THE EFFECT OF AN INFUSION OF HYPERONCOTIC ALBUMIN ON THE EXCRETION OF WATER AND SOLUTES [1, 2]

By R. G. PETERSDORF [3] AND L. G. WELT [4]

(From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.)

(Submitted for publication August 28, 1952; accepted December 24, 1952)

INTRODUCTION

Although there is good evidence that the rates of excretion of water and solutes are altered in response to a change in plasma volume (1–3), the specific stimuli and the precise mechanisms through which the kidney modifies the volume and composition of the urine are not well understood. A decrease in plasma volume due to dehydration or increased transudation is accompanied by an increase in the oncotic pressure of the plasma, and it has been suggested that this rise in oncotic pressure may be one of the functions of a decrease in plasma volume that promotes a compensatory alteration in renal function.

Several recent investigations (4, 5) have demonstrated that an increase in the concentration of albumin and, presumably, an increase in the colloid osmotic pressure of the plasma in normal subjects results in a decrease in the rates of excretion of salt and, less consistently, water. The present investigation was undertaken to collect further data on the question of whether or not an increase in plasma oncotic pressure serves as a stimulus to antidiuresis and to determine whether such an antidiuresis represents a primary effect on water or is a passive consequence of a change in the rate of tubular reabsorption of salt.

EXPERIMENTAL PROCEDURE AND METHODS

The subjects of these studies were seven healthy male medical students and two patients with diabetes insipidus. The origin of the diabetes insipidus appeared to be post-encephalitic in F. S. and due to reticuloendotheliosis in J. V. Both had an inability to concentrate the urine although the volumes in J. V. were not tremendous which may have been related to a coexisting mild hypothyroidism. Patient F. S. had the typical response of diabetes insipidus to the Hickey-Hare test (6). This was not performed on subject J. V. It is, of course, impossible to state whether the diabetes insipidus was "complete" in either instance.

Food, water, and tobacco were withheld 12 to 14 hours prior to and throughout each experiment, except in the studies in which fluids were permitted until the start of the experiment. The normal subjects were recumbent throughout the study except for the brief intervals attending voiding. Urines were collected through an indwelling catheter in the two patients with diabetes insipidus. The experiments started at about 8 a.m. and lasted 7 to 11 hours.

Infusions of 200 to 500 cc. of 25 per cent salt-poor purified human serum albumin were administered at a time when these subjects were in a steady state of physiological diabetes insipidus (7). This condition was achieved by the infusion of a 5 per cent solution of glucose in water in such a manner as to attain and maintain a positive balance of water of approximately 1 liter throughout the study. The infusion of the solution of glucose was administered initially through two needles in different veins of one forearm by the use of a Y tube leading from the infusion bottle. One of these needles was eventually used for the infusion of the solution of albumin and obviated the necessity of a venipuncture at the time of its administration. This infusion was started when the rate of flow of urine had been constant for four consecutive periods of approximately 30 minutes each. The concentration of sodium in 25 per cent salt-poor human albumin is 155 mEq. per liter. To avoid an increase in the concentration of sodium in the serum due to the infusion of albumin, the rate of administration of the 5 per cent glucose in water was accelerated by 300 cc. per hour coincident with the administration of the albumin. The most rapid infusion of albumin in any of the normal subjects was 100 cc. in 15 minutes (400 cc. per hour) and it, therefore, seems unlikely that the concentration of sodium in the serum could have been increased significantly. The experiments were continued beyond the period of the infusion of albumin until the rate of flow of urine was returning to or had reached the levels that characterized the control periods.

[1] This work was supported by Contract No. DA-49-007-MD-116 issued by the Medical Research and Development Board, Office of the Surgeon General, United States Army.

[2] The serum albumin used in these studies was supplied by the American Red Cross.

[3] This article represents work done in fulfillment of the thesis requirement for the degree of Doctor of Medicine at the Yale University School of Medicine.

[4] Present address: Department of Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina.

Among the normal subjects there were four studies in which the solution of albumin was administered slowly, and four in which its administration was rapid. Two normal subjects were studied during both a rapid and slow administration of the albumin. The effects of an infusion of albumin were also compared with the administration of 2.5 mU of pitressin in one subject. In one study, the subject sustained an antidiuretic response following each of two allegedly painless venipunctures.

Blood was drawn under oil at the start of each study, before and soon after the administration of the albumin, and at the end of the experiment. The second specimen of blood was drawn after three consecutive constant periods of urine flow and was followed by a fourth period

TABLE I

The effects of hyperoncotic solutions of albumin on the concentrations of proteins and electrolytes in serum and on the plasma volume

Study	Blood	Time	I-V alb.	Concentration in serum						Hkt.	Hgb.	Hgb./ Hkt.	PV_2/PV_1	Δ PV per gm Alb.
				T.P.	Alb.	Glob.	Na	Cl	K					
		min.	*gm.*		*gm. %*			*mEq./L.*			*gm. %*		%	*cc.*
1.	I			7.00	4.11	2.89	143	103	3.9	43.2	14.5	33.6		
J. A.	II	274		6.53	4.02	2.51	140	99	4.0	43.9	14.4	32.8	100	
	III	384	60	7.45	4.87	2.58	136	96	3.1	38.4	12.0	31.4	132	18.5
	IV	455		6.82	4.46	2.36	135	96	3.4	38.0	12.9	32.7	123	
2.	I			6.90	4.46	2.44	142	105	4.4	46.4	15.1	32.7		
K. B.	II	181		6.20	3.98	2.22	136	101	4.0	44.4	14.3	32.2	100	
	III	298	50	6.82	4.84	1.98	139	104	3.9	39.0	12.4	31.8	126	17.6
	IV	448		6.82	4.89	1.93	138	105	3.7	39.7	13.1	33.0	118	
3.	I			6.90	4.18	2.72	143	105	4.1	46.9	14.8	31.5		
M. T.	II	189		6.12	3.90	2.22	139	101	4.0	44.0	13.8	31.8	100	
	III	349	100	7.00	4.95	2.05	139	99	3.9	35.9	10.1	28.2	156	30.2
	IV	412		6.82	4.71	2.11	138	98	3.7	38.3	12.1	31.6	126	
4.	I			6.82	4.21	2.61	142	100	3.9	45.6	14.2	31.6		
H. W.	II	262		6.53	3.90	2.63	138	98	3.7	44.0	14.0	31.8	100	
	III	342	50	6.82	4.64	2.18	135	94	3.3	38.4	12.9	33.6	119	16.2
5.	I			6.82	4.35	2.47	140	105	4.3	46.2	13.6	29.5		
R. G.	II													
	III	295	65	6.82	5.21	1.61	134	96	3.3	38.2	12.2	31.9		
	IV	420		6.86	4.98	1.88	133	97	4.0	39.2	12.3	31.4		
6.	I			7.00	3.86	3.14	143	102	3.7	42.0	12.5	29.7		
J. L.	II	206		6.64	3.19	3.45	138	100	3.8	39.7	12.1	30.5	100	
	III	416	100	7.30	5.12	2.28	137	96	3.5	34.1	9.4	27.6	141	13.7
	IV	654		7.35	4.94	2.39	138	96	3.5	37.3	11.2	30.0	112	
7.	I			6.64	4.09	2.55	145	105	3.6	46.7	15.0	32.7		
H. W.	II	157		5.90	3.67	2.23	138	102	3.6	38.5	12.2	31.7	100	
	III	312	50	6.33	4.35	1.98	139	101	3.0	33.4	10.9	32.6	121	17.6
	IV	444		6.42	4.22	2.20	136	100	2.9	37.4	12.9	34.4	96	
8.	I			6.64	4.24	2.40	139	103	3.9	45.0	13.7	30.5		
M. T.	II	318		6.53	3.99	2.54	137	100	3.9	42.5	13.0	30.6	100	
	III	498	100	7.25	5.04	2.21	138	99	3.8	38.8	12.0	30.9	115	8.2
	IV	551		7.10	5.20	1.90	137	102	3.9					
9.	I			7.45	4.98	2.47	141	102	5.5	46.5	14.3	30.8		
F. S.*	II	65		6.46	4.11	2.35	135	97	4.7	42.4	12.5	29.5	100	
	III	165	62.5	7.05	4.94	2.11	136	97	4.3	37.6	11.1	29.5	122	19.2
	IV	257		6.68	4.84	1.84	137	93	4.5	38.4	11.4	29.7	117	
10.	I			7.05	4.46	2.59	138	100	4.7	44.1	13.0	29.5		
F. S.*	II	92		6.28	4.14	2.14	132	92	3.9	41.2	12.0	29.1	100	
	III	237	125	7.25	5.18	2.07	130	88	3.6	32.2	9.7	30.2	142	18.1
	IV	280		7.20	4.96	2.24	128	90	3.5	32.8	9.9	30.1	138	
11.	I			7.16	3.03	4.13		106	4.2					
J. V.†	II	131		6.82	2.84	3.98		103	4.2					
	III	210	60	7.65	3.73	3.92		102	4.0					

* Diabetes Insipidus—Post-encephalitis.
† Diabetes Insipidus—Reticulo-endotheliosis.

during which the rate of excretion of water was observed to make certain that the venipuncture itself did not induce an antidiuresis.

Many of the chemical methods and calculations have been described in previous publications from this department (8, 9, 10). The concentration of albumin in serum was determined by biuret (11) after the salting out of globulins by the method of Milne (12) as modified by Wolfson, Cohn, Calvary, and Ichiba (13). Creatinine in the serum and urine was determined by the method of Hare (14). The urines were not treated with Lloyd's reagent. The concentration of urea in urine and serum was determined as described by Conway (15). Since urinary ammonia was not determined, urea nitrogen was assumed to be equal to 93 per cent of urea plus ammonia nitrogen.

The clearance of endogenous creatinine was used as an estimate of the rate of glomerular filtration. The change in plasma volume, PV_2/PV_1, was estimated from the formula:

$$\frac{Hgb_1}{Hgb_2} \times \frac{1 - Hkt_2}{1 - Hkt_1} \times 100.$$

For purposes of estimating the approximate increase in plasma volume in cubic centimeters per gram of infused albumin, the original plasma volume was assumed to be 5 per cent of the body weight.

RESULTS

In every instance the infusion of albumin resulted in an expansion of the plasma volume (Table I). The magnitude varied between 8.2 and 19.2 cc. per gram of administered albumin. The average expansion of 16.1 cc. per gram is comparable

TABLE IIA

The effects of infusions of 25 per cent albumin on clearances, concentrations and rates of excretion of solutes in the urine (normal subjects)

Study	Period	Period alb. infusion	Time at end of period	Urine vol.	Concentration in urine					Rates of excretion						Cr U/S	C_{Cr}	$C_{U_{res}}$
					Na	Cl	K	Urea	Total	H_2O	Na	Cl	K	Urea	Total			
		min.	*min.*	*cc.*	*mOsm./L.*					*cc./min.*	*μOsm./min.*						*cc./min.*	
1. J. A.	A		109	508	29.5	27.5	14.8	75.7	164.4	4.7	134.5	255	67.8	351	750	30.4	147	
	B		217	2,021	7.5	8.5	1.5	20.1	38.1	18.7	140	159	28.0	376	712	7.7	144	
	C		268	926	6.3	4.9	1.4	18.7	34.3	18.2	115	89.9	25.1	340	623	7.7	140	
	D	297	294	469	6.4	4.9	1.4	18.3	34.0	18.0	115.5	89.2	26.0	330	612	7.3	131	
	E	|	321	435	6.4	3.8	1.6	18.5	34.5	16.1*	103.2	60.6	25.8	298	556	8.1	131	
	F	|	347	376	7.1	4.4	2.2	19.5	38.2	14.5	103.3	64.4	32.0	282	552	9.5	136	
	G	366	376	305	10.8	6.3	3.7	26.2	55.2	10.5	113.5	66.5	39.2	276	581	14.3	150	
	H		412	240	9.9	10.0	5.2	38.9	69.2	7.5	74.5	75.2	39.0	292	579	21.4	160	
	I		450	368	6.6	5.3	5.0	22.8	45.0	9.7	63.3	51.0	48.4	220	434	13.7	133	
2. K. B.	A		93	289	30.9	32.3	11.5	95.8	180.6	3.1	96.2	100.5	35.8	298	562	43.4	135	57.9
	B		168	1,348	8.4	9.9	2.4	20.2	41.7	18.0	146	178	42.6	363	750	7.6	137	75.9
	C	214	195	533	6.1	8.0	1.9	17.6	33.8	19.7	121.4	158.5	38.1	347	667	7.2	142	76.0
	D	|	231	395	10.7	11.3	4.9	24.9	56.1	11.0*	117.9	124	53.6	273	616	10.4	114	59.6
	E	283	281	303	13.8	13.2	9.3	44.3	90.5	6.1	83.7	79.6	51.0	268	548	21.7	132	63.6
	F		314	482	5.4	6.5	4.4	18.5	38.5	14.6	79.6	94.9	64.8	270	562	9.2	135	67.4
	G		368	832	5.8	7.0	3.8	18.0	37.3	15.4	90.0	118.0	59.0	277	572	9.0	133	70.5
	H		412	756	8.9	8.2	3.0	15.3	39.0	17.2	152.6	140.8	51.2	263	670	7.9	135	72.5
	I		436	458	10.3	8.4	2.7	14.6	40.5	19.1	196.5	160.0	50.8	279	773	7.9	151	73.0
3. M. T.	A		83	218	20.4	26.2	15.2	163.2	234.6	2.6	53.9	69.0	40.1	429	617	79.3	208	
	B		123	708	4.6	6.5	2.5	45.0	59.3	17.7	82.3	115.1	44.4	797	1050	13.9	245	
	C		180	1,021	3.9	6.7	2.8	35.2	51.6	17.9	70.1	119.5	49.7	685	925	12.4	226	
	D	240	237	982	3.3	6.0	3.8	36.1	50.3	17.2	56.8	103	65.8	622	866	13.1	226	
	E	|	258	323	3.9	4.3	3.9	35.5	51.0	15.4*	60.2	65.7	59.5	546	784	14.2	218	
	F	334	305	718	4.6	3.2	5.4	35.2	55.1	15.3	70.2	49.7	82.0	538	842	14.6	221	
	G		347	252	10.0	8.7	15.6	68.2	119.5	6.0	60.0	52.4	93.9	410	717	37.8	227	
	H		372	377	2.5	5.6	5.9	31.6	48.4	15.1	38.0	84.9	88.9	476	730	15.6	235	
	I		410	668	2.1	6.3	5.2	26.8	41.4	17.6	37.8	111.1	90.7	471	728	13.6	239	
4. H. W.	A		138	416	54.6	68.4	24.7	120.7	279.3	3.0	163.8	205	74.1	362	848	56.8	170	
	B		206	1,370	10.1	11.9	3.2	20.7	47.4	20.1	203	240	65.2	416	953	9.9	199	
	C		257	949	7.8	8.5	2.4	21.3	41.8	18.6	146	159	44.3	397	778	10.4	193	
	D	284	276	335	7.4	7.5	2.3	21.5	41.0	17.7	130.8	133.2	41.6	381	725	11.3	200	
	E	|	298	338	7.1	6.8	2.8	22.6	43.3	15.4*	108.8	105.4	43.2	348	667	12.3	190	
	F	324	329	373	8.1	4.8	5.2	26.2	52.7	12.0	96.8	57.5	62.0	320	629	15.9	191	
	G		354	268	5.7	4.4	6.1	28.5	52.1	10.7	61.2	48.1	66.2	305	558	17.9	192	
	H		374	258	5.2	6.2	4.3	25.2	44.2	12.9	66.6	79.5	56.2	325	571	15.4	200	

TABLE IIA—*Continued*

Study	Period	Period alb. infusion	Time at end of period	Urine vol.	Concentration in urine					Rates of excretion						Cr U/S	C_{Cr}	C_{Urea}
					Na	Cl	K	Urea	Total	H_2O	Na	Cl	K	Urea	Total			
		min.	*min.*	*cc.*	*mOsm./L.*					*cc./min.*	*μOsm./min.*							*cc./min.*
5. R. G.	A		90	155	35.7	58.0	31.3	158.8	292.8	1.7	64.1	99.8	53.8	273	504			
	B		114	275	25.8	16.8	6.2	41.7	105.7	11.5	296	192.2	71.1	478	1212	37.9	141	
	C		139	341	8.6	9.9	4.0	29.7	55.0	13.8	119	135.6	54.1	403	745			
	D	218	213	1,061	7.3	7.6	3.6	25.8	47.6	14.4	105	109	51.7	370	683	10.1	143.0	
	E	|	238	302	6.7	7.9	4.1	26.4	48.2	12.1*	81.5	94.9	50.1	316	582	10.6	128	
	F	282	320	889	6.5	5.4	5.5	28.8	52.8	10.9	71.0	58.5	60.0	315	576	13.7	149	
	G		371	652	7.7	4.0	2.9	23.6	44.9	12.8	98.4	51.1	37.6	301	523	11.4	146	
	H		433	815	9.2	4.3	2.0	22.5	44.9	13.2	121	56.8	26.7	296	590	11.5	151	
6. J. L.	A		91	170	14.0	20.9	10.2	215.0	263.4	1.9	26.2	39.1	19.1	402	493	87.6	159	
	B		241	1,726	2.2	3.2	2.9	49.0	59.3	11.5	25.6	37.4	33.8	564	682	14.4	166	
	C	261	255	154	2.0	2.7	4.2	46.7	59.3	11.0	22.3	30.2	46.6	514	653	15.8	173	
	D	|	281	263	1.8	2.0	3.2	47.1	57.1	10.1*	17.9	20.7	32.7	476	577	17.0	142	
	E	|	381	932	1.5	1.5	7.2	44.3	61.7	9.3	14.3	14.3	66.6	412	574	19.8	184	
	F	408	516	1,154	2.1	1.2	7.3	41.1	59.8	8.5	17.7	10.2	62.7	350	509	23.2	197	
	G		544	257	2.7	1.5	4.6	37.1	51.7	9.2	24.7	14.2	42.5	341	476	21.2	195	
	H		597	525	4.2	1.4	4.1	32.0	48.8	9.9	42.1	13.6	41.1	317	483	18.9	187	
	I		650	480	5.3	1.5	4.2	32.5	51.7	9.1	48.7	14.0	38.5	296	471	20.0	182	
7. H. W.	A		90	317	39.6	55.4	24.1	116.4	243.8	3.5	139.4	196.5	84.8	597	858	50.2	176	
	B		168	1,357	7.7	9.4	7.6	24.8	55.5	17.4	134.2	162.8	133	432	966	10.2	177	
	C	209	206	641	6.5	6.1	6.0	23.3	48.4	16.9	110.5	103.4	101.4	394	815	10.5	167	
	D	|	231	375	5.8	4.8	2.9	24.1	41.5	15.0*	86.8	71.5	44.0	362	623	11.8	178	
	E	|	281	753	5.5	3.2	3.4	23.6	41.4	15.0	83.1	48.5	50.7	354	621	12.0	179	
	F	303	327	355	4.8	3.9	3.7	24.3	41.4	13.6	65.5	53.2	50.7	331	563	13.1	178	
	G		365	794	5.6	3.7	3.1	23.1	40.5	13.6	76.6	50.1	41.9	314	551	13.3	181	
	H		421	845	7.3	4.6	2.4	19.8	39.2	15.1	109.7	69.3	36.5	299	592	12.5	189	
	I		440	329	8.3	4.8	1.9	18.7	39.1	17.3	143.2	82.5	33.5	327	676	12.2	212	
8. M. T.	A		43	747	4.5	7.2	2.9	24.9	39.7	17.4	78.7	125.0	50.5	433	691	13.2	229	
	B	69	66	405	4.3	6.5	2.7	25.0	39.0	17.6	76.0	114.4	47.0	440	687	13.1	231	
	C	|	88	373	4.2	6.5	2.9	24.3	38.6	17.0*	73.3	110.5	48.7	415	657	13.4	228	
	D	|	134	844	4.9	6.0	3.5	22.4	39.1	18.3	89.6	109.6	63.5	410	715	13.1	239	
	E	209	218	1,630	5.2	6.0	3.1	19.3	36.1	19.4	101.4	116.2	61.1	375	700	12.1	235	
	F		255	735	5.2	6.0	3.4	16.8	34.1	19.9	104.4	119.1	67.8	334	678	11.9	236	
	G		290	817	5.9	7.2	2.5	14.9	31.6	23.3	136.5	162.4	58.0	336	736	10.8	251	

* First period after start of infusion of albumin.

to that observed in another investigation (5) and is close to the theoretical value of 18 cc. per gram (16). The concentration of albumin in serum increased in all cases, providing evidence of an increase in the oncotic pressure of the plasma even after time for equilibration had been permitted. The infusions of albumin had no significant effect on the size of the red blood cells as measured by Hgb/Hkt. The initial decrease in the concentrations of total proteins, albumin, sodium, and chloride in the serum is the result of dilution by the positive balance of water.

In all but one study (no. 8) the rate of urine flow decreased in response to the infusions of 25 per cent albumin (Tables IIA and IIB). Although it is recognized that the clearance of endogenous creatinine may not be a precise measure of the rate of filtration at the glomerulus, the clearance of this substance in these studies would suggest that the changes in urine flow were unrelated to alterations in filtration rate except in study No. 9 in which the clearance of creatinine fell from 246 to 223 cc. per minute during the period of maximum antidiuresis. However, during the periods immediately preceding and following this, the clearance of creatinine did not decrease in spite of the fact that the rate of excretion of water was below the pre-albumin infusion levels. Moreover, when this patient was studied a second time (no. 10), there was no change in the clearance of endogenous creatinine during the antidiuretic phase. In studies 2 and 5 there were transient decreases in the clearance of creatinine immediately following the start of the infusion of albumin. However, this decrease did not coincide with the maximum antidiuresis during which the clearance of creatinine had returned to the pre-albumin infusion levels.

The magnitude of the antidiuresis in normal

TABLE IIB

The effects of infusions of 25 per cent albumin on clearances, concentrations, and rates of excretion of solutes in the urine (diabetes insipidus)

Study	Period	Period alb. infusion	Time at end of period	Urine vol.	Concentration in urine					Rate of excretion						Cr U/S	C_{Cr}	C_{Urea}
					Na	Cl	K	Urea	Total	H_2O	Na	Cl	K	Urea	Total			
		min.	*min.*	*cc.*	*mOsm./L.*					*cc./min.*	*μOsm./min.*						*cc./min.*	
9. F. S.	A		45	1,012	11.2	15.2	7.1	19.4	46.1	22.5	251.7	341.8	160.9	436	1037	10.7	242	126
	B	83	78	920	9.4	12.0	5.2	14.0	43.2	27.8	262.8	333.8	143.7	389	1200	8.3	230	115
	C	|	95	435	7.8	8.5	4.4	14.3	40.8	25.6*	200.2	218.9	113.6	366	1044	9.4	240	111
	D	|	113	371	6.5	4.6	6.6	18.3	44.6	20.6	134.4	94.7	136.1	377	918	11.9	246	116
	E	144	158	770	6.1	3.4	7.1	18.8	45.2	17.1	104	58.2	123.0	322	774	13.0	223	101
	F		203	963	6.0	4.3	3.3	15.4	34.0	21.4	127.8	92.0	71.7	330	728	11.3	242	110
	G		247	1,000	6.2	4.6	2.2	14.8	31.2	22.7	141.2	104.5	50.0	336	708	12.0	273	121
10. F. S.	A		87	2,080	9.1	6.0	2.5	14.4	37.5	23.9	217.8	143.0	58.8	344	897.2	9.0	220	119
	B		144	1,260	8.1	5.0	2.0	13.6	33.9	22.1	180.5	109.6	45.1	300	749.5	10.3	229	119
	C	156	155	242	8.7	4.4	1.8	13.0	33.9	22.0	190.5	97.8	39.0	286	745.6	11.1	245	119
	D	|	179	454	8.5	3.9	2.2	13.5	34.8	18.9*	160.5	74.3	41.2	255	657.4	12.7	240	108
	E	|	200	320	9.7	2.7	2.7	15.9	40.7	15.2	147.0	41.5	41.7	240	618.0	15.4	234	106
	F	|	220	335	7.8	2.6	2.8	15.1	36.5	16.8	131.9	43.0	47.9	254	613.1	15.4	259	113
	G	232	241	374	8.8	5.1	2.3	13.7	35.9	17.8	156.0	54.8	41.5	244	639.3	15.4	275	111
	H		258	357	8.6	4.3	2.1	11.9	33.3	21.0	180.0	89.8	45.2	250	699.4	13.5	283	116
	I		277	472	9.8	6.7	1.7	9.8	32.7	24.8	242.3	165.5	41.4	243	811.4	10.9	271	116
11. J. V.	A		31	185	21.6	23.3	15.4	23.2	97.2	6.0	129.5	139.8	92.4	139	583.0	26.6	160	
	B		56	242	18.1	18.1	5.9	15.0	63.0	9.7	175.5	175.5	57.2	145.6	611	17.2	166	
	C		127	900	15.5	14.1	2.7	10.6	47.0	12.7	196.8	179	33.9	134.1	597	13.2	168	
	D	150	147	245	12.4	9.1	3.1	10.0	41.0	12.2	151.9	111.1	37.8	122.5	502	12.9	158	
	E	|	169	218	8.7	5.5	4.1	11.7	37.3	9.9*	86.6	54.0	40.4	115.4	369	15.4	152	
	F	196	189	185	11.5	3.6	5.2	12.1	45.5	9.2	106.4	33.5	48.4	112.1	421	16.2	150	
	G		210	234	11.0	3.3	4.2	10.1	40.5	11.1	122.6	37.0	47.3	112.6	452	15.2	169	

* First period after start of infusion of albumin.

subjects was invariably related to the rate at which the initial 25 gm. aliquot of albumin was administered (Tables III and IV). When the initial administration was rapid, the antidiuresis averaged 60 per cent (no. 1 to no. 4), whereas a slower infusion resulted in an average drop in urine flow of 22 per cent in three studies (no. 5 to no. 7), and in a slight diuresis in study 8. It is doubtful that variations in the rate of administration of the remainder of the infusion had any effect on the rate of excretion of urine. The validity of these observations was tested by administering identical amounts of albumin to the same subjects at rapid and slow rates on two different occasions (studies 4 and 7, and 3 and 8). Their responses coincided with the pattern described above. The responses in the patients with diabetes insipidus were similar to those normal subjects to whom the albumin was administered slowly. The albumin was administered rapidly in each study of the patients with diabetes insipidus (no. 9 to no. 11) but the rate of excretion of urine diminished only 30 to 38 per cent.

TABLE III

The effects of variations in the rate of administration of 25 per cent albumin on the magnitude and duration of antidiureses

Study	Amt. alb. infused	Rate of adm. of first 25 gm. alb.	Rate of adm. of total amt. alb.	Max. antidiuresis
	gm.	*gm./min.*	*gm./min.*	%
1	60	1.66	0.86	58
2	50	1.47	0.72	75
3	100	1.56	1.06	65
4	50	1.38	1.25	40
5	65	0.78	1.01	24
6	100	0.78	0.68	25
7	50	0.69	0.53	17
8	100	0.65	0.71	No antidiuresis
9	62.5	1.25	1.02	33
10	125	2.77	1.89	30
11	60	2.08	1.30	38

The rate of excretion of total solutes was diminished during the periods of antidiuresis in all experiments except study 8 (Tables IIA and IV). These alterations were quite uniform and the delineation between slow and rapid infusions of albumin noted with respect to the excretion of water was not evident.

TABLE IV

The effect of infusions of 25 per cent albumin on the rates of excretion of H_2O, Na, and total solutes

Study	Rate of excretion before albumin			Rate of excretion during max. antidiuresis			% decrease in rate			% Δ Na / % Δ solutes	Cr U/S	
	H_2O	Na	Total solutes	H_2O	Na	Total solutes	H_2O	Na	Total solutes		Before alb.	Max. antidiuresis
	cc./min.	*μOsm./min.*		*cc./min.*	*μOsm./min.*							
1	18.0	116	612	7.5	75	519	58	35	15	2.33	7.3	21.4
2	19.7	121	667	6.1	84	548	75	31	18	1.72	7.2	21.7
3	17.2	57	866	6.0	38	717	65	33	17	1.94	13.1	37.8
4	17.7	131	725	10.7	61.2	558	40	53	23	2.30	11.3	17.9
5	14.4	105	683	10.9	69	573	24	34	16	2.12	10.1	13.7
6	11.0	22.3	653	8.5	17.7	509	25	21	22	0.95	15.8	23.2
7	16.9	111	815	13.6	66	563	17	41	31	1.32	10.5	13.3
8*	17.6	76	687	19.9	104.4	678	+12	+32	− 2		13.1	11.9
9†	25.6	200	1,044	17.1	104	774	33	48	26	1.84	9.4	13.0
10†	22.0	191	794	15.2	147	618	30	23	22	1.05	11.1	15.4
11†	12.6	187	576	9.2	106.4	421	38	43.1	26.9	1.60	12.9	16.2

* Diuretic response.
† Rapid infusions in patients with diabetes insipidus.

TABLE VA

The effects of ADH on clearances, concentrations, and rates of excretion of solutes

Study	Period	Time	Urine vol.	Concentration in urine					Rates of excretion						Cr U/S	C_{Cr}
				Na	Cl	K	Urea	Total	H_2O	Na	Cl	K	Urea	Total		
		min.	*cc.*	*mOsm./L.*					*cc./min.*	*μOsm./min.*						*cc./min.*
12. V. P.	A*	68	1,002	8.0	7.4	3.5	21.8	44.6	14.7	117.0	108.2	50.8	320	656	9.7	143
	B	231	565	22.3	23.1	11.8	66.1	132.3	3.5	78.0	80.8	41.3	231	463	43.1	151
	C	257	345	8.4	9.6	6.0	22.6	51.6	13.3	112.3	127.5	80.4	302	686	11.9	159
	D*	310	598	11.0	10.4	4.6	25.0	54.2	11.3	124.1	117.5	52.4	283	612	13.3	150
	E	364	323	21.4	19.5	4.6	43.5	95.5	6.0	128.5	117.0	27.6	261	523	24.7	148
13. K. B.	A	95	408	22.4	27.4	9.9	71.8	136.4	4.3	96.4	117.8	42.5	309	586	36.3	156
	B	194	1,482	4.2	6.3	2.8	21.7	35.7	15.0	63.3	94.8	41.4	326	536	10.5	157
	C†	216	314	3.1	4.8	3.2	20.3	32.9	14.3	45.1	68.5	45.3	291	471	10.4	149
	D	255	332	4.7	9.9	5.3	32.2	52.2	8.5	40.0	84.2	45.0	274	445	17.4	148
	E	281	320	2.4	5.5	5.0	22.6	37.3	12.3	29.2	67.3	61.4	278	459	12.3	151
	F	394	1,431	2.8	4.1	3.5	20.2	32.9	12.7	35.4	52.0	44.9	257	418	11.9	145
	G	414	294	3.8	3.6	3.0	18.1	31.6	14.7	55.3	52.8	44.3	266	465	11.3	166

* Venipuncture.
† 2.5 mU pitressin I-V.

TABLE VB

The effects of endogenous and exogenous ADH on the rates of excretion of H_2O, Na, and total solutes

Study	Rate of excretion in control period			Rate of excretion during max. antidiuresis			% decrease in rate			% Δ Na / % Δ solutes	Cr U/S	
	H_2O	Na	Total solutes	H_2O	Na	Total solutes	H_2O	Na	Total solutes		Control period	Max. antidiuresis
	cc./min.	*μOsm./min.*		*cc./min.*	*μOsm./min.*							
12*	14.7	117	656	3.5	78	463	77	33	30	1.1	9.7	43.1
	11.3	124	612	6.0	128	523	47	+ 4	14		13.3	24.7
13†	14.3	45	471	8.5	40	445	41	11	5	2.2	10.4	17.4
P†‡	14.4	94		7.9	104		45	+10				
Del†‡	6.9	160		2.7	123		61	23				
S†‡	14.8	139		3.4	86		77	38				
H†‡	13.6	73		4.7	55		65	25				

* Venipuncture (probably endogenous ADH).
† 2.5 mU pitressin administered I-V.
‡ From: Nelson, W. P., III, and Welt, L. G., J. Clin. Invest., 1952, **31**, 392.

The rate of excretion of sodium (and chloride) also diminished in all cases except no. 8. The magnitude of the antisaluresis was quantitatively similar in all studies. The alterations in the rate of excretion of sodium were relatively larger than those of total solutes as is demonstrated by examination of Δ Na/Δ solutes ratios presented in Table IV.

The rate of excretion of potassium was slightly accelerated during the antidiuretic phase in all cases. The rate of excretion of urea decreased in all studies during the antidiuresis. Although the rate of excretion of this solute remained low during the recovery periods in the face of a rising urine flow, the urea clearance returned to pre-albumin infusion levels during the recovery phase in those few instances in which it was measured (studies 2, 9, and 10).

One subject (no. 12) (Tables VA and VB) responded to two nontraumatic venipunctures with a marked inhibition in urine flow. Since this was not attended by a decrease in the clearance of creatinine, these antidiureses were presumed to be a consequence of the liberation of antidiuretic hormone by the posterior pituitary gland due to a non-specific emotional stimulus. The decrease in the rate of excretion of urine amounted to 77 and 47 per cent. In the first instance, the rate of excretion of total solutes as well as sodium diminished, but during the second antidiuresis the rate of excretion of total solutes diminished only slightly while that of sodium remained essentially unchanged.

In a final study, no. 13 (Tables VA and VB), an antidiuresis was produced by the intravenous administration of 2.5 mU of pitressin. This was associated with only a small change in the rates of excretion of sodium or total solutes.

DISCUSSION

The antidiuresis promoted by the infusions of hyperoncotic solutions of albumin may be explained within the framework of the current concepts of renal physiology (17) as a consequence of a decrease in the rate of glomerular filtration or an increase in the renal tubular reabsorption of water. This latter, in turn, may occur as a passive consequence of an enhanced reabsorption of solutes, presumably in the proximal tubule, or as a result of the action of the antidiuretic hormone of the posterior pituitary gland, presumably in the distal portion of the nephron.

There is evidence from other studies (4, 5, 18, 19) employing the clearance of mannitol and inulin, as well as creatinine, that the infusion of a 25 per cent solution of albumin does not result in a decrease in the rate of glomerular filtration. The clearances of endogenous creatinine in this investigation would tend to support this contention. These antidiureses appear, therefore, to be dependent on an enhanced reabsorption of water in the renal tubules, and the increases in the creatinine U/S ratios which accompanied the decreases in the rate of flow of urine support this thesis.

The importance of Verney's observations (20) concerning emotional stimuli as a factor in the liberation of ADH is vividly illustrated in study 12. This subject responded to two venipunctures with striking antidiureses. Since the venipuncture prior to the infusion of albumin did not cause an antidiuresis in studies 1 through 9 (see Experimental Procedure and Methods), and no further venipunctures were performed until after the antidiuresis had been observed, this type of trauma can be excluded as a cause for the decrease in urine flow observed in association with the infusions of albumin.

The antidiuresis promoted by the slow infusion of albumin was associated with a decrease in the rate of excretion of sodium, unaccompanied by an increase in the concentration of sodium or total solutes in the urine. The character of this antidiuresis was identical with that observed on three occasions in two patients with diabetes insipidus, and differed materially from that induced by a venipuncture and exogenous antidiuretic hormone. It appears unlikely, therefore, that the antidiuresis could have been mediated by a liberation of antidiuretic hormone from the posterior pituitary gland. Moreover, since the diminished rate of flow of urine was always associated with a decrease in the rate of excretion of solutes, it is most readily explained as an increased reabsorption of water secondary to increased solute reabsorption, presumably, in the proximal tubule.

The antidiuresis was more intense in those experiments on normal subjects in which the solution of albumin was administered rapidly. This is difficult to explain simply as a more profound expression of a single antidiuretic mechanism in re-

sponse to a more intense stimulus for the following reasons:

1. The intensity of the antisaluresis was not influenced by the rate of infusion of the solution of albumin.

2. The rate of infusion of albumin in the patients with diabetes insipidus was comparable with the rapid infusions in the normal subjects, but the degree of antidiuresis in these patients was more comparable with that observed in the normals who received the albumin slowly.

These data imply that there may well have been an *additional* antidiuretic mechanism operating in the normal subjects who received the infusion of albumin at a rapid rate. The facts that this *additional* antidiuresis was unassociated with an *additional* antisaluresis, and was not elicited in the patients with diabetes insipidus, suggest that the rapid infusion of albumin may have stimulated the secretion of the antidiuretic hormone of the posterior pituitary gland.

Two sets of paired studies were performed in which the same subject was infused with the solution of albumin rapidly on one occasion and more slowly in another experiment. The role of a conditioned response was eliminated by reversing the order in which the paired studies were performed. In each instance the antidiuretic response was more marked with the rapid infusion of albumin. These studies would appear to eliminate an emotional reaction as the stimulus responsible for a posterior pituitary antidiuretic response associated with the rapid infusions.

Study 8 is anomalous and there is no obvious explanation for this discordant experiment. The fact that a diuresis occurred may be attributed to the increased rate of excretion of sodium.

It is not clear from these data whether solutes other than sodium and chloride are reabsorbed more rapidly when the oncotic pressure of the plasma is increased. The rate of excretion of potassium appeared to be accelerated. Urea was the only other osmotically active urinary solute determined. Since it presumably escapes from the glomerular filtrate by passive diffusion the excretion of urea may be expected to vary directly with urine flow. There is no information at this time concerning the effect of an increase in oncotic pressure of the plasma on the tubular reabsorption of glucose, bicarbonate, or other solutes.

The precise mechanism by which an increase in the rate of reabsorption of sodium occurs remains to be established. It has been suggested that the increase in colloid osmotic pressure of the plasma in the tubular vessels might serve to withdraw water and solutes out of the tubular lumen (21). This neglects the fact that the *oncotic* pressure of the plasma is effective in the transfer of fluid between the vascular compartment and the interstitial fluid and would not be expected to alter the distribution of fluid across the cell membrane. It has been previously suggested that there might be a receptor organ within the vascular tree that responded to alterations in oncotic pressure and, as a consequence of stimulation, promoted alterations in renal tubular activity with respect to the reabsorption of salt (5). It is clear that more data must be obtained before any explanation can be offered.

SUMMARY AND CONCLUSIONS

The intravenous administration of hyperoncotic solutions of albumin to normal subjects undergoing maximal diureses of water and to patients with diabetes insipidus results in an expansion of plasma volume. Since the increase in plasma volume exceeds the volume of the solution of albumin infused it is inferred that the oncotic pressure of the plasma had been increased and that this had promoted the movement of interstitial fluid into the blood stream. These changes were accompanied by decreased rates of excretion of solutes and water unassociated with a decrease in the rate of glomerular filtration.

The antidiureses observed in the normal subjects who received the infusions of albumin at a slow rate were qualitatively and quantitatively similar to the antidiureses observed in the patients with diabetes insipidus and, therefore, may be assumed to be independent of the antidiuretic hormone of the posterior pituitary gland. The increased renal tubular reabsorption of water appears to be best explained as a passive consequence of an enhanced reabsorption of sodium chloride, presumably in the proximal tubule.

The *rapid* administration of the solution of albumin increases the magnitude of the antidiuretic response in normal subjects, but not in patients

with diabetes insipidus. In addition, the antidiuresis under these circumstances has some of the characteristics of a response to ADH. It *may* be that a very rapid increase in oncotic pressure of the plasma promotes the secretion of ADH in addition to the acceleration of the tubular reabsorption of solutes.

ACKNOWLEDGMENT

The authors are indebted to Gloria E. Nassif, A.B., and Jane V. Lee, A.B., for their aid in these studies.

REFERENCES

1. Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. C., Production of increased renal sodium excretion by hypotonic expansion of the extracellular fluid volume in recumbent subjects. J. Clin. Invest., 1952, **31**, 80.
2. Lombardo, T. A., Eisenberg, S., Oliver, B. B., Viar, W. N., Eddleman, E. E., and Harrison, T. R., Effects of bleeding on electrolyte excretion and on glomerular filtration. Circulation, 1951, **3**, 260.
3. Peters, J. P., Sodium, water and edema. J. Mt. Sinai Hosp., 1950, **17**, 159.
4. Goodyer, A. V. N., Peterson, E. R., and Relman, A. S., Some effects of albumin infusions on renal function and electrolyte excretion in normal man. J. Applied Physiol., 1949, **1**, 671.
5. Welt, L. G., and Orloff, J., The effects of an increase in plasma volume on the metabolism and excretion of water and electrolytes by normal subjects. J. Clin. Invest., 1951, **30**, 751.
6. Hickey, R. C., and Hare, K., The renal excretion of chloride and water in diabetes insipidus. J. Clin. Invest., 1944, **23**, 768.
7. Verney, E. B., The antidiuretic hormone and the factors which determine its release. Proc. Roy. Soc., London, 1947, **SB** 135, 25.
8. Welt, L. G., and Nelson, W. P., III, Excretion of water by normal subjects. J. Applied Physiol., 1952, **4**, 709.
9. Hald, P. M., The flame photometer for the measurement of sodium and potassium in biological materials. J. Biol. Chem., 1947, **167**, 499.
10. Elkinton, J. R., and Taffel, M., Prolonged water deprivation in the dog. J. Clin. Invest., 1942, **21**, 787.
11. Gornall, A. G., Bardawill, C. J., and David, M. M., Determination of serum proteins by means of the biuret reaction. J. Biol. Chem., 1949, **177**, 751.
12. Milne, J., Serum protein fractionation: A comparison of sodium sulfate precipitation and electrophoresis. J. Biol. Chem., 1947, **169**, 595.
13. Wolfson, W. Q., Cohn, C., Calvary, E., and Ichiba, F., Studies in serum proteins. V. A rapid procedure for the estimation of total protein, true albumin, total globulin, alpha globulin, beta globulin and gamma globulin in 1.0 ml. of serum. Am. J. Clin. Path., 1948, **18**, 723.
14. Hare, R. S., and Hare, K., Endogenous creatinine in serum and urine. Proc. Soc. Exper. Biol. & Med., 1950, **74**, 148.
15. Conway, E. J., Microdiffusion Analysis and Volumetric Error. C. Lockwood, London, 1947, p. 357.
16. Scatchard, G., Batchelder, A. C., and Brown, A., Chemical, clinical and immunological studies on the products of human plasma fractionation. VI. The osmotic pressure of plasma and serum albumin. J. Clin. Invest., 1944, **23**, 458.
17. Smith, H. W., The Kidney: Structure and Function in Health and Disease. Oxford Univ. Press, New York, 1951, pp. 241–352.
18. Cargill, W. H., Effect of intravenous administration of human serum albumin on renal function. Proc. Soc. Exper. Biol. & Med., 1948, **68**, 189.
19. Elkinton, J. R., Crosley, A. P., Jr., Barker, H. G., and Clark, J. K., Alterations in renal hemodynamics and excretion of electrolytes. Federation Proc., 1950, **9**, 37.
20. Verney, E. B., Absorption and excretion of water. The antidiuretic hormone. Lancet, 1946, **2**, 739.
21. Greiner, A., and Podhradszky, L., Kidney function in diabetes insipidus. Lancet, 1947, **2**, 498.