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PLASMA PROTEIN CONCENTRATION AFTER HAEMORRHAGE

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After haemorrhage the blood volume is rapidly restored to its pre-haemorrhage level in cats (Robertson, 1935) and more slowly in human subjects (Stead, 1940; Wallace and Sharpey-Schafer, 1941) and in dogs (Price *et al.*, 1941). It is generally assumed that the fluid from the tissue spaces which enters the blood stream to restore the blood volume is weak in plasma proteins. These substances have been shown by Madden and Whipple (1940), in long-term experiments, to be replaced either from existing plasma protein stores or from protein synthesized from ingested food-stuffs. There are few data, however, on the replacement of plasma proteins from existing stores in the early hours after haemorrhage. The experiments recorded here throw some light on the movement of plasma protein into the blood stream during the first 2 hours after known quantities of blood had been withdrawn from the circulation.

and are thoroughly mixed when the 30-minute samples are taken, then the subsequent falls in haemoglobin concentration would be due to movement of fluid into the blood stream. If no new protein enters the blood stream, then the ratio of haemoglobin concentration at the 30-minute sample to the haemoglobin concentration in a subsequent sample would be identical with the ratio of the plasma protein concentration at the 30-minute sample to the plasma protein concentration in the same subsequent sample—e.g.,

$$\frac{\text{Hb conc. (30 min.)}}{\text{Hb conc. (75 min.)}} = \frac{\text{Pl. protein conc. (30 min.)}}{\text{Pl. protein conc. (75 min.)}}$$

Calculating the expected plasma protein concentration at the 75-minute samples, which allow slightly more than 1 hour after the end of the haemorrhage, the values in Table II, column 3, are obtained. Similarly, the expected values for plasma protein concentration are calculated for the last sample in each experiment. These are given in Table II, column 6.

TABLE I.—Haemoglobin (Hb) and Plasma Protein (P.P.) Concentrations after Haemorrhage

No.	Before Haemorrhage		Minutes after Haemorrhage																	
			15		30		45		60		75		90		105		120		135	
	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.
60	100	8.06	91.0	7.01	92.7	6.90	90.3	6.97	92.3	—	90.3	—	89.7	7.31	89.7	7.18	—	—	—	—
63	100	6.63	94.3	6.36	91.3	6.29	94.1	6.26	88.1	6.29	88.7	6.22	86.3	6.02	84.8	6.16	88.7	6.16	82.6	6.46
64	100	7.09	93.8	6.60	87.2	6.53	85.7	6.24	83.3	5.70	80.6	5.68	76.1	5.54	—	—	—	—	—	—
65	100	7.01	87.7	5.92	83.3	5.71	75.0	5.82	75.0	5.85	73.9	5.88	72.8	5.82	75.0	5.68	71.4	5.82	62.2	6.09
76	100	7.92	94.8	6.73	93.4	6.56	90.8	6.39	90.0	6.36	80.6	6.39	80.6	6.29	79.5	6.22	—	—	—	—
103	100	7.04	98.8	6.39	98.0	6.46	96.9	6.33	95.2	6.39	96.2	6.33	95.8	6.26	95.5	6.26	—	—	—	—

Methods

Cats anaesthetized with nembutal injected intraperitoneally (50 mg. per kg. of body weight) were used. After induction 4 hours was allowed for stabilization of blood volume before an experiment was started. The animals were heparinized during an experiment, and blood or plasma from heparinized animals was used for transfusions. Blood samples of 1 c.cm. and blood for haemorrhage were taken from a femoral artery, while transfusions were given by a femoral vein. Haemoglobin was estimated in 0.05-c.cm. samples by the alkali-haematin method, using a photo-electric colorimeter. Plasma specific gravities were estimated by the falling-drop method of Barbour and Hamilton (1926). Plasma protein values were deduced from the plasma specific gravities, using the formula of Weech *et al.* (1936), or determined direct by the biuret method of Robinson and Hogden (1940).

Observations

Single Haemorrhages

The changes in haemoglobin and plasma protein concentrations after 20% haemorrhages are shown in Table I. If it be assumed that all erythrocytes discharged from "stores" during and after the haemorrhage find their way into the circulation

A comparison of the expected values at 75 or 90 minutes in column 3 with the observed values in column 2 shows that 4 out of 5 animals had expected values lower than those observed, and one animal had observed and expected values almost identical. The expected and observed values at the end of each experiment are shown in Table II, columns 5 and 6. The animals which showed expected values lower than the observed ones at 75 or 90 minutes show a lower expected value at 105 or 135 minutes than that observed. The observed and expected values in Cat 103 were almost identical. Cat 64 differed from the rest of the experiments in this group. Dilution had progressed from 87.2 to 76.1 haemoglobin concentration, but the fall in plasma protein concentration was greater than that to be expected from the fall in haemoglobin.

TABLE II

No.	Observed Plasma Protein	Expected Plasma Protein	Time after Haem. (Min.)	Observed Plasma Protein	Expected Plasma Protein	Time after Haem. (Min.)
60	7.31	6.68	90	—	—	—
63	6.22	6.11	75	6.46	5.84	135
64	5.54	5.70	90	—	—	—
65	5.88	5.06	75	6.09	4.26	135
76	6.39	5.66	75	6.22	5.58	105
103	6.33	6.34	75	6.26	6.30	105

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Haemorrhages followed by Blood Transfusions

The animals in this series (5) were bled, and after varying times had the blood which had been removed re injected. The quantity re injected approximated closely to that removed (Table III). At the end of the period allowed for dilution—

of 75 minutes after the transfusion the observed plasma protein concentration was less than that expected (Table VI, columns 5 and 6). The amount of plasma given to this animal was less than one-third of the volume of blood removed. Cat 101 was bled 50 c.cm. and given 40 c.cm. of plasma with a high protein

TABLE III.—*Haemoglobin (Hb) and Plasma Protein (P.P.) Concentrations after Haemorrhage and Blood Transfusions*

No.	Before Haem. and Blood Trans.		Minutes after Haemorrhage and Blood Transfusions																			
			15		30		45		60		75		90		105		120		135		150	
	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.
123	99.7	6.36	100.0	5.68	98.9	5.58	100.6	5.71	101.5	5.68	102.0	5.71	109.4	5.71	102.6	6.22	106.5	6.26	108.2	6.33	106.9	6.33
124	100.3	6.53	106.0	6.36	111.0	6.36	109.4	6.43	110.4	6.43	108.2	6.29	111.7	7.04	110.4	6.97	112.0	6.90	110.4	6.77	109.1	6.80
*126	100.0	7.11	91.3	6.33	91.6	6.33	91.6	6.26	90.3	6.22	190.1	6.26	97.7	7.04	98.6	7.04	98.9	6.90	99.1	6.94	99.8	6.87
127	100.0	6.46	95.7	5.88	94.9	5.88	92.7	5.68	90.6	5.88	93.2	5.71	93.2	5.78	98.8	6.36	101.2	6.36	100.0	6.36	101.0	6.33
131	100.0	8.64	97.8	7.62	96.4	7.26	103.8	8.81	103.8	8.81	105.3	8.81	106.0	8.57	—	—	—	—	—	—	—	—

* Previous plasma transfusion before haemorrhage.

† Blood transfusion given immediately after these samples.

75 or 90 minutes (except Cat 131)—the differences between the expected and observed values for plasma protein were small, with one exception in which the values were identical. The observed values were slightly higher in 3 out of 4 animals (Table IV, columns 4 and 5). After the reinjection of the

content (7.89 per 100 c.cm.) 15 minutes after the end of bleeding. The expected plasma protein concentration at the end of the experiment was higher than that observed (Table VI, columns 5 and 6). Cat 107 was bled 60 c.cm. and given only 20 c.cm. of plasma with a protein content of 5.85 g. per 100 c.cm. 30 minutes after the end of bleeding. At the end of 105 minutes after the transfusion the observed plasma protein concentration was less than that expected (Table VI, columns 5 and 6).

Cats 89 and 90 were given plasma transfusions equal to half the volume of the subsequent haemorrhage about 45 minutes before bleeding was started. Cat 89 was bled 30 c.cm. and given 15 c.cm. of plasma with a protein content of 6.87 g. per 100 c.cm. 1 hour after haemorrhage. The observed value of plasma protein concentration was considerably greater than that expected immediately before transfusion (Table VI, columns 3 and 4). Forty-five minutes after transfusion the observed value was only slightly lower than that expected (Table VI, columns 5 and 6). Cat 90 was bled 38 c.cm. and given 19 c.cm. of plasma with a plasma protein content of 7.35 g. per 100 c.cm. 65 minutes after haemorrhage. Before the plasma transfusion the observed value of plasma protein concentration was slightly higher than that expected (Table VI, columns 3 and 4); 45 minutes later the observed plasma protein level was higher than that expected (Table VI, columns 5 and 6).

TABLE IV

No.	Observed Plasma Protein before Haemorrh.	Observed Plasma Protein 30-Min. Sample	Observed Plasma Protein before Blood Trans.	Expected Plasma Protein before Blood Trans.	Observed Plasma Protein after Blood Trans.	Expected Plasma Protein after Blood Trans.
123	6.36	5.58	5.71	5.61	6.33	6.48
124	6.53	6.36	6.29	6.20	6.80	6.88
*126	7.11	6.33	6.26	6.22	6.87	7.19
127	6.46	5.88	5.78	5.78	6.33	6.50
131	8.64	7.26	7.26	—	8.57	9.00

* Plasma transfusion of 30 c.cm. at 63 minutes before haemorrhage.

blood the experiments were continued for at least an hour. In every experiment the amount of plasma protein expected from changes in haemoglobin concentration was greater than that actually observed (Table IV, columns 6 and 7).

Cat 131 had its blood returned 30 minutes after haemorrhage. The observed value for its plasma protein was less than the expected value by a considerable margin 1 hour after the reinjection.

TABLE V.—*Haemoglobin (Hb) and Plasma Protein (P.P.) Concentrations after Haemorrhage and Plasma Transfusions*

No.	Before Haem. and Plasma Trans.		Minutes after Haemorrhage and Plasma Transfusions																			
			15		30		45		60		75		90		105		120		135		150	
	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.	Hb	P.P.
67	100.0	7.92	95.3	7.18	92.0	7.07	93.1	7.11	92.0	6.87	187.2	6.70	78.3	7.21	77.6	7.18	76.9	7.18	78.3	7.24	80.5	7.24
*89	100.0	7.55	95.1	7.58	96.5	7.65	93.5	7.96	88.5	7.89	84.7	7.86	89.8	7.96	—	—	—	—	—	—	—	—
*90	100.0	7.62	100.7	7.01	100.4	7.07	103.2	7.24	101.0	7.18	88.9	7.21	87.9	7.28	88.9	7.45	—	—	—	—	—	—
101	101.2	7.04	94.9	6.05	79.7	7.21	77.6	6.80	76.7	7.11	77.0	6.87	76.5	—	75.3	—	74.1	6.46	—	—	—	—
107	100.0	7.58	100.7	7.04	100.3	7.04	98.2	7.01	95.0	7.01	101.8	7.48	102.7	7.35	103.0	7.18	100.0	7.31	100.0	7.01	—	—

* Plasma transfusion before haemorrhage.

† Plasma transfusion given immediately after these samples.

Haemorrhages followed by Plasma Transfusions

The observations are shown in Table V. Cat 67 was given plasma of a lower protein content than that of its own plasma before haemorrhage. Before the plasma transfusion the observed and expected plasma protein concentrations were almost identical (Table VI, columns 3 and 4). At the end

Discussion

The necessity for eliminating the influence of erythrocytes added from "stores" is the reason why it is not possible in these experiments to make a comparison between the haemoglobin and plasma protein values before haemorrhage with those subsequent to bleeding. As it has been shown (Ebert and Stead, 1941) that in man no such stores exist comparable to the spleen of the dog and cat, it is possible to use in human experiments the pre-haemorrhage values for comparison with those after bleeding. Wallace and Sharpey-Schafer (1941) have published observations on plasma protein concentrations with simultaneous haemoglobin concentrations in convalescent human subjects bled varying amounts from 1,150 to 465 c.cm. In their series, 17 subjects had their plasma protein concentrations estimated before haemorrhage and also either at the end of bleeding or after 1 hour, or both. Twelve subjects were also examined for plasma protein concentration at the time of maximum dilution. Calculating the expected plasma protein concentration from the haemoglobin values, the figures set out in Table VII, columns 8, 11, and 15, were obtained.

TABLE VI

No.	Observed Plasma Protein before Haem.	Observed Plasma Protein before Plasma Trans.	Expected Plasma Protein before Plasma Trans.	Observed Plasma Protein after Plasma Trans.	Expected Plasma Protein after Plasma Trans.
67	7.92	6.70	6.69	7.29	7.41
*89	7.55	7.96	7.41	7.96	8.02
*90	7.62	7.18	7.11	7.45	7.21
†101	7.04	6.05	—	6.46	6.70
†107	7.58	7.04	—	7.01	7.14

* Plasma transfusion before haemorrhage: Cat 89 received 15 c.cm. at 43 minutes before haemorrhage, and Cat 90 received 19 c.cm. at 48 minutes before haemorrhage.

† Plasma transfusion after haemorrhage: Cats 101 and 107 received plasma at 15 and 30 minutes after haemorrhage.

TABLE VII.—*Effect of Haemorrhage on Haemoglobin and Plasma Protein Concentration in Man. Compiled from Data given by Wallace and Sharpey-Schafer (1941)*

No.	Amount Bled (c.cm.)	Duration of Bleeding (Min.)	Before Haemorrhage		End of Bleeding			1 Hour after Bleeding			Maximum Dilution			
			Hb	P.P.	Hb	P.P.	Expected P.P.	Hb	P.P.	Expected P.P.	Time in Hours	Hb	P.P.	Expected P.P.
1	1,150	12	73	8.0	68	8.0	7.45	—	—	—	19	53	8.0	5.81
3	1,150	10	107	7.6	101	7.6	7.17	—	—	—	23	86	7.2	6.11
5	1,150	11	96	8.2	88	—	7.52	87	7.9	7.43	23	74	7.8	6.32
7	1,100	12	63	6.8	60	—	6.48	61	6.4	6.58	24	52	—	5.61
8	1,100	18	95	5.9	88	—	5.47	85	7.0	5.28	5	78	—	4.85
9	1,100	12	70	7.4	68	7.2	7.19	66	—	6.60	26	56	6.8	5.60
11	1,060	20	107	7.1	103	7.0	6.77	103	—	6.77	9.5	90	6.3	5.97
14	900	20	77	6.2	74	6.4	5.96	77	—	6.20	24	68	6.5	5.48
16	800	10	89	7.8	86	7.8	7.54	86	—	7.54	19	71	7.8	6.22
18	800	15	95	6.6	95	—	6.60	95	6.5	6.60	22	84	6.5	5.84
19	750	24	105	6.7	100	6.6	6.38	95	—	6.06	4	83	6.9	5.30
21	720	15	84	7.8	77	7.2	7.15	75	—	6.97	19	62	6.8	5.76
22	720	22	120	6.5	—	—	—	111	—	6.01	48	92	6.6	4.98
23	700	12	77	7.3	77	7.1	7.30	74	7.1	7.02	90	61	6.9	5.78
25	650	18	74	6.5	73	—	6.41	71	6.5	6.24	3	69	—	6.06
26	550	10	89	8.0	83	8.0	7.46	87	—	7.82	—	83	—	7.46
27	465	10	95	7.1	92	7.1	6.88	95	—	7.10	4	87	6.7	6.50

Eleven subjects had plasma protein concentrations determined after haemorrhage. Of these, 8 (Nos. 1, 3, 11, 14, 16, 19, 26, 27) showed an excess of plasma protein over that expected as calculated from the haemoglobin concentrations, 2 (Nos. 9, 21) had observed and expected values in close agreement, and 1 (No. 23) showed a protein value less than that expected. The amount of protein produced in excess of that expected was not correlated either with the amount bled or with the time taken for bleeding. After 1 hour, 3 (Nos. 5, 8, 25) out of 6 subjects showed observed values in excess of that expected, 2 (Nos. 18, 23) had observed and expected values closely similar, and 1 (No. 7) had an expected value in excess of that observed. There was again no correlation between bleeding time, the amount of blood withdrawn, and the amount of protein in excess of the expected value. At the time of maximum dilution 13 subjects showed observed values in excess of that expected. Four of the 17 subjects were not observed for plasma protein concentration at this period. There was no correlation between the time taken to reach maximum dilution and the amount of protein in excess of that expected.

There is clear evidence, therefore, that in man plasma protein in considerable quantities can enter the blood stream during the actual haemorrhage, which may be as brief as 10 minutes or as long as 24 minutes. The fact that there is no correlation between the amount of protein entering the blood stream and either the bleeding time, the amount bled, the duration of active dilution of the blood, or blood pressure changes or the duration of such changes, suggests strongly that these factors are not concerned in the movement of protein into the blood stream, whether in small quantities contained in the actual fluids entering the blood stream from the tissues or in larger quantities entering it from some specific protein store such as the liver.

When these human results are compared with those obtained in the series of experimental animals recorded above, the same variations between observed and expected plasma protein values are found. Four out of 6 animals (Table II) showed evidence of plasma protein production, 1 showed no evidence of such production, and 1 showed a plasma protein concentration less than that expected. Of the 4 animals observed towards the end of the second hour or the beginning of the third hour after haemorrhage, 3 showed values in excess of that expected, and 1 slightly lower than that expected. The latter animal was that which had shown no change 75 minutes after haemorrhage.

It would appear, therefore, that what is being observed both in man and in the experimental animals might be related to the amount of protein "in store" in the individual animals. Hence those animals with poor reserves of protein would show a close approximation of expected and observed plasma proteins, while those with a depleted store might be expected to show an observed plasma protein value less than that expected. It is obvious that the magnitude of the effects of haemorrhage on plasma protein concentration is much greater in the human series than in the animals. This may be in part due to the fact that while in man it is possible to compare pre- with post-haemorrhage values, that cannot be done in

cats owing to the unknown number of erythrocytes liberated from the blood stores. Splenectomy in cats diminishes considerably but does not eliminate the storage capacity for red blood cells.

When blood is reinjected into animals which have been bled, the blood volume is increased considerably above the pre-haemorrhage level immediately after transfusion. This is due, of course, to the fact that dilution had progressed considerably before transfusion, and the reinjection of the blood withdrawn produces an increased blood volume. The changes in haemoglobin values (Table III) show clearly that in 3 animals out of 5 there must have been considerable reinforcement of the red cell population from erythrocyte stores. The 2 animals remaining show that their stores must have been either depleted before haemorrhage or were inactive during and after bleeding.

The increased blood volume undergoes reduction in all the animals after blood transfusion, as is shown by the rise in haemoglobin values. At the same time it will be noted that the change in haemoglobin value is not paralleled by a similar change in plasma protein concentration: the expected values are in each experiment higher than those observed. This suggests that the movement of fluid out of the blood stream is accompanied by a movement of protein out of the circulation. It is significant that in these 5 experiments (Tables III and IV) the amount of protein contributed to the blood after haemorrhage was small, which might, as suggested above, indicate poor reserves of protein. This view is supported by the fact that in all these animals the outward movement of protein after blood transfusion was well marked, except in Cat 124. Cat 126, which had had a preceding plasma transfusion (63 minutes before haemorrhage), must have had poor protein reserves, as it was not able to mobilize any significant quantity of protein after haemorrhage. The same animal depleted its circulating plasma protein considerably after its blood transfusion.

In the third series of experiments, plasma was transfused after haemorrhage. Two animals (89 and 90) had plasma transfusions at about 45 minutes before haemorrhage. One of these animals (89) added protein to the blood after haemorrhage in sufficient quantity to produce a plasma protein concentration of 7.96 as compared with an expected value of 7.41 g. per 100 c.cm. This may be interpreted as showing that the animal had an adequate protein reserve. This is confirmed when the expected and observed values after plasma transfusion are examined. They are almost identical. On the other hand, the second animal (90), which showed a small addition of plasma protein after haemorrhage, added a considerable amount of protein to the circulation after its second (post-haemorrhage) plasma transfusion. All the other animals (67, 101, and 107), which had had no plasma transfusion previous to haemorrhage, showed lower observed values than those expected. It would seem, therefore, that movement of protein out of the circulation was to reinforce the plasma protein reserves.

An Important Factor

It is obvious from the animal experiments that the state of the plasma protein stores—whether adequate or depleted—must

be the most important factor in determining the amount of protein entering the circulation after haemorrhage and also in deciding the rate at which this addition is made. If the stores are depleted completely, then the plasma protein concentration after haemorrhage will be less than that expected, as the protein requirements of the body must be met from the circulating plasma protein. The gap between expected and observed values will continue to widen unless new protein is added direct to the blood by blood or plasma transfusions or is synthesized from the breakdown products of protein taken by mouth.

If the adequate stimulus to movement of protein into the blood stream is a low plasma protein content of the blood, then some correlation might be expected between the degree of protein deficit (difference between plasma protein values before and 30 minutes after haemorrhage) and the amount of protein entering the blood stream at, say, the end of 1 hour after haemorrhage, indicated by the difference between the expected and observed plasma protein values. Such a correlation does not exist. Consequently, it would seem that either hypoproteinaemia is not the adequate stimulus or, alternatively, such stimulus is effective only when protein reserves exist outside the blood stream. The balance of evidence so far would suggest that the latter view is more likely to be correct. It is not suggested, however, that the protein in the plasma stores exists precisely in the form of the albumin-globulin complex present as plasma protein in the blood. The speed with which protein does appear in the blood stream and the amounts contributed after haemorrhage lend strong support to Whipple's view that the precursor of the plasma proteins in the plasma protein stores requires very little change before it can be discharged across the cell membrane into the blood stream.

The state of the protein reserves of the body may be determined by the response to plasma transfusions. After allowing 15 minutes for thorough mixing of the infused plasma, a blood sample is taken, followed by further samples at 45 and 75 minutes after the end of transfusion. The movement of the haemoglobin values is determined, and from these are calculated the expected plasma protein value for the 45-minute and 75-minute samples. If the observed values are greater than those expected it can be concluded that the movement of protein from blood to body cells is slow, and presumably protein stores are adequately filled. If the expected and observed values are equal or approximately equal, then protein-free fluid only is moving out of the blood stream. If the expected value is greater than the observed value, then protein movement from the circulation is rapid, and unless there are signs of massive protein movement into the tissue fluid—e.g., oedema—it must be presumed that the plasma protein stores are low. Such results give a useful indication of the state of the protein stores.

Conclusion

It is clear from these experiments that after haemorrhage the restoration of blood volume is independent of the restoration of plasma protein. Restoration of both concurrently would imply considerable protein stores. The speed of blood volume restoration in the cat apparently always outstrips the rate of plasma protein movement into the blood stream. In man the data of Wallace and Sharpey-Schafer make it clear that even after large haemorrhages (1,150 c.cm.) the plasma protein concentration can remain unchanged, although blood dilution is proceeding rapidly. One subject (19) apparently restored his blood volume after a haemorrhage of 750 c.cm. within 4 hours, and at the end of that time had increased his plasma protein concentration from 6.6 to 6.9 g. per 100 c.cm. This subject had a blood volume of 4 litres before haemorrhage and one of 4.2 litres after haemorrhage.

After haemorrhage and subsequent dilution of the blood, a blood transfusion is followed by a rapid increase in haemoglobin concentration. This haemococoncentration is not pathological but is due entirely to fluid movement out of the blood stream. The restoration of the blood volume to its pre-haemorrhage level takes place independently of a movement of erythrocytes into the blood stores or of plasma proteins out of the circulation. A movement of erythrocytes out of active circulation after blood transfusion would give an expected plasma protein value lower than the observed value. The fact that no animal showed such excess of observed plasma protein over

that expected even more strongly suggests that there had been rapid movement of plasma protein out of the circulation.

Summary

There is evidence of movement of plasma proteins into the blood stream within 2 hours after haemorrhage in cats anaesthetized with nembutal.

Blood transfusions at varying times after haemorrhage are followed by movement of plasma proteins out of the circulation within 1 hour of completion of transfusion.

Plasma transfusions after haemorrhage are followed by plasma protein movement out of the circulation within 1 hour of completion of transfusion.

The rate and amount of plasma protein movement into the circulation are independent of the amount or rate of bleeding, the amount or rate of dilution by fluid from the tissue spaces, and blood-pressure changes.

The amount of plasma protein contributed to the blood, and therefore the plasma protein concentration at any time after haemorrhage (provided no food containing protein has been administered), is probably dependent on the state of the plasma protein stores outside the circulation.

A method of testing the adequacy or otherwise of plasma protein stores is suggested.

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CIRCULATORY OVERLOADING FOLLOWING RAPID INTRAVENOUS INJECTIONS

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Authorities differ widely in advising the amount of serum or blood to be injected and the rate at which it should be given. Many stress the dangers of overloading the circulation. In 1894 Bayliss and Starling showed that rapid injection of crystalloid solutions or blood caused a rise of venous pressure, observations which have been amply confirmed by others in the experimental animal (Bainbridge, 1915; Wiggers, 1921). Meek and Eyster (1922) showed in dogs that the immediate effect of an intravenous injection was a rise of venous pressure associated with an increase in the diastolic size of the heart; these effects were only transitory, and there was evidence that the peripheral capillaries and venules were acting as reservoirs. There have been fewer observations in man. Eyster and Middleton (1924) investigated 4 normal subjects. In the case showing the most pronounced change 600 c.cm. of blood was given at the rate of 43 c.cm. a minute; this produced a rise in venous pressure of 2 cm. H₂O but no increase in the size of the heart. Caughey (1935) found no rise of venous pressure in normal sub-

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