the operating room. From then on, she did quite well, and eventually recovered. Renal plasma clearances of inulin and hippurate were measured again 28 hours after injury and were found to be well within the normal range.

Besides exhibiting the usual findings of profound shock, due to loss of blood following multiple fractures, this case presented the following interesting features: (*1*) the large increase of plasma volume following injection of concentrated human albumin (plus a small amount of crystalloid solution); (*2*) the extreme degree of anemia, induced by hemorrhage and precipitated by large shift of water to, or retention in the circulation as a result of albumin therapy; (*3*) a cardiac output increase above normal and out of proportion to total blood volume and oxygen consumption increase; (*4*) the high alkali reserve observed after completion of albumin therapy which is probably accounted for simply on the basis of the large ratio of plasma to red cells, due to the acute anemia, and not related to the alkali (sodium acetate) present in the albumin solution; and (*5*) prompt reversal of the shock-induced renal ischemia.

In brief, this patient, in advanced shock from injury and loss of blood, was brought out of shock by the use of large amounts of albumin; and passed then into a state of severe but compensated acute anemia, with increased cardiac output, making up in part for loss of hemoglobin.

The second case was one of shock developing in a patient following perforation of a peptic ulcer, with marked hemoconcentration.

Case. 2. M. C., a 43-year-old white female, was first diagnosed as an acute pancreatitis on the basis of: acute onset of severe pain localized to the epigastrium, extreme tenderness around the umbilicus with localized skin cyanosis, rigidity, and rebound tenderness, no x-ray evidence of air under the diaphragm or of intestinal distension, and no history of peptic ulcer. She was first studied 29 hours after the onset of pain.

The patient appeared mentally alert and restless. The extremities were cold, clammy, and cyanotic, the pupils markedly constricted; she had been vomiting. The peripheral venous pressure and the mean arterial pressure were normal, but the pulse pressure was decreased. This contrasted, as shown in Figure 3, with marked changes in other measurements of the circulation, namely, reduction in plasma volume to about 50 per cent of normal; marked hemoconcentration, and slightly low plasma protein concentration; decrease in the total blood volume to about 75 per cent of normal; considerable decrease in auricular pressure; very low cardiac output and stroke volume, respectively, 1.33 liters per minute per sq. M., and 14 cc. per beat. The oxygen arterio-venous difference of 114 cc. per liter of circulating blood was very large and the oxygen consumption, in spite of elevation of the central body temperature, was only 152 cc. per sq. M. The other measurements indicated a large increase in ventilation, with a pCO_2 arterio-venous difference of 9 mm. Hg. The alkali reserve was low, the pH was normal, the blood lactate was elevated to 30 mgm. per cent, the arterial blood oxygen saturation was normal.

Within the next 1½ hours, 3 ampules of concentrated human albumin (75 grams) were injected with an additional 150 cc. of isotonic saline solution. A second series of studies was begun one half hour after completion of the infusion. Cyanosis had then disappeared, the extremities were pink and warm, sweating and restlessness were no longer present. The arterial blood pressure was 130/87. The blood volume studies showed a large increase in plasma volume, a decrease of the hematocrit from 64 to 48, and a small increase in total blood volume. Blood volume determinations recorded an apparent loss from the blood stream of 280 cc. of red blood cells, although there was no evidence of hemorrhage. This discrepancy, already referred to above, accounts for the lack of any larger increase in total blood volume. In spite of this small change in total blood volume, as recorded, the cardiac output had doubled. The peripheral resistance, although still elevated, was much lower than previously. The hyperventilation had partly subsided. The alkali reserve was slightly low, the blood lactate was still approximately 30 mgm. per 100 cc., the pH_s was normal.

Improvement persisted for 4 hours, and as the diagnosis

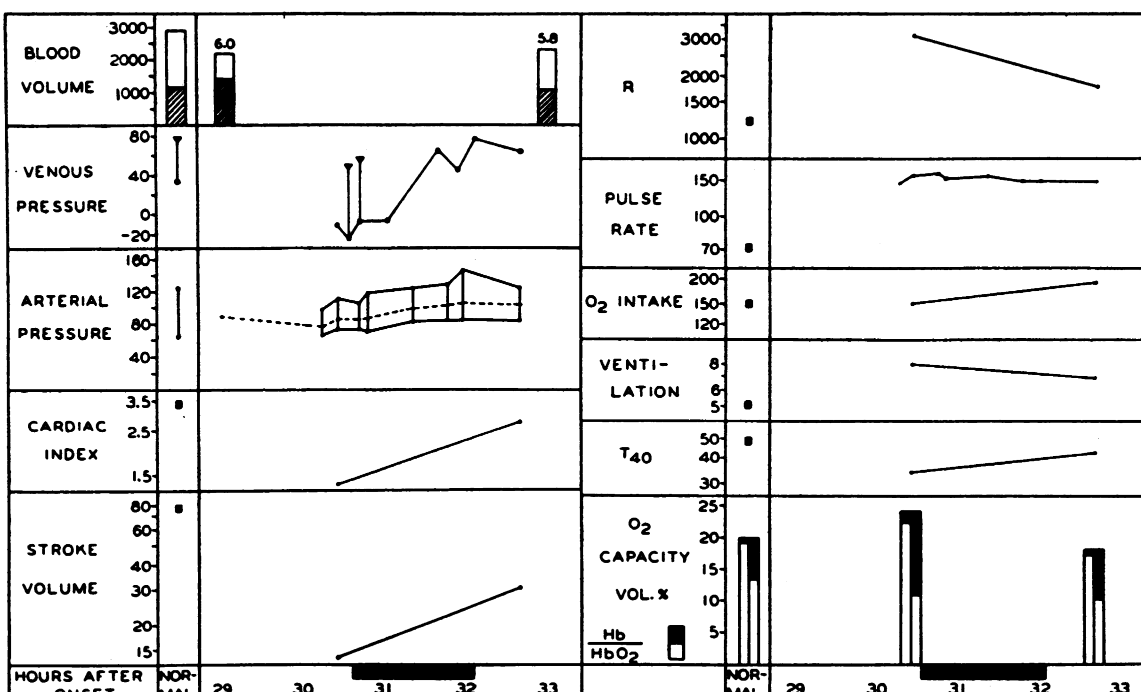

FIG. 3. CASE OF M. C., SEVERE SHOCK FOLLOWING PERFORATED PEPTIC ULCER

For explanation of symbols, see legend under Figure 2.

TABLE III

Measurements of the circulation and of oxygen transport in 10 cases before and after whole blood transfusion

Patient (body surface)	Diagnosis	Degree of shock	Fluid replacement: Blood: Transfused	Fluid replacement: Blood: Retained*	Fluid replacement: Crystalloid sol.	Blood volume: Plasma	Blood volume: Total	Blood volume: Hemat.	Auricular pressure	Cardiac output	Arterial mean press.	Peripheral resistance	Arterial oxygen transport	O2 consumption
			cc.	*per cent*	*cc.*	*cc. per sq. M.*	*cc. per sq. M.*	*per cent*	*mm. H_2O*	*L. per minute per sq. M.*	*mm. Hg*	*dynes cm.$^{-5}$ second*	*cc. per minute per sq. M.*	*cc. per minute per sq. M.*
C. C.	Fract. pelvis	+++				1300	1950	30	0	1.82	22	567	186	164
(1.70)			850 500 (pl)	82	200	1950	2790	30	+20	2.66	60	1060	282	190
W. Bl.	Fract. pelvis, torn	+++				1130	1670	32	−5	1.26	36	1250	126	93
(1.82)	urethra		1230	100	1400	1520	2300	34	+18	2.76	72	1145	315	110
M. M.	Fract. pelvis, ribs	+++				1050	1550	32	+16	1.75	46	1430	220	149
(1.47)			1270	83	1010	1460	2240	35	+71	3.95	90	1240	561	216
V. B.	Fract. extrem. skull,	+++				1570	2240	30	+30	1.84	50	1440	201	152
	ribs, lac. scalp, brain, lung		270	100	650	1770	2530	30	+60	2.91	53	940	294	198
J. V.	Fract. limbs, pelvis,	+++				1020	1620	37	−10	1.30	43	1468	190	131
(1.80)	ribs, hematoma		970	68	1330	1330	2080	36	0	3.16	87	1215	427	178
J. E.	G-I hem.	++				1240	2000	36	−31	2.99	60	1145	389	223
(1.41)			380	80		1360	2210	38	−31	2.96	85	1640	438	206
C. F.	Severe lacerations	++				850	1410	40	+24	1.38	60	2200	202	119
(1.58)			690	65	910	1180	1860	37	+64	2.26	100	2240	341	129
H. M.	G-I hem.	++				1380	1960	30	+20	1.96	32	828	229	130
(1.58)			840	100	1380	1680	2540	34	+22	2.24	38	861	289	132
A. H.	G-I hem.	+++				1150	1440	20	+10	1.69	50	1060	134	95
(1.70)			815	100		1350	1850	27	+40	2.57	28	915	275	129
A. S.	G-I hem.	+++				1180	1500	21	+7	1.58	28	2000	134	109
(1.51)			775	100	1145	1620	2210	27	+72	3.35	85	1560	342	126

* Approximate estimate on the basis of calculated increase in circulating red blood cells.

of acute pancreatitis still appeared most probably correct, operation was deferred. Tympanism in the lateral decubitus, suggesting air under the diaphragm, appeared later, but by that time, the patient had taken a turn for the worse and death with hyperthermia occurred 48 hours after the onset of pain.

The autopsy revealed a perforation of the duodenum with acute peritonitis and extension of the inflammation to the right diaphragm and to the pleura.

The special features of this form of shock, developing after rupture of a viscus, with peritonitis, were as follows: (*1*) persistence of a normal mean arterial blood pressure with a small pulse pressure in spite of a considerable reduction in cardiac output, indicating a marked increase in peripheral vascular resistance; (*2*) marked hemoconcentration with only slightly lowered protein content of the serum; (*3*) persistence of a normal pH_s in spite of an elevated blood lactate, probably associated with a loss of chloride through vomiting.

From the point of view of concentrated human albumin therapy, the same outstanding features noted before are again present: increase in cardiac output, out of proportion to total blood volume and oxygen consumption increase, and marked decrease in peripheral resistance.

The immediate response to concentrated albumin administration was excellent, with increase in plasma volume, auricular pressure and cardiac output, and decrease in hematocrit and peripheral resistance.

IV. Comparison of concentrated albumin therapy with treatment by (1) rapid saline infusion and (2) whole blood transfusion

(*1*) For purposes of comparison with concentrated albumin therapy, 6 clinical cases have been selected from our data showing the effects on the circulation of rapid intravenous saline infusion. The group is not very homogeneous, either as regards severity of shock or uniformity of treatment. Three cases received saline only, the amounts varying from 1515 cc. to 1930 cc. One of these was in severe shock, the other 2 were injuries with little or no shock. The other 3 cases received also some whole blood by transfusion, but blood volume studies indicated that little or none of this whole blood was retained in the circulation, as the patients were bleeding. Despite these variations in the conditions of study, the effects of treatment on the circulation were the same in each of these small sub-groups, so that the average results, as given in Table IV, can be said to indicate the trend.

Saline infusion, in these 6 cases, produced a relatively small increase in plasma volume, the figures varying from 10 cc. to 350 cc. per sq. M. of body surface; a small decrease in hematocrit; relatively large increase in cardiac output; small increases in auricular pressure, oxygen consumption, and arterial oxygen transport. In two subjects, repeated measurements carried out an hour or two later (not shown in Table IV) indicated that the cardiac output had begun to fall again; and blood transfusion was then given.

Thus, with saline infusion, one finds, as one would anticipate, a much lesser degree of improvement in the circulation, and less sustained, than with concentrated albumin solution, although on an average, the various changes that do occur are of the same pattern with saline as with albumin. It should be noted that saline infusion does temporarily raise cardiac output, more than one would expect from the small change in blood volume.

(*2*) Measurements of the circulation in 10 cases of injury, treated with whole blood transfusion, are given in Table III.

There were 5 patients with severe skeletal trauma and 5 with hemorrhage, either internal or external. All were suffering from moderate or severe shock. The amount of blood transfused ranged, in 8 cases, from 680 cc. to 1270 cc.; 2 cases received approximately 300 cc. of blood. Variable amounts of crystalloid solution were also administered. Most of the red blood cells given during transfusion were retained, according to

TABLE IV

Comparison of average hemodynamic response and increase in oxygen transport following treatment with (a) albumin, (b) blood, (c) isotonic saline solution

Type of therapy		No. of cases		Average total blood volume	Average hematocrit	Average auricular pressure	Average cardiac output	Average oxygen consumption	Arterial oxygen transport	Peripheral resistance
				cc. per sq. M.	*per cent*	*mm. H_2O*	*L. per minute per sq. M.*	*cc. per minute per sq. M.*		*dynes cm.$^{-5}$ second*
ALBUMIN*										
Injected alb.	66 grams	6	Initial	1863	36	0	2.27	154	298	1212
Retained alb.	42 grams		Final	2207	26	+27	4.15	189	425	845
Added crystalloid	852 cc.		Diff.	+344			+1.88	+35	+127	−367
BLOOD										
Infused blood	809 cc.	10	Initial	1734	31	+10	1.76	137	201	1339
Retained blood	88 per cent		Final	2261	33	+41	2.88	161	356	1282
Added crystalloid	921 cc.		Diff.	+527		+31	+1.12	+24	+155	−57
CRYSTALLOID SOLUTION										
Infused	1644 cc.	6	Initial	2070	37	+37	2.81	154	379	1318
			Final	2234	32	+57	3.94	170	487	1157
			Diff.	+164		+20	+1.13	+16	+108	−160

* Albumin, 6 cases. Including only those with either skeletal trauma or hemorrhage. See text.

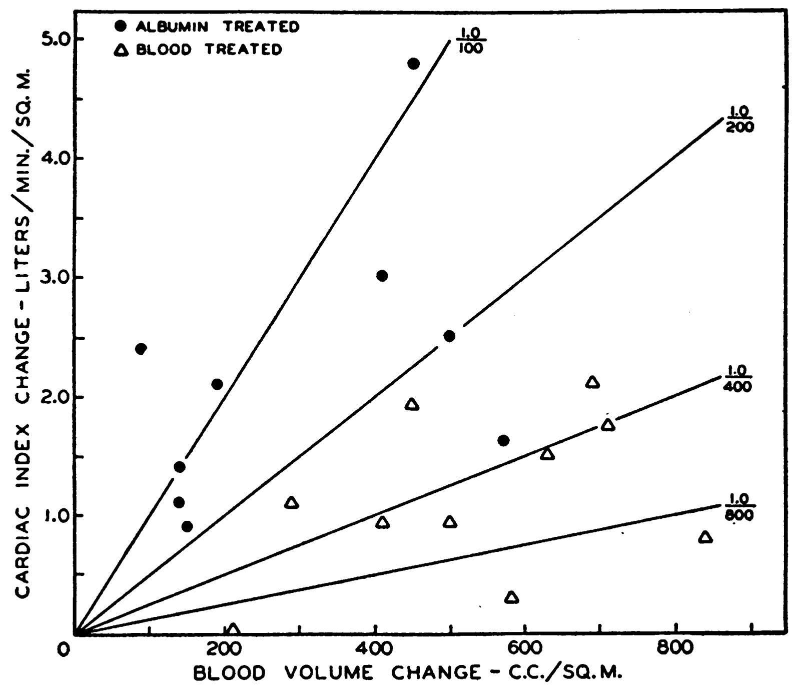

FIG. 4. RELATION OF BLOOD VOLUME CHANGE TO CARDIAC OUTPUT CHANGE, FOLLOWING ALBUMIN (SOLID DOTS), AND WHOLE BLOOD TRANSFUSION (OPEN TRIANGLES)

blood volume determinations (Table III). As shown by blood volume before treatment, as well as by mean arterial and auricular pressures and cardiac output, these cases were on the average in more severe shock than the group in Table II, treated with albumin. Of the blood treated cases, 2 failed to respond. One (J. E.) probably received inadequate treatment. The other (H. M.) had a rise in blood volume but little or none in pressures or cardiac output; this may have been a case of "irreversible shock." The other 8 cases responded satisfactorily to transfusion, with the characteristic changes seen during recovery from shock following restoration of blood volume: rise in auricular and arterial pressures, in cardiac output, and in arterial oxygen transport.

Comparison of the effects of whole blood transfusion with those of concentrated albumin, is given in the average figures of Table IV. In this table are included only the 6 cases in the albumin series which had either skeletal trauma or hemorrhage, since all the whole-blood-treated cases were injuries of these types. This comparison can be only approximate, since the 2 series still differed clinically; but certain trends are apparent. Both series retained roughly comparable volumes in treatment, 712 cc. of blood (88 per cent of 809 cc.), versus 42 grams of retained albumin (equivalent to $42 \times 18 = 756$ cc. of isotonic fluid).

Of the various items in Table IV describing the comparative hemodynamic responses in the 2 groups, the changes in blood volumes, and in auricular pressures, were approximately the same. There was, of course, a decrease in hematocrit, following albumin therapy.

The rise in cardiac output, in the albumin-treated group, was significantly greater than in the whole-blood-treated group. While various factors may have contributed to this difference, an excessive response in cardiac output, in the albumin treated cases, is suggested by the fact that the average figure of 4.15 liters per minute per sq. M. of body surface, after treatment, is nearly one liter per minute greater than the average value for normal subjects by the same technic (3).

This excess cardiac output increase is a favorable compensation, making up for the

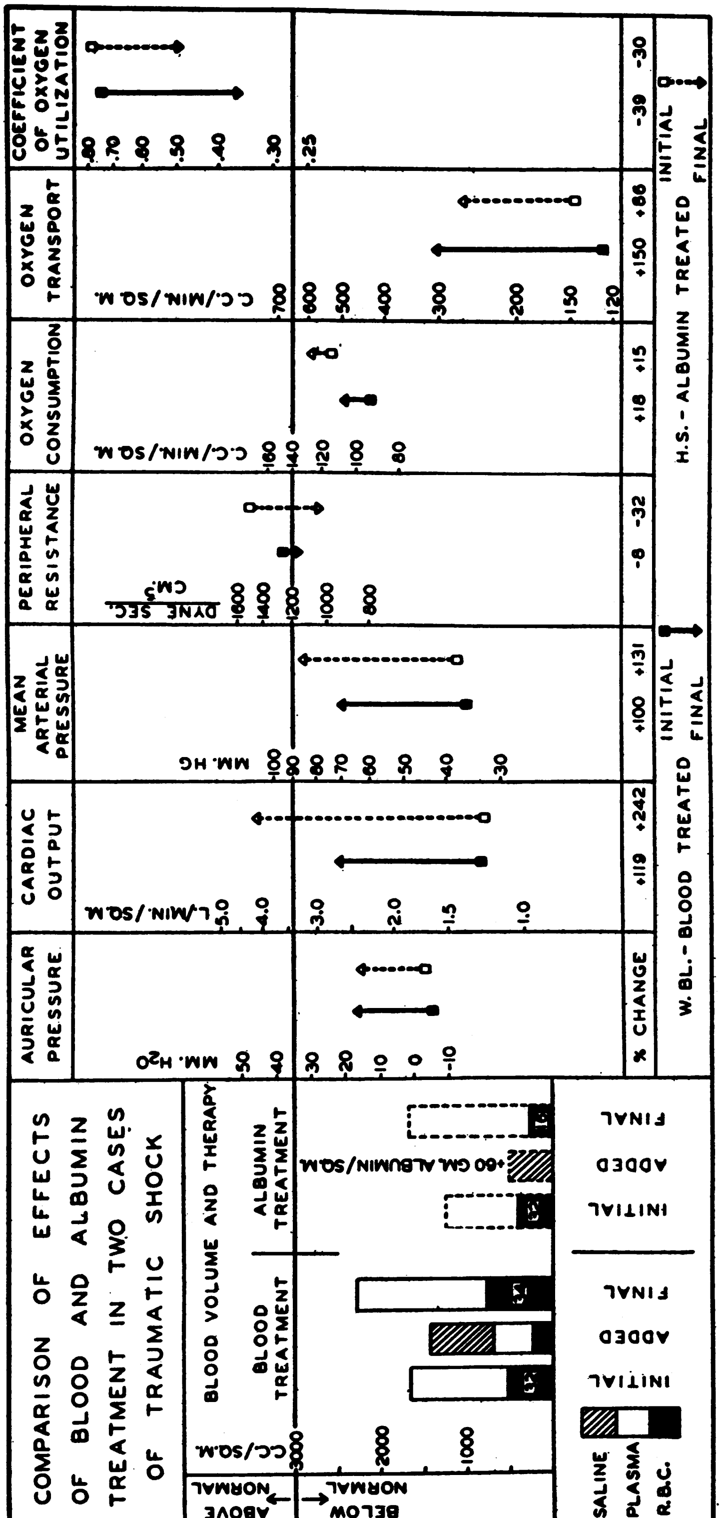

FIG. 5. COMPARISON OF EFFECTS OF TREATMENT IN 2 CASES OF TRAUMATIC SHOCK

With the log scales used as ordinates, the length of the arrows represents the percentage change in the measurement, during recovery from shock.

decreased hematocrit; and resulting in essentially the same increase in average arterial oxygen transport, after treatment, in the albumin as in the whole blood series.

Figure 4 demonstrates the larger cardiac output response in all the albumin-treated cases as compared with the whole-blood-treated cases, in relation to the changes in blood volume.

Increase in total oxygen consumption by the tissues, which is another regular feature of recovery from shock (3), was the same in the 2 groups, and greater than in the saline-treated group, a further indication of restoration of tissue metabolism both by albumin and by whole blood therapy.

A further striking difference between the 2 groups is the decrease in "peripheral resistance" following treatment in the albumin-treated cases, whereas the blood-treated cases showed no change in this function. The function of peripheral resistance, which is essentially the drop in blood pressure per unit of blood flow per second, is measured by the ratio, mean arterial pressure to cardiac output per second. In practical terms, a lowering of peripheral resistance indicates either a decrease in blood viscosity or a widening of blood vascular channels, or both.

To give more emphasis to the different modes of action of concentrated albumin and whole blood, measurements in 2 individual cases, one treated with whole blood transfusion, the other treated with concentrated albumin, are compared in Figure 5. Both cases were almost identical before treatment with regard to the initial degree of shock, amount of plasma and total blood volume loss, auricular pressure, and cardiac output and arterial oxygen transport. The following differences are revealed after treatment: (*1*) With the same increase in oxygen consumption, total blood volume, and auricular pressure, the cardiac output increase in the albumin-treated case was larger, and the increase in arterial oxygen transport was less, than in the whole-blood-treated case. (*2*) There was a considerable decrease in peripheral resistance and in hematocrit in the albumin treated case.

DISCUSSION

The data obtained in the present investigation indicate that concentrated human albumin solution is an effective agent in the treatment of acute traumatic shock in man.

The albumin injected into the circulation is largely retained, providing no further bleeding or exudation of plasma occurs. It is still remaining in the circulation at the end of 6 hours. The albumin retained holds in the blood stream amounts of fluid approximately comparable to its osmotic activity. Thus, in our series, 1 gram of albumin retained resulted in an average increase of plasma volume of 23 cc. This fluid may have been drawn into the blood from the tissues, or may have been simply retained, if additional crystalloid solution was also administered. No unfavorable side effects have been noted from the use of this preparation.

The increase in plasma volume produced by the injection of albumin effects a marked improvement in the circulation. Specifically, all the primary changes associated with recovery from acute shock (3) are observed: increase in right auricular pressure (venous return), in arterial pressure, and in cardiac output. Clinically, the patients were correspondingly improved.

Comparison of the effects of albumin with those of rapid saline infusion have shown that the two are qualitatively similar; but, as would be expected, saline produces a much smaller and more transitory increase in blood volume, and the increase in cardiac output with saline infusion, while considerable, is not sustained.

In comparing albumin therapy with that of whole blood, it is important to recognize that recovery of tissues from the state of shock requires restoration of oxygen transport to the tissues by the circulation; in other words, adequate circulation of hemoglobin. A normal total blood flow or cardiac output, does not provide normal oxygen transport if the hemoglobin concentration is low. As a measure of oxygen supplied to the tissues, one may use the total arterial oxygen transport, which is actually the cardiac output times the total oxygen content of the arterial blood. This determines the total amount of oxygen brought to the tissues per unit of time.

In shock due to skeletal trauma or hemorrhage, the reduction in blood volume is regularly associated with *hemodilution* (3). By giving whole blood in such cases, both the blood flow and the amount of hemoglobin which is circulated are increased.

By giving albumin (or plasma), the arterial oxygen transport is restored to normal only if the cardiac output is correspondingly increased above normal. Our figures show that this is actually what occurred in the cases treated in the present series (Table IV). As the available hemoglobin becomes progressively less, for example in continued hemorrhage, there will, of course, be a limit in the capacity of the heart to produce the compensatory increase in blood flow. Case H. S., presented in detail, was probably near this limit.

In brief, after treatment with albumin or plasma, such a patient has recovered from shock, but is still suffering from acute anemia.

The physiological adaptation here is, in fact, that which has long been known to exist in clinical anemia (7, 8). The ultimate effect, also, must be the same, *i.e.*, eventually the heart and circulation can no longer compensate and cardio-circulatory failure will occur (8). In cases recovering from shock, this danger will be greater in the presence of any additional strain, such as operation, or if infection, or other complication, subsequently develops. The use of whole blood or red cells, as soon as available, would thus be logically indicated as additional treatment even when clinically the circulation seems to be restored to normal.

In cases of shock associated with hemoconcentration, as in abdominal injuries and burns, the effects of concentrated albumin administration were favorable, reducing the hematocrit, increasing plasma and blood volume, and restoring or improving the circulation in all but one instance.

In the process of recovery from shock, it is of interest that auricular pressure, arterial pressure, and cardiac output tend to return to normal at a time when the vascular bed is still reduced, as shown by a blood volume not yet restored to normal.

SUMMARY

1. Concentrated human serum albumin solution has been administered in 12 clinical cases of traumatic injury in varying degrees of shock, with measurements of the circulation before and after this treatment.

2. In patients who were not actively bleeding, or losing plasma into burned tissues or peritoneum, the albumin was well retained in the blood. In 9 cases (including 3 burns), an average of 62 grams of albumin was given and an average of 43 grams retained. The albumin tended to remain in the circulating blood for at least 6 hours, when there was no continued blood or plasma loss at the site of injury.

3. Albumin therapy was effective in producing recovery from shock. It increased right auricular pressure, arterial pressure, and cardiac output.

4. Compared with treatment by whole blood transfusion, albumin therapy brought about a relatively larger cardiac output during recovery from shock.

5. In cases of shock due to skeletal trauma or to hemorrhage, where *hemodilution* is regularly found, this increased cardiac output is a compensatory effect, since the tissues can receive adequate oxygen only by more rapid circulation of the diminished amount of hemoglobin in the blood.

6. The persistence of acute anemia in many cases, after albumin therapy, suggests that whole blood should be given subsequently, when available.

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