Summary. Tolerance to both gold sodium thiosulphate and to gold sodium thiomalate can be developed in rats, as well as a cross tolerance between the 2 compounds. A minimum dose is necessary for tolerance formation, but with a sufficient dose, tolerance can be developed with only 2 doses. The tolerance lasts for considerable time.

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Distribution of Body Water Following Hemorrhage.

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Circulating blood increases its water content following hemorrhage.[1] This dilution is generally believed to result from the passage of non-vascular extracellular water into the vascular space due to a reduced capillary pressure following a reduction in blood volume. On the other hand, a few investigations as those of Milroy,[2] Gamble, Ross and Tisdall,[3] Kerr,[4] and Stewart and Rourke[5] have suggested the possibility that cellular fluids may be drawn upon to replace a deficit in blood volume.

The development of practical methods whereby the volume of extracellular water may be determined (Crandall and Anderson,[6] Gregerson and Stewart,[7] Brodie and Friedman,[8] Wallace and Brodie[9]) has suggested the desirability of applying these technics in an attempt to determine the changes in the volume of cellular and extracellular water that take place following hemorrhage. This was attempted by measuring the volume of sulfocyanide available water

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[1] Adolph, E. W., Gerbasi, M. J., and Lepore, M. J., *Am. J. Physiol.*, 1933, **104**, 502.

[2] Milroy, T. H., *J. Physiol.*, 1917, **51**, 259.

[3] Gamble, J. L., Ross, G. S., and Tisdall, F. F., *J. Biol. Chem.*, 1923, **57**, 633.

[4] Kerr, S. E., *J. Biol. Chem.*, 1926, **67**, 689.

[5] Stewart, J. D., and Rourke, G. M., *J. Clin. Invest.*, 1936, **15**, 697.

[6] Crandall, L. A., and Anderson, M. X., *Am. J. Digest. Dis. Nutrition*, 1934, **1**, 126.

[7] Gregersen, M. I., and Stewart, J. D., *Am. J. Physiol.*, 1939, **125**, 142.

[8] Brodie, B. B., and Friedman, M. M., *J. Biol. Chem.*, 1937, **120**, 511; 1939, **130**, 555.

[9] Wallace, S. B., and Brodie, B. B., *J. Pharmacol. and Exp. Therap.*, 1939, **65**, 214.

both of the whole animal and of some of its organs after hemorrhage and by comparing these values with those obtained from normal animals.

Methods. Cats anesthetized with pentobarbital sodium (40 mg per kilo of body weight) were used throughout. In 7 experiments the spleen was left intact. In 8 others, the spleen was carefully removed through an incision in the lateral abdominal wall without appreciable loss of blood. A known amount of sodium sulfocyanide (as a 5% solution to make about 200 mg per kg of body weight) was injected into the circulation by way of the femoral vein, 30 to 60 minutes being allowed for its distribution. The carotid artery was then cannulated and about 10 ml of blood removed for the various analyses. Following this, the artery was again opened and the cat bled until a total of 15.2 to 26.1 ml of blood per kg of body weight had been removed. Sixty to 120 minutes later, a final sample of blood was taken for analysis and the animal sacrificed by asphyxia. Various organs were removed, carefully blotted to remove excess blood, minced, weighed and dried for 24 to 48 hours in an oven maintained at 105°C. The dry tissues were then dissolved in normal KOH and analyzed for sulfocyanide.[8] Normal control values used for comparison in these experiments are those of Lands, Cutting and Larson[10] uncorrected for fat content. Interfering colors make sulfocyanide analysis of the liver difficult. For that reason the extracellular water is here computed from its chloride content. The chloride was determined by the method of Sunderman and Williams.[11] Methods of computation are described in an earlier publication.[10] Excretion of water and injected sulfocyanide was so small under the conditions of these experiments that this can be disregarded.

The following analyses were made on blood; specific gravity of whole blood and serum,[12] serum chloride,[13] serum sulfocyanide,[6] and serum potassium.[14, 15]

Results. Following hemorrhage, the total volume of water available for the solution of sulfocyanide was increased 34.9 to 121.0 ml per kg of final body weight (Table I). This increase was associated with a reduction in the chloride concentration of serum water in all experiments but one. For example, in Experiment I (Table II) the chloride concentration of serum water was reduced

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[10] Lands, A. M., Cutting, R. A., and Larson, P. S., *Am. J. Physiol.*, 1940, **130**, 421.

[11] Sunderman, F. W., and Williams, P. J., *J. Biol. Chem.*, 1933, **102**, 279.

[12] Barbour, H. G., and Hamilton, W. F., *J. Biol. Chem.*, 1926, **69**, 625.

[13] Van Slyke, D. D., *J. Biol. Chem.*, 1923, **58**, 523.

[14] Shohl, A. T., and Bennett, H. B., *J. Biol. Chem.*, 1928, **78**, 643.

[15] Hartzler, Eva R., *J. Biol. Chem.*, 1937, **122**, 19.

TABLE I.
Change in Total Volume of Sulfocyanide Available Water Following Hemorrhage.

Exp. No.	Sulfocyanide available H_2O, ml/kg	Hemorrhage, ml/kg	Time elapsed after hemorrhage, min.	Final sulfocyanide available H_2O, ml/kg final body wt	Inc. sulfocyanide available H_2O, ml/kg final body wt
1.	234	24.0	60	342	121.0
2.	169	15.2	60	247	81.6
3.	204	16.1	60	263	67.6
4.	300	17.7	70	330	34.9
5.	288	26.1	80	354	71.0
6.	261	16.5	150	317	58.5
7.	242	20.9	90	320	85.6
9.*	154	a. 11.2	a. 10	179	29.9
		b. 17.5	b. 40	207	39.4
10.	358	0.0	290	358	0.0
11.	303	0.0	285	303	0.0

*Not splenectomized.

TABLE II.
Changes in Serum Chloride Concentration Following Hemorrhage.
All values in mM/kg serum water.

Exp. No.	Before hemorrhage	After hemorrhage	Conc. in water added
1.	127	109	74
2.	141	130	122
3.	123	105	53
4.	113	119	175
5.	122	114	46
6.	125	118	107
7.	125	120	93
8.	118	113	98
9*	144	129	71

*Not splenectomized.

Serum protein values determined from the specific gravity according to the formula $P = 345(G - 1.0076)$; Kagan.[20]

from 127.0 mM to 109 mM per kg whereas at the same time there was an increase of 121.0 ml per kg of body weight in the sulfocyanide available water. In 3 experiments serum analysis for potassium indicated a definite increase. Before hemorrhage values for serum potassium were 6.7, 5.1 and 6.1 mM per kg of serum water; after hemorrhage 12.1, 9.35 and 14.1 mM per kg of serum water.

Analyses of skeletal muscle for changes in total water and for sulfocyanide available water gave results which suggest no significant change in the distribution of water in this organ following hemorrhage. In one instance there was found an increase in total water of 30 ml per 100 g of solids and in 2 instances a decrease of 22 ml per 100 g of solids (Table III). Similar results were obtained

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[20] Kagan, Benj. M., *J. Clin. Invest.*, 1938, **17**, 369.

TABLE III.
Change in Total Water Content Following Hemorrhage.
(All values in ml/100 g solids.)

Exp. No.	Gastrocnemius muscle	Diaphragm muscle	Cardiac muscle	Liver	Pancreas	Lung	Pylorus	Duodenum	Colon	Skin
1.	6	—4	9	—13	264	22	77	50		55
2.	30*									92*
3.			32	41	28	11	51	6	17	10*
4.	— 8*									14*
5.	—22*		49	17	101	—4		70	80	—22*
9.	—22	16	11		23		65	18	—4	5
A.	26	11		14	231		77	32	21	93
B.	8	—24	45	36	108		72	32	40	25
C.	19	—63	52	52	91	3	50	0	16	—17
D.	10	12	68	41	41	70	85	13	69	28
E.	— 5	—61	52	14	55	10	57		8	22

*Control tissue taken from same experimental animal. In all other instances the differences are based on the normal averages. (12 experiments uncorrected for fat; Lands, Cutting and Larson, 1940.)

TABLE IV.
Changes in Sulfocyanide Available Water Following Hemorrhage.
(All values in ml/100 g solids.)

Exp. No.	Gastrocnemius muscle	Diaphragm muscle	Cardiac muscle	Liver†	Pancreas	Pylorus	Duodenum	Colon	Skin
1.	25.8	8		50	93	112	91	100	96
2.	— 9.0*								74*
3.	4.0	—40	10		29	78	22	10	9*
4.									35*
5.	33.0*		40	18		88	2	—9	2*
6.	— 1.2	— 7	59		3	122	52	143	18
A.	—10.3	8		18	255	11	0	47	—9
C.	—21.7	28	59	34	5	66	171	101	7
D.	35.8	64		31	73	157	103	97	58
E.	24.0		—36	14	123	42	—62	—96	38

*See footnote, Table III.

†No sulfocyanide analyses could be made on liver due to interfering colors. The values given here are those for chloride available water.

for diaphragm. In cardiac muscle, liver, pancreas, lung, pylorus, duodenum, colon and skin significant increases were found in the total water content and in the sulfocyanide available water content (Tables III and IV). This was considerable for the pancreas and for the alimentary tract. In general, when the total extracellular compartment was increased most there were large increases in both the total water and in the sulfocyanide available water of the pancreas and alimentary tract.

Discussion. The experimental findings presented here are inconsistent with the simple concept which attributes blood dilution to the movement of a lymph-like fluid from the interstitial spaces into the blood stream. A reduction of body water by hemorrhage should lead to a corresponding reduction in the sulfocyanide available (extracellular) water. Quite the opposite was found to be the case, the sulfocyanide available water being increased after hemorrhage. The results of the experiments here reported suggest the increase in sulfocyanide available water comes from either (1) an increase in the permeability of some of the tissue cells to sulfocyanide following hemorrhage or (2) an increase in the volume of extra-cellular water at the expense of cell water. Inasmuch as the total water as well as the sulfocyanide available water increased in some of the organs (as intestine, pancreas and other visceral organs) it would seem more plausible to assume that the increase in the volume through which the sulfocyanide is distributed actually represents an increase in the total extracellular water at the expense of the water content of some organs of the body. The possibility that the cellular compartment may lose water after hemorrhage had been suggested as early as 1917 when Milroy[2] reported, on the basis of changes in the specific gravity of both whole blood and serum and a diminished alkaline reserve of plasma, that a hypotonic tissue fluid low in bicarbonate entered the blood stream. Johnston and Wilson[16] likewise found a reduced alkaline reserve after hemorrhage. Gamble, Ross and Tisdall,[3] Gamble[17] and Butler, McKhann and Gamble[18] have shown that tissue fluid may be drawn upon to replace extracellular water and that this water is made available through the destruction of protoplasm. Kaump and Parsons[19] report an increase in the concentration of blood urea nitrogen following hemorrhage, this increase being at its maximum 24 to 48 hours following hemorrhage when blood dilution is greatest. This would be expected to follow if cell water is liberated through the destruction of protoplasm. Kerr[4] found the serum sodium and chloride diminished without a reduction in the concentration of serum potassium following hemorrhage. This, he believed indicated a mobilization of intracellular water relatively rich in potassium and low in sodium and chlorides. In 3 experiments, in which serum potassium was determined, we found potassium elevated to a value about twice the normal. Careful analysis of skeletal muscle failed to demonstrate any significant change in either its total water content or its sulfocyanide available water content. This organ, the most probable source of available water because of its large mass, could have given

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[16] Johnston, C. G., and Wilson, D. W., *J. Biol. Chem.,* 1929-30, **85**, 727.

[17] Gamble, J. L., Ross, G. S., and Tisdall, F. F., *J. Biol. Chem.,* 1923, **57**, 633.

[18] Butler, A. M., McKhann, C. F., and Gamble, J. L., *J. Pediat.,* 1933, **3**, 84.

[19] Kaump, D. H., and Parsons, J. C., *Am. J. Digest. Dis. Nutrition,* 1940, **7**, 191.

up water to the extracellular compartment only by a reduction of its mass of protoplasm.

Summary. 1. The volume of sulfocyanide available water of cats is definitely increased after hemorrhage. 2. The chloride concentration of serum water was found to be decreased in all experiments save one. 3. The total water and sulfocyanide available water content of cardiac muscle, pancreas, pylorus, duodenum, colon, skin and liver (chloride available water) was increased after hemorrhage. No significant differences were found in the case of skeletal muscle (gastrocnemius and diaphragm). 4. The significance of the above findings is discussed.

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A Simple Method for Prolonging Therapeutic Insulin Coma.*

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In the treatment of psychoses, insulin coma[1] (or the period of unconsciousness) is generally not allowed to persist beyond an hour or an hour and a half. In cases inadvertently allowed to linger in coma beyond that period, an irreversible insulin coma[2] frequently follows that can no longer be relieved by intravenous glucose. This dangerous and sometimes fatal complication has, however, directed the attention of several investigators to the important fact that patients who survive several hours or days of this relatively irreversible coma often show dramatic psychiatric improvement on awakening. Kraulis[3] attempted to utilize this phenomenon for therapeutic ends by prolonging insulin coma with periodic small glucose feedings sufficient to sustain the patient but not sufficient to rouse him. The difficulties in the clinical management of these sporadic feedings, however, and the frequent presence of gastric retention[2] (which

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[1] Sakel, Manfred, *Insulin Shock Treatment of Schizophrenia*, Nervous and Mental Disease Monograph No. 62, New York, 1937.

[2] Wortis, Joseph, and Lambert, R. H., *Am. J. Psychiatry*, 1939, **96**, 335.

[3] Kraulis, W., *Schweiz. Arch. f. Neur. u. Psychiat.*, Erganzungsheft, 1937, **39**, 219.