THE EFFECT OF THE ADMINISTRATION OF HYPER-
TONIC SALT SOLUTION ON THE BLOOD
VOLUME AND CERTAIN RELATED
BLOOD CONSTITUENTS*

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INTRODUCTION

Weed and McKibben¹ demonstrated that the intravenous administration of hypertonic salt solution to animals was attended by a decrease in the size of the brain and a fall in cerebrospinal pressure. These results were soon applied to patients by Cushing and Foley,² Sachs and Belcher³ and others.⁴ The usual intravenous dose was 100 c.c. 15 per cent. sodium chlorid solution (in some instances 30 per cent.). As a result of these injections cerebral herniae often disappeared or were much diminished, the swollen brain decreased in size so that operations on it could be performed more easily, and the elevated cerebrospinal pressure of patients with brain tumor was usually reduced promptly. The effects were, in general, so satisfactory that the adoption of intravenous hypertonic salt solution as a valuable therapeutic measure appeared likely. With these facts in mind, it seemed to us desirable to ascertain what alterations took place in the blood as a result of its use, and especially the degree and significance of these alterations. The various factors investigated were: the blood volume, blood chlorids, the relation between blood volume and blood chlorids, the effects produced on the red corpuscles and hemoglobin, and the oxygen and carbon dioxid content of venous blood. We regret that a greater series was not obtained for each factor, but this would

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*This study is No. 28 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospital, a part of the expense of which has been defrayed by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

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2. Cushing, H., and Foley, F. B.: *Proc. Soc. Exper. Biol. & Med.* **17**:217, 1920.

3. Sachs, E., and Belcher, G. W.: *J. A. M. A.* **75**:667 (Sept. 4) 1920.

4. Cobb, S., and Ayer, J. B.: At the Massachusetts General Hospital. Personal communication.

have necessitated the withdrawal of an inconveniently large amount of blood. Since the procedure was relatively new and untried, it was undertaken only in the case of patients whose condition definitely indicated its use, a fact which further limited the series obtained. The intravenous human dosage was 100 c.c. of 15 per cent. sodium chlorid solution. The animals received a corresponding or relatively larger dose. Hypertonic salt solution was administered intravenously to seven patients, by mouth to one patient and one normal person and intravenously and by mouth to eight rabbits.

HISTORICAL

Blood hydremia has been observed in animals following the intravenous administration of hypertonic solutions by Brasol,⁵ Kilkowitz,⁶ Magnus⁷ and others. Magnus demonstrated the hydremia following hypertonic salt solution by reduction in the hemoglobin percentage, the specific gravity and dried ash of the blood. No measurements of the absolute changes in plasma volume after hypertonic salt administration have been encountered. Other effects observed in animals have been a prompt diuresis, a depression of the freezing point of the serum,⁷ a hyperglycemia and glycosuria,⁸ and occasional fever.⁹ Magnus⁷ found that the increase in chlorids in the blood after the injection was apparently less than the chlorids introduced.

Hypertonic salt solution was first administered intravenously to patients by Velden¹⁰ in 1909. Beginning with 5 c.c. of a 10 per cent. solution, he gradually increased the dose to 100 c. c. He discovered that a striking acceleration of the coagulation time of the blood took place, and used it with good results in cases of hemorrhage.¹¹ The diminished coagulation time after hypertonic sodium chlorid solution has been confirmed and has been shown to occur after the intravenous administration of other hypertonic salt solutions, as calcium chlorid¹² and sodium citrate.¹³ It also occurs after the oral administration of sodium chlorid.¹⁴ It has been supposed that some coagulation furthering substance present in tissue juice is drawn into the blood along with the

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9. Rolly, F., and Christjanson, A.: *Arch. f. exper. Path. u. Pharmakol.* **77**: 34, 1914.

10. Van der Velden, R.: *Deutsch. med. Wehnschr.* **35**:197, 1909.

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12. Schenk, P.: *Ztschr. f. d. ges. exper. Med.* **11**:166, 1920.

13. Blumel: *Med. Klin.*, 1910.

14. Neuhoof, H., and Hirshfeld, S.: *New York M. J.* **133**:95 (Jan. 15) 1921.

tissue fluid. In man a hypoglycemia without glycosuria has been observed after the injection, in contrast to the hyperglycemia found in rabbits.¹⁵

It has recently been reported that the administration of hypertonic solutions produces a general inhibition of glandular secretions, including sputum, sweat, gastric juice, milk, bile and the thyroid secretion.¹⁶ For these effects 50 per cent. dextrose solution was generally used in preference to hypertonic salt solution. The clinical results may be mentioned briefly. Night sweats have been diminished, gastric hyperacidity has been controlled, with relief of symptoms, and profuse expectoration associated with suppurative bronchitis, asthma, tuberculosis or pulmonary edema generally has been much decreased after the employment of these hypertonic solutions.¹⁷ Profuse choleraic diarrhea and severe toxic dysenteries have been suppressed in like manner. In fourteen out of fifteen cases of hyperthyroidism and pronounced exophthalmic goiter, Stejskal¹⁸ observed distinct diminution in the size of the thyroid after the injection of hypertonic solutions, with marked improvement in the symptoms and signs of the disease. Two of his patients continued to work two and three months, respectively, after treatment without evidence of symptoms. The glandular inhibition presumably arises because the tissue lavage into the blood diminishes the supply of fluid to the glands. It has been claimed also that there is an accelerated absorption of drugs introduced into the body, as sodium iodid by mouth, cocain applied to the mucous surfaces, and arsphenamin intravenously.¹⁶

Wynn¹⁸ tried the effect of hypertonic salt in the treatment of neurosyphilis, since it has been shown that with the fall in cerebrospinal pressure a considerable amount of subarachnoid fluid entered the substance of the central nervous system.¹⁹ He gave 200 c.c. of 15 per cent. sodium chlorid solution intravenously in the hour following intraspinal injection, but found no serologic or cytologic improvement over the usual course of intraspinal treatment. Corbus²⁰ and his co-workers used hypertonic salt as a method of spinal drainage, having shown that six hours after the injection there was a reabsorption of serum from the blood stream into the cerebrospinal fluid which carried the arsphenamin introduced intravenously into the spinal canal.

Bürger and Hageman²¹ recommend 50 per cent. sugar solution (grape sugar) in doses of 1 gm. dextrose per kilo body weight. They

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16. Stejskal, K.: *Wien. klin. Wchnschr.* **34**:200, 343, 1921.

17. Singer, G.: *Wien. klin. Wchnschr.* **34**:86, 1921.

18. Wynn, J.: *Arch. Int. Med.* **29**:72 (Jan.) 1922.

19. Foley, F. B., and Putnam, T. J.: *Am. J. Physiol.* **53**:464, 1920.

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21. Bürger, M., and Hageman, E.: *Deutsch. med. Wchnschr.* **47**:207, 1921.

are now applying it to cases of lumbago and sciatica. In this country favorable results following hypertonic sugar solutions have been reported in influenzal pneumonia,²² in other severe infectious diseases,²³ in traumatic shock,²⁴ and in glaucoma.²⁵ Such a varied usage of this relatively new therapeutic measure would seem to offer a wide field for future clinical research. In this report, in addition to the effect on the composition of the blood, the clinical results in the patients with increased cerebrospinal pressure will be mentioned.

METHODS

Absolute changes in blood volume were determined by the vital red method of Keith, Rowntree and Geraghty,²⁶ the principle of which depends on the color dilution of a known amount of dye when circulated in the blood stream. A sample of blood is first drawn, the dye is injected and allowed to circulate for three minutes for thorough mixing of dye and blood, and a second blood sample is withdrawn. The color dilution of the dye in the plasma gives a quantitative determination of the plasma volume, from which with the hematocrit, the total blood volume can be calculated. By utilizing the fact that no appreciable amount of the dye is excreted in the first ten minutes, it was possible to make a second determination of the blood volume within this period. The hypertonic salt solution was injected and a third blood sample was removed within this interval. Two readings were thus made on the identical quantity of dye injected, which served as an accurate control and in addition allowed the measurement of blood changes taking place immediately after the injection. Other methods of recording absolute blood changes are more time consuming and apt to result in a merging of the early swift changes in plasma volume. A third determination with this method is not possible for twenty-four hours, or until all traces of the dye have left the blood stream. Six satisfactory determinations were made in this manner in Case 1 (Table 1).

Relative changes in blood volume were determined by changes in hemoglobin content, the red blood cell count, and the hematocrit percentage. The formula used was that of Boycott and Douglas,²⁷ and may be illustrated as follows:

$$\frac{120\% \text{ (hemoglobin before)}}{80\% \text{ (hemoglobin after)}} \times 100 = 150 \text{ per cent., or the blood}$$

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26. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: *Arch. Int. Med.* **16**:547 (Oct.) 1915.

27. Boycott, A. E., and Douglas, C. J.: *J. Path. & Bacteriol.* **13**:256, 1909; *ibid.* **16**:485, 1912.

volume after saline injection in per cent. of the normal or original blood volume.

This method depends on the assumption that the volume of circulating hemoglobin is constant under control conditions. It is known that the red corpuscle content of the blood is altered by a number of conditions, among them low oxygen tension,²⁸ fright,²⁹ exercise, sweating, administration of epinephrin, abdominal massage,³⁰ and also that it varies at different periods of the day.³¹ Consequently, the calculation of the blood volume changes for any length of time on the basis of variations in red cell or hemoglobin percentages would seem to be fraught with error. Bogert, Underhill and Mendel,³² however, found that the hemoglobin of rabbits did not vary appreciably for a period of several hours. In Case 1 of this series comparisons were made between the blood volume changes as determined by vital red method and the relative changes as determined by dilution of hemoglobin, red corpuscles and hematocrit. The immediate changes following the infusion were quite comparable, but at the end of twenty-four hours a discrepancy occurred. It seems probable that for short periods of time relative blood volume changes can be determined fairly by methods that depend on hemoglobin dilution, but for periods as long as twenty-four hours an error may be introduced.

The analyses of the blood oxygen and carbon dioxide were done by the method of Van Slyke and Stadie.³³ The hemoglobin was calculated from the oxygen capacity. The chlorid determinations were carried out by the method of Wetmore.³⁴ Except when the oxygen and carbon dioxide contents were determined, the blood was not withdrawn under oil. The influence of a diminishing tension of carbon dioxide on the distribution of chlorids between plasma and red corpuscles would make our figures for the plasma chlorids a little high.³⁵ For this reason no precise comparisons of the exchange of chlorids between plasma and cells following injection of hypertonic salt solution have been made.

In the case of rabbits the salt solution was injected into the ear vein, and the blood withdrawn from the heart. In the patients, the brachial veins were used.

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DISCUSSION OF RESULTS

Blood Volume.—The most striking result of the intravenous injection of hypertonic saline solution was an immediate and marked increase in the plasma volume. The administration of 100 c.c. of 15 per cent. sodium chlorid solution was followed within one or two minutes after the injection by an elevation of from 15 to 30 per cent. of the total blood volume, representing a pouring into the blood stream of from 500 to 1,200 c.c. of tissue fluid. The greatest increase in blood volume was noted approximately thirty seconds after the injection, i. e., as soon after as the blood could conveniently be drawn. From then on it progressively diminished, and in most cases returned nearly to the original volume within three and one-half hours. In one case in which the plasma volume was abnormally lowered before the injection, the increased blood volume persisted for four days. The factors that govern the magnitude, the time relationship, and the relative permanency of the changes in plasma volume may be grouped as follows: (1) the total increase in chlorids present in the entire circulating blood at the time of the analysis; (2) the condition of the kidneys. Other factors, such as the amount and concentration of the solution, the speed of injection, the weight of the subject, and the amount of chlorids in the body, may be considered subdivisions of the first group. In order to show how these factors explain the mechanism of the elevation in blood volume, the chlorid content of the entire blood was determined before and after the injection of hypertonic salt solution. The total increase in sodium chlorid was then compared to the increase in blood volume. It was found the volume response was essentially that which would fulfil the isotonic requirements of the increased salt. In other words, the normal isotonic concentration of the blood was in the main preserved. The detailed calculations follow.

The chlorid content of the entire circulating blood may be determined by multiplying the absolute blood volume by the chlorid concentration in grams per liter of whole blood. Similarly, the chlorid content of the entire plasma is determined by multiplying the plasma volume by the plasma chlorid concentration. The difference between these two figures gives the chlorid content of the entire red cells. With the hematocrit the chlorid concentration of red corpuscles in grams per liter can be calculated (Table 1). If, in case 1, these figures are charted graphically together with the blood and plasma volume after the intravenous administration of hypertonic salt solution, a close parallelism is found between the blood and plasma volume, on the one hand, and the total quantity of chlorid in the circulating blood or plasma on the other. Slight discrepancies exist which will be discussed later. Between the blood volume and the chlorid concentration in grams per liter of whole blood or plasma an approximate parallelism is present. In the other

TABLE 1.—BLOOD ALTERATIONS FOLLOWING INTRAVENOUS ADMINISTRATION OF HYPERTONIC SALT SOLUTION. THE RELATION BETWEEN THE INCREASE IN BLOOD VOLUME AND THE INCREASE IN TOTAL CHLORIDS

Case No., Age, and Diagnosis	Date	Time of Observation (Note: Each injection = 15 gm. NaCl in 100 c.c. of Water)	Hemo- globin (Calcu- lated from Oxygen Capac- ity), per Cent.	Red Blood Cells, per C.Mm.	Hema- to- crit Cells, per Cent.	Blood Volume Data			Blood Chlorid Data						Comparison of Volume and Chlorid Data		Remarks	
						Total Blood, C.c.	Total Plasma, C.c.	Total Cells, C.c.	Concentra- tion in			Total in Circulating			Total Increase in Chlorids	Actual Increase in Blood Vol- ume		Volume Theo- retically Necessary to Render Increased Chlorids Isotonic, C/0.9
									Whole Blood, Gm. per Liter	Plas- ma A, Gm. per Liter	Cells B, Gm. per Liter	Blood, Gm.	Plasma, Gm.	Cells, Gm.				
1 26 years, Cyst of the cerebellum	5/26	Before 1st injection...	104.5	4,136,000	41.6	2,979	1,739	1,240	4.38	5.68	2.55	13.07	9.88	3.19	...	...	Stupor and inar- tulate; twitching of hands	
		2 min. after injection (duration of injec- tion, 3 min.)	82.7	3,424,000	34.6	3,740	2,445	1,295	5.31	...	...	...	19.85	...	...	6.78	761	754
		1 hr. after injection...	88.3	3,480,000	36.0	3,618*	2,315	1,303	5.11	6.57	2.53	...	18.47	15.40	3.07	5.40	639	601
	5/27	24 hrs. after injection	90.6	3,480,000	39.0	3,880	2,363	1,517	4.60	6.01	2.41	17.85	14.20	3.65	4.78	901	532	Twitching of hands continues
	5/31	Before 2d injection...	90.4	3,536,000	31.0	3,781	2,606	1,175	4.82	6.02	2.16	18.24	15.70	2.54	...	...	...	...
½ min. after injec- tion (duration of injection, 4 min.)		80.4	3,192,000	25.0	4,675	3,508	1,167	6.16	7.29	2.76	...	28.80	25.59	3.21	10.56	894	1173	...
		3¼ hours after injec- tion	88.2	3,300,000	31.0				5.35	6.68	2.38				...	...	Brighter; less twitching	
	6/ 1	Before 3d injection... (24 hrs. after 2d injection)	86.2	3,328,000	30.8	4,075	2,819	1,256	4.85	6.17	1.88	19.77	17.38	2.89	1.53	294	170	Twitching again
10 min. after injec- tion (duration of injection, 7 min.)		72.7	2,840,000	25.0						6.82	...				...	...	...	Unchanged
3 hrs. after injection		83.3	3,392,000	30.6						5.28	6.30	2.97				...	...	Brighter and stronger
	6/ 6	5 days after injection	91.7		28.6				4.54	5.46	2.27					...	...	Carpopedal spasm

* In this instance, the blood volume was calculated from the previous vital red determination and the relative difference in hematocrit. In all others the vital red method was used directly.

TABLE 2.—BLOOD ALTERATIONS FOLLOWING HYPERTONIC SALT SOLUTION

Case No., Age, and Diag- nosis	Administration of Hypotonic Salt				Red Blood Cells		Hema- to- crit	NaCl Concentration			Venous Blood			Blood Volume Calculated from		Fragility of Red Blood Cells	Remarks
	Amount	Dura- tion	Avenue	Time of Observa- tion	Capillary Blood, per C.Mm.	Venous Blood, per C.Mm.		Whole Blood, Gm. per Liter	Plasma A, Gm. per Liter	B, Gm. per Liter	Oxy- gen Con- tent, Vol. per Cent.	Oxy- gen Satu- ration, Vol. per Cent.	Carbon Dioxid Con- tent, Vol. per Cent.	Hema- to- crit, per Cent.	Hemo- globin, per Cent.		
2 35 years Tumor of cerebellum	100 c.c. 15% NaCl	5 min.	Intra- venous	Before..... 3 min. after.. 24 hrs. after..	4,256,000 3,480,000 3,704,000		35.3 26.6 34.5	4.72 6.68 6.17	6.31 8.08 7.13	1.81 2.82 4.35	15.83 10.15 15.84	76.5 63.1 88.5	51.0 54.0 48.0	100 133 102	100 128 115	Hemolysis 42-34; cells gone at 26 Hemolysis 38-32; cells gone at 24 Hemolysis 42-34; cells gone at 28	Marked stupor Wide awake; cheerful
3 40 years Tumor of cerebellum	100 c.c. 15% NaCl	8 min.	Intra- venous	Before..... 12 min. after..			41.4 36.6	4.74 5.08	5.77 7.29	2.56 1.12	9.08 6.93	42.0 40.2	60.3 60.8	100 113	100 125	Control cells plus plasma dilution; hemolysis 38-24 Control cells plus plasma dilution; hemolysis 36-24	Stuporous More cognizant of surround- ings
4 22 years Fracture of skull	100 c.c. 150% Ringer's solu- tion	5 min	Intra- venous	Before..... 2 min. after.. 20 hrs. after..	5,228,000 5,160,000 5,296,000	5,184,000 4,728,000 5,048,000	46.7 42.0 43.8	4.51 4.83 4.46	5.93 6.33 5.89	2.89 2.76 2.46	15.43 14.43 19.33	66.9 65.3 85.2	61.3 57.0 55.1	100 111 106	100 104 102		Serum clear Serum hemo- lyzed Serum clear
5 26 years Normal	50 c.c. 15% NaCl	7 min.	By mouth	Before..... 15 min. after.. 1½ hrs. after	4,928,000 4,824,000 4,712,000		43.4 43.0 42.7	4.80 4.89 5.05	6.11 6.33 6.51	3.09 6.93 7.23	11.95 11.24	56.0 50.5	56.7 54.5	100 101 102	100 100 106		One hour after lunch

human cases, as well as in the experiments on rabbits, an approximate parallelism between the relative blood volume after the administration of hypertonic salt solution and the chlorid concentration of whole blood or plasma is also present (Tables 1, 2 and 4). The chlorid concentration in the red corpuscles and the chlorid content of the entire red blood cells show no constant relationship to the blood volume.

Relation between blood volume and blood chlorids following the intravenous administration of hypertonic salt solution. Results obtained in Case 1: *B*, whole blood; *P*, plasma; *C*, cells. The upper group shows the total blood, plasma and cell volume, expressed in liters (L.); the middle group, the total sodium chlorid in whole blood, plasma and cells, expressed in grams; the lower group, the concentration of sodium chlorid in whole blood, plasma and cells, expressed in grams per liter.

Observation (Obs.) 1 was made just before an injection of 100 c.c. of 15 per cent. sodium chlorid. Obs. 2, two minutes after; Obs. 3, one hour after; Obs. 4, twenty-four hours after; Obs. 5, one hundred hours after and just before the second injection; Obs. 6, thirty seconds after the second injection; Obs. 7, twenty-four hours after the second injection.

It thus appears from the chart that the increase in total chlorids of either blood or plasma is proportional to the volume increase in either blood or plasma. It may be mentioned at this point that the increase in blood volume after hypertonic salt injection is due almost entirely to the increase in the plasma volume. An exception to this occurred in Case 1, twenty-four hours after the first injection, when apparently a considerable increase in cell volume took place. For the most part, however, the blood volume reflects the changes in the plasma volume. A more accurate basis for comparing the blood volume and the blood chlorids may be had by calculating the number of cubic centimeter of water theoretically necessary to bring the increased chlorids in the blood into an isotonic state. This is done simply by dividing the total chlorid increase in grams by 0.9. If this number, conveniently called the isotonic equivalent of the chlorid increase, is compared to the actual increase in blood volume reckoned in cubic centimeter, it is found that at times they are approximately equal to each other, and at other times there is a certain divergence (Table 1). When the actual increase in blood volume after injection of hypertonic salt solution is equal to the isotonic equivalent of the chlorid increase, it is evident that the blood remains isotonic. When the actual increase in volume is less than the number of cubic centimeter of water necessary to bring the increase in chlorids to isotonicity (less than the isotonic equivalent), the blood is obviously to some extent hypertonic, provided other conditions remain constant. Thus, in Case 1, after the first injection the increase in chlorid content of the entire blood was 6.78 gm., its isotonic equivalent was 754 c.c., and the recorded increase in blood volume 761 c.c. In this instance it would appear that the increase in blood volume was the amount necessary to bring the chlorid increase in the blood into an isotonic state, and consequently that the osmotic pressure of the blood remained approximately as it was before the injection, i. e., equal to a solution of sodium chlorid of a concentration of 0.9 per cent.

If the immediate changes after the second injection are now examined, the chlorid increase is seen to be 10.56 gm., its isotonic equivalent 1173 c.c., and the recorded increase in blood volume 894 c.c. In this case, 279 c.c. of fluid are theoretically still needed to bring the chlorid increase to an isotonic state. The blood would thus appear to be hypertonic, containing a total excess of 2.51 gm of chlorid above the physiologic concentration, or 0.537 gm. per liter.

The provision was made in these calculations concerning the isotonicity of the blood that the other factors involved remained constant. The other factors involved in maintaining the osmotic pressure of the blood do not, however, remain constant, but undergo marked changes. Their alterations complicate but at the same time strengthen the conclusions drawn.

Assuming that the osmotic pressure of the blood before the second injection was equal to that of physiologic solution of sodium chlorid, 0.9 per cent., the part played by the chlorids in the blood in maintaining the osmotic pressure is equivalent to 0.482 per cent. (The chlorid concentration of whole blood before the second injection was 4.82 gm. per liter.) There are, thus, 0.418 per cent. (of the osmotic pressure of the blood in terms of physiologic sodium chlorid solution) to be furnished by other substances, such as glucose, sodium bicarbonate, other salts, and colloids. After the second injection, the chlorid concentration of whole blood was 6.16 gm. per liter, an increase of 1.34 gm. per liter. It would appear at first glance that each liter of blood was hypertonic to the extent of 1.34 gm. per liter, whereas in the previous calculations from the increase in blood volume, the hypertonicity was estimated at 0.537 gm. per liter. The difference between the two, 0.803 gm. per liter, does not, however, represent additional hypertonicity, but takes the place of the osmotic substances other than chlorids that are lost from each liter of blood by dilution with tissue fluid. Thus, after the injection, 894 c.c. of new fluid was found in the blood stream. The substances making up the 0.418 per cent. of the osmotic pressure (glucose, sodium bicarbonate, etc.) of necessity spread equally throughout the new blood volume and become correspondingly diminished in each liter of blood, so that the concentration of these substances became 0.338 per cent., or a loss of 0.80 gm. per liter. This is equal to the discrepancy noted above, and represents a replacement by chlorid of the osmotic substances lost by dilution. The concentration of these substances after the injection, 0.338 per cent., plus the chlorid concentration after the injection, 0.616 per cent., equals 0.954 per cent., representing a hypertonicity equivalent to 0.54 gm. per liter, which corroborates the original calculation of 0.537 gm. per liter (0.338 per cent., or the concentration of the other osmotic substances in terms of sodium chlorid after salt injection, is derived as follows: 0.418 per cent. [concentration of substances before injection] $\times$ 3781 [blood volume before] $\div$ 4675 [blood volume after] = 0.338 per cent.).

Similar calculations applied to the results immediately after the first injection indicate that the blood was practically isotonic in this instance, corroborating the agreement between the isotonic equivalent of the chlorid increase and the actual increase in blood volume.

Twenty-four hours after the first injection, the actual increase in blood volume appears somewhat greater than the isotonic equivalent of the sodium chlorid increase. Thus, the sodium chlorid increase of the entire blood was 4.78 gm., its isotonic equivalent 532 c.c., the actual increase in blood volume 901 c.c. It must be remembered, however,

that the osmotic substances other than sodium chlorid which become diluted through the ingress of tissue fluid probably revert to their original concentration after twenty-four hours, and restore the osmotic substances lost by dilution. If this calculation is carried out on that basis, the blood concentration is practically isotonic. Similarly, the increase in blood volume twenty-four hours after the second injection is in excess of the isotonic equivalent, but that excess is again equivalent to the osmotic substances that presumably enter the blood from the tissues to maintain the original concentration. The calculation on this basis again yields a practically isotonic concentration. (Thus, 0.485 per cent. [concentration of osmotic substances before second injection] + 0.418 per cent. [chlorid concentration after injection] = 0.903 per cent.).

It would appear from these results that the total increase in chlorids present in the circulating blood at the time of analysis is the primary determinant of the blood volume following hypertonic salt solution injection. The amount of increase of the blood volume corresponds approximately to the amount of fluid necessary to render the increased chlorids isotonic.

The discrepancies, which occur twenty-four hours following the injection, have been explained above. Thirty seconds after the second injection, the blood was apparently to some degree hypertonic, inasmuch as the increase in blood volume did not fully meet the requirements for isotonicity. Thorough mixing of blood and chlorides was probably not established, so that this may not have represented the condition throughout the entire body. It will be remembered that a depression of the freezing point of the serum after hypertonic salt has been demonstrated in animals, but in these investigations the amount of salt injected was relatively much larger.

The second important factor in determining the permanency of the increased blood volume appears to be the condition of the kidneys. Boycott and Douglas³⁶ showed that after the injection in rabbits of a quantity of physiologic solution of sodium chlorid equal to the calculated blood volume, the original blood volume returned to normal within thirty minutes. Two thirds of the injected quantity left the circulation during the administration, the duration of which was five minutes. This occurs with both ureters ligated, but in rabbits in whom uranium nephritis had been produced, the blood volume failed to return to normal in the allotted time. When double strength Ringer's solution was injected, only one third of the injected amount left the circulation in the first five minutes. White and Erlanger³⁷ found that

36. Boycott, A. E., and Douglas, C. J.: *J. Path. & Bacteriol.* **19**:221, 1914.

37. White, H. L., and Erlanger, J.: *Am. J. Physiol.* **54**:1, 1920.

in dogs a strongly hypertonic solution of glucose and gum acacia solution caused a marked increase in relative blood volume which gradually fell but did not return to normal in several hours. Magnus⁷ studied the diuresis taking place in rabbits after the intravenous administration of salt solutions of varying concentrations, and found the degree of diuresis ran parallel to the degree of blood dilution. Galeotti³⁸ found that the diuresis varied inversely as the molecular concentration of the blood. The urinary output could not be followed in the present study as most of the patients were incontinent. None of the patients had

TABLE 3.—RELATIVE BLOOD VOLUME FOLLOWING HYPERTONIC SALT SOLUTION

Case No., Diagnosis, and Age	Administration of Salt Solution				Hemato- crit, %	Blood Volume Calcu- lated from Hemato- crit, %	Remarks
	Amount	Dura- tion	Avenue	Time of Observa- tion			
6 Brain tumor ? 30 years	100 c.c. 15% NaCl	5 min.	Intra- venous	Before.....	47.2	100	Sleepy; severe headache Felt very hot
				1 min. after....	36.9	128	
				2 min. after....	36.8	128	Headache gone No longer sleepy Patient brighter; no headache
				30 min. after....	39.3	120	
				1½ hrs. after....	39.0	121	
				24 hrs. after....	41.2	114	
7 Brain tumor 28 years	100 c.c. 15% NaCl	7 min.	Intra- venous	Before.....	46.0	100	Slight headache Face felt hot
				½ min. after....	39.1	118	
				1 min. after....	42.5	108	Headache gone
				3 min. after....	44.0	105	
				3 hrs. after....	44.0	105	
8 Brain tumor 29 years	100 c.c. 15% NaCl	12 min.	Intra- venous	Before.....	46.4	100	Headache Felt very hot
				1 min. after....	40.3	115	
				3 min. after....	41.8	111	Headache gone; no complaints
				10 min. after....	43.8	106	
				22 min. after....	44.1	105	
				40 min. after....	44.6	104	
9 Polycy- themia vera 55 years	100 c.c. 10% NaCl	3 min.	By stom- ach tube	Before.....	72.0	100	
				15 min. after....	69.0	104	
				30 min. after....	68.4	105	
				1 hr. after.....	67.5	107	
				1½ hrs. after....	67.8	106	

demonstrable nephritis. In some of the rabbits, however, chlorid retention was present in the blood, shown by the immediate increase in blood chlorids failing to drop to normal subsequently. In these rabbits there was a parallel maintenance of the increased blood volume. Instances of the normal reaction in rabbits, an abrupt rise in blood volume immediately after the injection followed by a gradual fall, may be seen in experiments 1 and 3 (Table 5). In experiments 5, 6, 7 and 8 (Table 4) the relative blood volume showed an immediate increase which either remained stationary or became further elevated, and the chloride concentration of the blood and plasma likewise remained elevated. It is to be remembered that the chlorids of the entire blood were

38. Galeotti, G.: Arch. f. Physiol., 1902, p. 200.

TABLE 4.—BLOOD CHLORIDS AND RELATIVE BLOOD VOLUME IN RABBITS FOLLOWING HYPERTONIC SALT SOLUTION

Experi- ment Number and Weight of Rabbit	Administration of 15% Salt Solution			Hemato- crit Red Cells, %	Red Blood Cells (Venous Blood), per C.Mm.	Blood Volume Calculated from		Blood Chlorid Concentration			Blood With- drawn, C.c.
	Amount	Duration	Avenue			Hema- to- crit, %	Red Blood Cells, %	Whole Blood, Gm. per Liter	Plasma, Gm. per Liter	Cells, Gm. per Liter	
4 2.4 kg.	3 c.c.	½ min.	Intra- venous	Before.....		100	...	4.68	6.01	2.98	17
				3 min. after.....	30.9	141	...	6.15	7.25	3.72	18
				20 hrs. after.....	25.0	...	...	4.76	5.71	1.92	17
5 3.2 kg.	7 c.c.	1 min.	Intra- venous	Before.....	32.6	100	...	4.76	5.79	2.62	7
				5 min. after.....	29.0	112	...	5.52	6.68	2.69	7
				13 min. after.....	25.0	130	...	5.39	6.49	2.12	7
				24 hrs. after.....		...	...	5.52	6.59		7
6 2.2 kg.	5 c.c.	1 min.	Intra- venous	Before.....	46.0	100	...		5.70		5
				2 min. after.....	34.6	133	...		6.87		5
				12 min. after.....	36.4	126	...		6.92		5
				1½ hrs. after.....	32.8	140	...		6.56		5
				8 hrs. after.....	24.0	...	...				...
7 2.8 kg.	18 c.c.	1 min.	By stomach tube	24 hrs. after.....	18.0	...	...				...
				Before.....	36.6	100	...	5.85	7.36	3.25	6
				10 min. after.....	30.9	118	...	6.19	7.49	3.30	7
				1 hr. after.....	30.6	119	...	7.01	8.35	3.98	6
				24 hrs. after.....	29.0	126	...	7.25	8.42	5.10	6
8 2.5 kg.	18 c.c.	1 min.	By stomach tube	Before.....	19.6	100	100	5.64	6.51	2.99	7
				5 min. after.....	17.8	110	105	5.80	6.72	1.57	7
				30 min. after.....	18.4	106	130	6.30	7.20	2.12	6
				24 hrs. after.....	14.5	135	136	6.99	8.00	1.03	7

not obtained so that precise relationships between blood volume and blood salt are not intended. In experiments 7 and 8, the hypertonic salt solution was administered by stomach tube, the blood volume becoming progressively higher during the twenty-four hours following the ingestion of the salt, and the chlorid concentration of the blood steadily rising in parallel fashion. It becomes apparent from these data that in the case of rabbits unable to excrete salt the retention of chlorids in the blood is associated with the retention of an increased plasma volume.

There are other factors that have a more or less obvious bearing on the elevation in blood volume due to hypertonic salt solution. The slower the speed of administration, the less will be the amount of increase in blood volume, since the increased fluid is constantly leaving the blood stream. Where a uniform amount of solution is administered, the weight of the subject will be an evident factor. In Case 1, it was seen that 6.78 gm. of salt were found increased in the blood two minutes after the first injection of 15 gm., and 10.56 gm. one-half minute after the second injection of 15 gm. Granting that a certain amount of chlorids were excreted through the kidney and intestine, it is evident that the larger part was taken up by the tissues. Before the first injection the total chlorids, as well as the chlorid concentration were low, whereas before the second injection the total chlorids and the chlorid concentration were considerably higher. This suggests that the paucity of body chlorids in the first instance was responsible for the tissues taking up more chlorid than in the second instance, in which the chlorid concentration and total chlorids were already relatively high. The suggestion is purely a tentative one, and it must be admitted that the differing time intervals following the injection may be partly the cause of the discrepancy.

From our results in the series of patients studied, no typical curve of blood volume following the administration of hypertonic salt solution was found. It is obvious that there are sufficient reasons for this. The persons studied were not normal but severely ill. The treatment of each patient varied, and the diet and fluid intake likewise varied according to the therapeutic indications. Although a uniform amount of solution was generally given, this meant a varying dosage in terms of salt per kilogram of body weight. The speed of injection, as well as the time of making observations, was not kept constant. No typical response of the blood volume was thus found but certain general characteristics can be described as well as the probable mechanism.

After the intravenous injection a rapid rise in blood volume was followed by a gradual fall. The greatest increase appeared to be present immediately after, i. e., 30 seconds after the end of the injection. In all of the determinations, except one, a substantial return toward the original blood volume occurred in from one to three and

one-half hours after the injection (Tables 1, 2 and 3). In the one case referred to the elevated blood volume persisted for four days, an observation which was confirmed by a vital red determination. Estimations of blood volume from hemoglobin determinations twenty-four hours after the injection cannot be considered reliable, as pointed out earlier in this paper. It is believed, however, that relative variations in blood volume can fairly be told from hemoglobin determinations taken within from one to four hours of each other.

TABLE 5.—RELATIVE BLOOD VOLUME FOLLOWING INTRAVENOUS ADMINISTRATION OF HYPERTONIC SALT SOLUTION

Experiment Number and Weight of Animal	Injection of 15% NaCl			Hematocrit Red Cells, %	Blood Volume Calculated from Hematocrit, %	Blood Withdrawn, C.c.	Remarks
	Amount	Duration of Injection	Time of Observation				
1 3 kg. Rabbit	8 c.c.	1 min.	Before.....	24.0	100	1	Marked tachypnea
			7 min. after.....	13.5	178	1	
			22 min. after.....	16.5	155	1	
			26 min. after.....	17.3	139	1	No ill effects
			1½ hrs. after.....	18.5	130	1	
2 3 kg. Rabbit	8 c.c.	1 min.	Before.....	30.0	100	1	No ill effects
			½ min. after.....	27.0	111	1	
			5 min. after.....	27.0	111	1	
			30 min. after.....	27.5	109	1	
			45 min. after.....	27.0	111	1	
			2 hrs. after.....	27.0	111	1	
			3 hrs. after.....	21.5	139	1	
			24 hrs. after.....	21.2	...	1	
3 3.5 kg. Cat	7 c.c.	1 min.	Before.....	36.6	100	15	Ether anesthesia
			3 min. after.....	23.9	153	15	
			1 hr. after.....	30.0	122	15	

It is interesting to note that the example of a persistently elevated blood volume occurred in a patient who had an abnormally low plasma volume associated with a low blood chlorid concentration and a low total chlorid content. After the first injection, the plasma volume and the chlorid figures were approximately normal, and maintained their normality until the second injection. After the second injection, a rapid rise in blood volume occurred, followed by a substantial return to the previous figure in three and one-half hours, as shown by the hemoglobin determinations. Similarly, after the third injection, the relative blood volume (as calculated from the hemoglobin, red corpuscle, and hematocrit dilution) showed a sharp elevation, followed by a gradual fall, approaching normal in three hours (Table 1). The reason for this variation in response may, perhaps, be found in the tendency of the organism to revert to or maintain the normal. In the presence of a low blood volume and a low total chlorid content the increase in volume and chlorid content of the blood persisted. In the presence of a normal blood volume and blood chlorid the elevation above the normal on two occasions was quite temporary, returning largely to the normal

figures within three and one-half hours. It is freely admitted that this reasoning is hypothetical and may not at all account for the facts.

It was shown in Case 1 that the increase in blood volume was approximately equal to the number of cubic centimeters of water theoretically required to render the increased chlorids in the blood isotonic. On this basis, the maximum increase due to administration of 15 gm. salt would be 1,666 c.c. As a matter of fact, however, this amount is never actually reached since a certain portion of the chlorids enters the tissues or is excreted the moment it arrives in the blood stream. The maximum increase, expressed in terms of relative blood volume, varied in individual cases from 115 to 130 per cent. of the original blood volume. This would represent a range of increase of from 500 to 1,200 c.c. of tissue fluid. In the two instances in which the absolute blood volume was measured by the dye, the maximum increase was 761 c.c. after the first injection and 894 c.c. after the second injection.

In Case 4 (Table 2), 100 c.c. of 1,500 per cent. Ringer's solution (fifteen times stronger than standard Ringer's solution) was injected. This patient was unrelieved of his headache, and there was no fall in spinal pressure, as shown by manometer readings. It is interesting to note that the increase in blood volume and in blood chlorids was of very slight degree. The reason for this can, in part, at least, be accounted for by the lessened amount of chlorids present in Ringer's solution, but the changes still seem of lesser degree than one would expect. The serum directly following the injection was deeply hemolyzed, an effect presumably due to the excess potassium in the solution. It is of some interest to note that in this case a hypertonic salt solution was given without any fall in cerebrospinal pressure, and with minimal evidence of blood dilution. In the other cases so tested, the fall in cerebrospinal pressure was accompanied by considerable blood dilution. The findings strongly suggest that the drop in cerebral pressure when it does occur is due to a volume change dependent on egress of fluid from the brain to the blood stream.

In the two persons to whom the salt was administered by mouth either a smaller amount or a smaller concentration was given. The result was that a much smaller increase in blood volume occurred and that the maximum increase took place more than one-half hour after the injection rather than immediately afterward. The rabbits received a much larger dose by mouth than they did intravenously, but the resultant increase in blood volume was about the same in the two groups. The two rabbits, which received the salt by mouth showed a progressively increasing blood volume associated with a progressively increasing blood concentration, as was discussed above. It may be mentioned in this connection that Foley and Putnam¹⁹ found that the

oral administration of hypertonic salt caused a fall in cerebrospinal pressure similar to the intravenous administration provided that larger amounts of salt were given.

Red Corpuscles and Hemoglobin.—There were no significant changes in the red blood cells, except their decrease in number due to dilution. No hemolysis occurred as a result of hypertonic sodium chlorid injection. In the case in which hypertonic Ringer solution was given, the hemolysis was probably due to the abnormal amount of potassium present. Examination of the serum spectroscopically for traces of hemoglobin or for increased amounts of bilirubin was done in two cases with negative results.³⁹

In Case 2 (Table 4) the red cells showed a slight increased resistance to hypotonic saline three minutes after injection with a return to the normal fragility twenty-four hours later. Before the injection the chlorid content of the red corpuscles was 0.64 gm. per liter; three minutes after 0.75 gm. per liter; twenty-four hours after 1.50 gm. per liter. The finding of temporary lessened fragility is probably explainable on the supposition that the increased chlorid content of the cell had not been reduced to isotonicity within three minutes. In this case it appears that the red corpuscles had swollen at the end of twenty-four hours, inasmuch as the hemoglobin and red blood cell count still showed dilution and the hematocrit had largely returned to the original value. The striking increase in the chlorid content of the red cell from 0.64 to 1.50 makes this seem plausible. In Case 3 (Table 2) the fragility test was made with control cells but with equal quantities of the plasma before and after the injection of hypertonic salt solution. No change in fragility resulted from admixture with plasma taken after the salt injection.

Oxygen and Carbon Dioxid Content of Venous Blood.—The venous oxygen content was markedly lowered, reflecting and largely due to the diminution in oxygen capacity. There was in one instance (Case 2, Table 2) a lowering of the venous saturation that may have represented a slight slowing up of blood flow due to sudden increase in blood volume. In the other three cases, the lowering of the venous saturation was too slight to be significant. The carbon dioxid content of venous blood showed no constant or decided changes in the three cases in which this was carried out (Table 2).

Clinical Results.—No harmful effects following the administration of hypertonic salt solution were observed. The precaution was taken to exclude any case that gave evidence of renal disease. The six patients with brain tumor who had increased cerebrospinal pressure were all symptomatically improved. The symptoms that were especially relieved

39. These examinations were performed by Dr. Chester M. Jones.

were headache and stupor (remarks in Tables 1, 2 and 3). In one instance a patient was inarticulate before the injection and afterward could make herself understood by a slurring speech. The relief of symptoms generally lasted one day. One patient, who for six weeks had suffered continuously from severe headache and stupor, became wide awake and completely free from headache twenty minutes after the injection, and remained so for three days, when her symptoms began gradually to return. Among the immediate effects was the sensation of feeling very hot. All the patients who were able to talk complained of it. This disappeared within twenty or thirty minutes of the injection. There was a temporary rise in pulse rate of between five and fifteen beats and in systolic blood pressure of between 10 and 40 mm., maximal immediately after the injection and returning to normal usually within thirty minutes of the injection. In no instance was there a rise in temperature of more than 1 degree (F). In the patient, who had a fracture of the skull and to whom 1,500 per cent. Ringer's solution was given, no beneficial effects were observed. In the patient with polycythemia to whom the salt was administered by mouth, no definite change in condition was manifest.

SUMMARY AND CONCLUSIONS

1. Hypertonic salt solution was administered intravenously to six patients with brain tumor and to one patient with a fractured skull, by mouth to one patient with polycythemia and to one normal person, intravenously and by mouth to eight rabbits. Observations were made on the blood volume, the blood chlorid concentration, the total chlorid content of the blood, the effects on red corpuscles and hemoglobin, the venous oxygen and carbon dioxid content, and the clinical condition of the patients.

2. The immediate effect of the intravenous injection of 100 c.c. of 15 per cent. sodium chlorid solution was a marked increase in plasma volume. Reckoned in terms of relative blood volume, the increase was between 15 and 30 per cent. of the original blood volume, and the calculated increase on this basis between 500 and 1,200 c.c. of tissue fluid. In two instances in which the absolute blood volume was determined by the vital red dye method the maximum increase in one case was 761 c.c. and in the other 894 c.c. The increase in blood volume reflected and was almost wholly due to the increase in plasma volume.

After the injection there was a more gradual fall in blood volume, in most cases largely, although not entirely, returning to the original volume within three and one-half hours. In one case that had an abnormally low blood volume the increase persisted for four days.

3. An increase in blood volume followed the oral administration of hypertonic sodium chlorid, but was relatively of lesser degree and slower onset.

4. The mechanism of elevation and maintenance of the blood volume after hypertonic salt administration appeared to be dependent on the behavior of chlorids in the blood. Following the injection of 15 gm. sodium chlorid solution in two determinations in Case 1, there was found an increase of approximately 6 gm. in the first and 10 gm. in the second.

In the first instance the amount of increase in plasma volume was equal to the amount of water theoretically required to render the increased chlorids isotonic. In the second instance the plasma volume increase was slightly less than the theoretic requirement of the added chlorid, indicating that in a portion of the blood stream at least the blood was slightly hypertonic. Essentially, however, the increase in blood volume corresponded to the isotonic equivalent of the introduced salt. In the other human cases and in the animal experiments the rise and fall in blood volume generally ran approximately parallel to the blood chlorid concentration.

In rabbits showing an inability to excrete chlorid, the increased blood volume persisted elevated with a parallel maintenance of the increased blood chlorid concentration.

5. The red corpuscles showed no impairment due to the introduction of hypertonic sodium chlorid solution. In one case there was a temporary lessening of fragility. The oxygen carrying power of the hemoglobin was intact. There was no free hemoglobin spectroscopically, or any increase in bile pigment. In one patient, to whom a markedly hypertonic Ringer's solution was given, evidence of hemolysis appeared in the serum, due presumably to the abnormal amount of potassium present.

6. No significant changes in oxygen saturation or carbon dioxide content of the venous blood were found.

7. In the six patients with brain tumor, who had an increased cerebrospinal pressure, symptomatic improvement occurred in all. This was mainly manifested in the relief of headache and stupor. No harmful effects were observed. It appears likely that the fall in cerebrospinal pressure that follows the intravenous or oral administration of hypertonic salt solution is a volume change dependent on the egress of fluid from the brain to the blood stream.

We wish to express our thanks to Dr. Stanley Cobb and Dr. James B. Ayer for finding us neurologic cases at the Massachusetts General Hospital, and to Dr. James H. Means for his interest and aid during the course of the work.