MECHANISM OF POSTOPERATIVE LIMITATION IN SODIUM EXCRETION: THE ROLE OF EXTRACELLULAR FLUID VOLUME AND OF ADRENAL CORTICAL ACTIVITY [1]

By RUSSELL E. RANDALL, Jr.[2] and SOLOMON PAPPER

(From the Medical Service and the Research Laboratory, Boston Veterans Administration Hospital, and the Departments of Medicine, Boston University School of Medicine and Tufts University School of Medicine, Boston, Mass.)

(Submitted for publication June 2, 1958; accepted July 24, 1958)

Decreased renal excretion of sodium is a well-known feature of the immediate postoperative state (1–3). The mechanisms responsible have, however, not been clearly defined. While increased adrenal cortical secretion such as is generally associated with major surgical procedures (4–9) has been causally implicated by many investigators (1, 3, 10–13), there is considerable evidence that the changes in sodium excretion are independent of variations in the supply of adrenal cortical hormones (14–18).

The extracellular fluid volume, or more precisely that portion of it which is physiologically "effective," has been shown to be a major determinant of renal sodium excretion in normal individuals (19–21). Therefore variation in this volume warrants consideration as a possible etiological factor in the decreased postoperative excretion of sodium. The observations that fluid sequestration occurs in and about the traumatized tissues both in animals and in man indeed suggests that a dislocation of the body fluids may occur in the surgical patient and result in a contraction of the effective extracellular fluid volume.

The present study was designed to investigate the effect of isotonic expansion of the extracellular fluid volume on the postoperative response to the administration of sodium chloride. The data indicate that the usually observed impairment in natriuretic response is corrected by isotonic extracellular fluid volume expansion. In addition, studies in a patient with Addison's disease suggest that decreased natriuresis postoperatively occurs independently of enhanced adrenal cortical hormone secretion.

[1] An abstract of this paper appeared in the J. clin. Invest. 1958, 37, 923.

[2] Present address: Travis Air Force Base, Calif.

METHODS

Five young males without cardiovascular, renal, hepatic or endocrine disease were studied before and after orthopedic surgical procedures of sufficient extent to produce major surgical trauma (Table I). One patient (No. 3, A and B) was studied before and after two Moore arthroplasties performed five weeks apart. Orthopedic patients were chosen for study in order to avoid the complicating factors of major gastrointestinal losses of fluids and electrolytes and to allow continued oral intake in the postoperative period. Commencing on the fifth or sixth day before surgery and continuing through the third postoperative day the patients were provided a daily diet containing approximately 43 mEq. of sodium and in addition received nonenteric coated sodium chloride tablets four times daily so that the total sodium intake was 197 mEq. per day. On the day of surgery sufficient isotonic saline solution was given intravenously to maintain the total intake, including the sodium content of the citrated blood, at 197 mEq. Blood loss during surgery was replaced so that in no instance was significant hypotension observed. Oral intake of fluid and food was usually re-instituted by evening of the day of surgery. The daily intake of fluids was recorded in five studies and it was possible to weigh three patients daily. Urine collected over 24 hour periods was analyzed daily for sodium, potassium, chloride, total solute and creatinine by methods previously described from this laboratory (22). Pre- and postoperative 17-hydroxycorticosteroid excretion was measured by the Reddy method (23).

On the second, third or fourth day before surgery each patient was studied as follows: After the usual breakfast and two hours of "basal" observation in recumbency a challenging infusion of 2,000 ml. of 0.9 per cent saline was administered intravenously over a 90 minute period. Urine was generally collected at 30 minute intervals from the beginning of the "basal" period until at least three hours after the infusion was begun; thereafter urines were collected at varying intervals for a minimum of three additional hours. Venous blood was obtained at the start of the infusion, 45 minutes later, and at the end of the infusion. Urine and blood were analyzed for sodium, potassium, chloride, creatinine and total solute. In those studies in which inulin and para-aminohippurate clearances were determined, blood was drawn at least hourly for these determinations (24, 25).

All postoperative experiments were carried out on the second day after surgery. In three of the orthopedic patients (Nos. 1, 3A & 4) the postoperative study was identical with that described preoperatively, except that urines could not always be collected at precisely 30 minute intervals. In the other three studies (Nos. 2, 3B and 5) the challenging infusion of 2,000 ml. of 0.9 per cent saline was administered *only after* the extracellular fluid volume had been expanded to such an extent that the lowered postoperative "basal" rate of sodium excretion approximated the preoperative "basal" rate. This initial expansion was achieved after two hours of observation by infusing normal saline solution at a rate similar to that used in the preoperative tests. Urine specimens collected during this infusion were analyzed immediately for sodium. When the lowered rate of sodium excretion reached the preoperative "basal" level the challenging infusion of 2,000 ml. of saline was administered over a 90 minute period. The rest of the study was carried out in a manner identical to the preoperative experiments and to the other postoperative studies.

In addition to the five orthopedic patients, one patient (No. 6) with well-documented Addison's disease was studied before and after cholecystectomy. The relevant clinical data in this patient have been reported elsewhere in connection with other studies (26). This patient had been symptom-free while taking 50 mg. of cortisone orally each day and receiving monthly injections of desoxycorticosterone trimethylacetate (50 mg.). His last injection of the latter had been given 24 days prior to surgery and none was given subsequently until after the conclusion of the studies reported here. Just preceding the present study the patient had undergone other investigative procedures while receiving a daily diet containing less than 5 mEq. of sodium and an oral dose of 50 mg. of cortisone daily. He was prepared for surgery in the following manner: From the fifth preoperative day through the third postoperative day he

TABLE I

Clinical data

Patient no.	Operation (grade of trauma)*	Age	Anesthesia†	Postoperative medication		Volume of blood transfusion
				First day	Second day‡	
						ml.
1	Sub-trochanteric osteotomy and hip fusion (8)	25	Thiopental sodium Nitrous oxide Nisentil® Succinyl choline chloride	Morphine sulfate	Meperidine hydrochloride, 75 mg. (× 2)	3,000
2	Open reduction of tibial fracture with iliac bone grafts (6)	40	Pontocaine spinal	Meperidine hydrochloride	Codeine phosphate, 60 mg. (× 1)	0
3A	Left Moore arthroplasty (5)	36	Nupercaine spinal I.V. Nembutal®	Morphine sulfate	Codeine phosphate, 60 mg. (× 2)	300
3B	Right Moore arthroplasty (5)	36	Nupercaine spinal Promethazine	Morphine sulfate	Codeine phosphate, 30 mg. (× 2)	500
4	Posterior lumbar spine fusion (5)	46	Thiopental sodium Nitrous oxide Nisentil® Succinyl choline chloride	Morphine sulfate	Meperidine hydrochloride, 50 mg. (× 1) Codeine phosphate, 60 mg. (× 2)	1,000
5	Hemi-laminectomy L4–5 with disc removal (4–5)	22	Thiopental sodium Nitrous oxide Xylocaine®, local	Meperidine hydrochloride	Meperidine hydrochloride, 50 mg. (× 1) Codeine phosphate, 60 mg. (× 2)	0
6	Addison's disease: cholecystectomy and appendectomy (4–5)	41	Thiopental sodium Ether d-Tubocurarine Succinyl choline chloride	Meperidine hydrochloride	Codeine phosphate, 60 mg. (× 2)	0

* Grade of trauma based on a scale of 1–10 (1).

† Pre-anesthetic medication in all patients included: Nembutal® 100 mg.; either atropine 0.4 mg. or scopolamine 0.4 mg.; and morphine sulfate 10 mg., except in Patients 4 and 6 who received meperidine hydrochloride 100 mg. and 50 mg., respectively.

‡ Medication given for pain either during or within three hours after the challenging infusion of saline. The figures in parentheses represent the frequency of dosage during this period.

TABLE II

Daily balance data *

Patient no.	Day no. →	−5	−4	−3	−2	−1	0 Surgery	+1	+2	+3
1	Intake Na	197	197	197	505†	197	287‡	197	505†	197
	Urine Na		82	226	414	300	110	100	162	144
	Urine K		38	59	83	74	56	47	48	39
	Urine Cr		1,171	1,466	1,750	1,512	1,126	1,733	1,505	2,012
	Urine vol.		710	1,715	3,423	2,400	2,035	1,065	1,440	1,500
	Intake vol.		3,000	3,100	5,100	3,100	3,400	3,190	5,130	2,850
2	Intake Na	197	197	523†	197	197	197	197	831†	197
	Urine Na	167	196	495	192	107	180	167	540	280
	Urine K	116	88	70	44	81	100	79	69	47
	Urine Cr	2,217	2,074	2,520	1,157	1,209	1,980	2,066	2,000	1,841
	Urine vol.	2,026	1,920	4,925	1,860	1,780	978	3,680	5,970	2,500
	Weight		185	184.5	185	182.3	180		183	184
	17-OH steroids (urine)		4.7		3.0	6.2		18.4		5.2
3A	Intake Na	197	197	197	505†	197	197	197	505†	197
	Urine Na	186	174	196	469	284	182	148	230	171
	Urine K	52	50	51	63	66	39	43	52	22
	Urine Cr	1,690	1,646	1,602	1,777	1,650	1,593	1,880	1,836	1,790
	Urine vol.	2,600	2,180	2,370	5,453	3,300	1,125	1,730	4,077	2,450
	Intake vol.	4,100	4,100	4,100	6,100	4,100	4,100	3,700	6,100	4,100
	17-OH steroids (urine)			6.1		2.9		17.5		10.4
3B	Intake Na	197	197	505†	197	197	197	197	800†	197
	Urine Na	149	160	414	269	158	135	169	465	265
	Urine K	75	68	66	59	53	45	42	56	17
	Urine Cr	1,691	1,780	1,794	1,878	1,850	1,716	2,224	2,106	1,760
	Urine vol.	1,500	2,620	3,658	1,890	943	852	1,540	4,302	2,350
	Intake vol.	3,685	4,100	3,100	3,100	3,100	3,100	4,100	8,000	4,100
	17-OH steroids (urine)				8.1	7.3		13.2		
4	Intake Na	197	197	197	532†	197	197	197	532†	197
	Urine Na	131	190	177	443	194		195§	237	295
	Urine K	35	39	40	63	43		105§	34	18
	Urine Cr	1,622	1,534	1,576	1,772	1,339		3,093§	1,736	1,720
	Urine vol.	660	760	1,000	3,109	1,800	100	1,730	1,295	1,590
	Intake vol.	3,000	3,000	3,000	5,000	3,000	2,500	3,800	5,000	3,000
	Weight	168.8	164.5	168	169	168.5	166		167.8	170.5
	17-OH steroids (urine)		3.1	4.8				22§		4.8
5	Intake Na	197	530†	197	197	197‖	197	197	705†	197
	Urine Na	140	366	247	152	123	156	110	526	208
	Urine K	35	66	83	71	48	63	35	34	19
	Urine Cr	2,512	2,360	2,620	2,609	1,805	1,750	1,780	2,234	1,821
	Urine vol.	1,445	3,156	1,580	1,570	922	733	532	1,841	3,220
	Weight	151	151.3	151.2	150	147.5		148.5	147.6	147.5
	17-OH steroids (urine)			7.8	3.7			15.7		1.7
6	Intake Na	197	197	197	530†	197	197	197	530†	197
	Urine Na	28	83	124	392	198	56	153	332	106
	Urine K	90	94	87	113	70	25	49	46	20
	Urine Cr	1,485	1,645	1,484	1,703	1,345	780	2,145	1,663	1,409
	Urine vol.	910	2,720	2,560	4,193	3,230	413	1,805	3,316	1,695
	Intake vol.	4,000	4,000	4,000	6,000	4,000	3,280	3,000	6,000	4,000
	Weight	154.7	156.5	157.3	159	158	157.5		160	159

* Units of measurement: Sodium and potassium in mEq./day; creatinine in mg./day; volumes in ml./day; urinary 17-hydroxycorticosteroids in mg./day; weight in pounds.

† Day of challenging infusion of saline.

‡ Additional 90 mEq. of sodium was contained in the citrated blood.

§ Pooled two days' urine collection.

‖ Unknown electrolyte loss by emesis.

received two infusions daily, one in the morning and one at night, each containing 75 mg. of hydrocortisone administered over a six hour period for a total of 150 mg. daily. These infusions contained a total of 154 mEq. of sodium. An additional 43 mEq. of sodium was given orally, for a daily total of 197 mEq. The pre- and postoperative infusion studies were carried out in the manner outlined for the experiments in Patients 1, 3A and 4 above.

RESULTS

A. Orthopedic patients (Numbers one to five)

1. Postoperative daily excretion of sodium. On the day of surgery and for the three succeeding days all patients demonstrated some limitation of sodium excretion as evidenced by the fact that they excreted only 42 to 88 per cent of their sodium intake (Table II). Patient 1, who had the most extensive surgery, had the greatest degree of postoperative salt retention. On the day of surgery and the first postoperative day the decreased quantity of sodium excreted was almost always associated with an even greater reduction in the volume of water excreted, resulting in a more concentrated urine (Table II). By the second postoperative day there was, in general, slight reduction in the serum concentrations of sodium, chloride, total solute and creatinine, associated with a slight gain in body weight in those patients who could be weighed (Table III).

2. Natriuretic response to the challenging infusion of saline without prior expansion of the extracellular fluid volume. Postoperatively, all the patients had lower "basal" rates of sodium excretion than preoperatively (Table IV, Figures 1, 2, 3 and 4). All demonstrated increased natriuresis in response to the challenging infusions of saline. However, in two of the three patients (Nos. 1 and 4) the natriuretic response following surgery was only one-third as great as the preoperative response (Table IV, Figure 5).

3. Natriuretic response to the challenging infusion of saline with prior expansion of the extracellular fluid volume. Two thousand ml., 1,900 ml. and 1,300 ml. of 0.9 per cent saline were administered to Patients 2, 3B and 5, respectively, to raise the "basal" rate of sodium excretion in the postoperative study to the preoperative "basal" level. In each instance the challenging infusion, after prior expansion of the extracellular fluid volume, evoked a greater natriuresis postoperatively than preoperatively (Table IV, Figures 2, 4 and 5).

4. The renal excretion of total solute, chloride and potassium. For the most part, the excretion of total solute and chloride closely paralleled the excretion of sodium. Daily postoperative potassium excretion was generally somewhat lower than in the preoperative period. In most patients there was an increase in potassium excretion following the challenging infusions of sodium chloride in both the pre- and postoperative periods.

5. Changes in glomerular filtration rate (GFR) and renal plasma flow (RPF). In general, the clearances of creatinine, inulin and para-aminohippurate were higher in the postoperative "basal" periods than preoperatively (Table IV). The challenging infusion of saline did not result in any consistent change in GFR or RPF.

B. Patient No. 6, with Addison's disease, who re-received a constant dose of hydrocortisone and underwent cholecystectomy

The patient with Addison's disease had been taking a diet extremely low in sodium content (5 mEq. daily) for the week prior to the present study in conjunction with other investigations. During that time, while receiving 50 mg. of cortisone daily, he demonstrated a normal response to sodium restriction, reducing his urinary excretion to 8 to 10 mEq. daily. The abrupt change on the fifth preoperative day to a dietary intake of 197 mEq. of sodium daily and the administration of 150 mg. of hydrocortisone daily was associated with steady weight gain during the preoperative phase of this study, while daily sodium excretion increased progressively (Table II). After cholecystectomy sodium excretion decreased (Table II) and a lesser natriuretic response to the challenging infusion of saline was observed (Table IV). This patient had difficulty with complete bladder emptying on the day of receiving the challenging infusion postoperatively. Accordingly his sodium excretion is expressed in terms relative to creatinine excretion (Table IV).

DISCUSSION

The results of the present study confirm previous observations of sodium retention (1–3, 27–31) and decreased natriuretic response to salt ad-

TABLE III

Concentrations of the blood constituents on the days of the saline "test" infusions

Patient no.		Preoperative									Postoperative								
		Serum							Venous blood		Serum							Venous blood	
		Na	K	Cl	Solute	Cr	In*	PAH*	Hgb	Hct	Na	K	Cl	Solute	Cr	In*	PAH*	Hgb	Hct
		mEq./L.	*mEq./L.*	*mEq./L.*	*mOsm./L.*	*mg. %*	*mg. %*	*mg. %*	*Gm. %*	*%*	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mOsm./L.*	*mg. %*	*mg. %*	*mg. %*	*Gm. %*	*%*
1	a.†	141	4.3	105	278	0.61			13.1	42	138	4.3	102	280	0.64			13.0	40
	b.‡	143	4.2	110	282	0.61			11.8	38	138	4.3	106	278	0.66			11.6	36
2	a.	137	4.6	104	276	0.82	10.7	1.28	14.0	48	135	4.2	101	266	0.71	8.8	1.17	13.1	45
	b.	139	4.3	109	277	0.74			12.7	47	140	4.1	110	279	0.64			11.4	37
3A	a.	139	3.8	106	281	0.69			14.0	42	130	3.9	97	264	0.65			11.7	38
	b.	141	4.0	112	283	0.62			12.5	38	133	4.1	105	266	0.64			9.9	31
3B	a.	140	3.9	105	284	0.79			15.5	46	132	3.7	100	269	0.71			12.1	36
	b.	140	4.1	111	285	0.75			13.1	39	135	3.8	110	273	0.65			10.0	29
4	a.	141	4.0	105	283	0.71	14.8	1.76	14.8	45	131	3.9	97	265	0.74	11.5	1.14	11.7	36
	b.	143	4.0	110	286	0.76			13.9	42	133	3.7	103	268	0.68			10.6	32
5	a.	139	3.9	104	274	0.76	14.4	1.29	16.4	49	133	3.6	98	264	0.62	8.9	0.73	15.5	46
	b.	141	3.9	109	278	0.66			15.4	47	134	3.7	104	267	0.64			13.5	42
6	a.	138	3.7	102	283	0.82	17.2	1.77	15.3	48	135	3.5	95	276	0.89	12.9	1.25	12.5	40
	b.	140	3.8	107	285	0.73			14.0	43	137	3.5	100	273	0.82			12.4	39

* Average values of inulin and para-amino hippurate when the serum levels were constant.
† a—Values immediately before the saline infusion.
‡ b—Values immediately after the saline infusion.

TABLE IV

Renal excretion of fluid and solutes during the experimental periods *

Patient no.	Preoperative									Postoperative								
	Time elapsed	Na	K	Cl	Solute	Flow	C_{Cr}	C_{In}	C_{PAH}	Time elapsed	Na	K	Cl	Solute	Flow	C_{Cr}	C_{In}	C_{PAH}
	min.	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μOsm./min.*	*ml./min.*	*ml./min.*	*ml./min.*	*ml./min.*	*min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μOsm./min.*	*ml./min.*	*ml./min.*	*ml./min.*	*ml./min.*
1	− 60 to 0	281	89	311	1,200	2.1				−120 to 0	17	32	20	371	0.4	186		
	0 to 120	408	101	442	1,373	8.3	190			0 to 120	87	52	112	628	0.9	176		
	120 to 180	808	142	818	2,128	7.7	174			120 to 270	232	61	253	964	1.7	181		
	180 to 270	913	161	926	2,349	7.1	198											
2	− 60 to 0	163	60	89	938	4.2	167			− 80 to 0	105	47	100	830	10.0	213		
	0 to 90	445	103	413	1,471	7.0	175	147	720	0 to 90	266	73	288	1,112	7.1	194	172	900
	90 to 180	641	148	633	1,895	4.5	178	166	670	90 to 180†	750	103	798	2,137	10.0	208	177	840
	180 to 240	522	108	514	1,580	3.8	169	152	640	180 to 240	465	90	502	1,430	2.6	210	168	700
3A	− 60 to 0	146	44	180	586	2.6	164			− 60 to 0	50	35	83	498	0.7	230		
	0 to 90	234	74	242	795	7.5	176			0 to 90	74	38	149	660	3.9	230		
	90 to 150	557	103	613	1,385	5.7	178			90 to 150	276	69	382	1,075	2.8	220		
	150 to 210	481	77	542	1,265	3.0	178			150 to 210	422	72	511	1,365	2.6	226		
3B	−130 to 0	113	37	149	635	1.5	170			−120 to 0	38	30	70	822	1.8	240		
	0 to 120	292	104	358	1,139	4.7	179			0 to 120†	150	35	241	885	2.7	212		
	120 to 180	484	161	605	1,608	4.7	176			150 to 210	668	62	775	1,930	7.3	227		
	180 to 270	460	88	520	2,530	4.7	176			210 to 270	413	77	507	1,313	5.8	204		
	270 to 390	409	33	404	1,243	4.9	175			300 to 360	659	112	769	1,815	5.2	210		
4	− 60 to 0	169	35	118	785	1.5	194	141	607	−300 to 0	111	34		676	0.9	220		
	0 to 90	448	58	362	1,311	6.5	171	127	590	0 to 210	222	36		928	1.3	212	122	710
	90 to 210	605	82	578	1,368	4.4	159	127	570									
	210 to 600	449	45	495	1,060	2.0	168			210 to 580	253	27		770	1.2	203		
5	− 90 to 0	180	46	113	955	5.6	186	113	763	− 90 to 0	70	24	70	624	1.8	206	190	1,040
	0 to 90	477	78	438	1,523	4.7	175	127	750	0 to 90	248	36	280	1,041	2.0	240	214	1,368
	90 to 180	587	119	611	1,697	3.3	188	129	726	90 to 180†	599	50	631	1,728	4.5	240	190	1,300
	180 to 240	498	76	501	1,460	2.4				180 to 240	419	42	456	1,247	2.0			
	240 to 510	434	33	440	1,290	3.4				240 to 510	470	38	490	1,400	3.4			
6‡	− 90 to 0	111	87	57	600	2.0				−390 to 0	70	20	70	320	0.6			
	0 to 90	310	30	293	1,014	5.6	136	107	490	0 to 90	176	17	166	573	2.4			
	90 to 180	618	35	538	1,628	4.8				90 to 180	343	16	330	924	2.7	149	125	683
	180 to 390	448	35	419	1,124	3.9				180 to 330	309	21	307	834	1.8			

* Two thousand ml. of 0.9 per cent saline was infused from 0 to 90 minutes unless otherwise specified.

† The challenging infusion of 2,000 ml. of 0.9 per cent saline was administered after the postoperative "basal" rate of sodium excretion was raised to at least the preoperative "basal" level by the prior administration of 2,000 ml. of 0.9 per cent saline in Patient 2, 1,900 ml. in Patient 3B, and 1,300 ml. in Patient 5.

‡ All excretion rates for Patient 6 are expressed per mg. of excreted creatinine because of difficulty with complete bladder emptying. Clearance data are averaged for the entire period of testing.

ministration in the postoperative period (28, 32, 33). Renal excretion of sodium is determined both by the filtered load (GFR × serum sodium concentration) and the tubular reabsorption of sodium (34). In Patients 2 and 5, whose GFR was measured by inulin clearance, the calculated filtered load of sodium was actually greater in the postoperative period than preoperatively, despite a decreased serum sodium concentration after surgery. These data in conjunction with similar results in other patients in whom only creatinine clearance was determined, suggest that postopera-

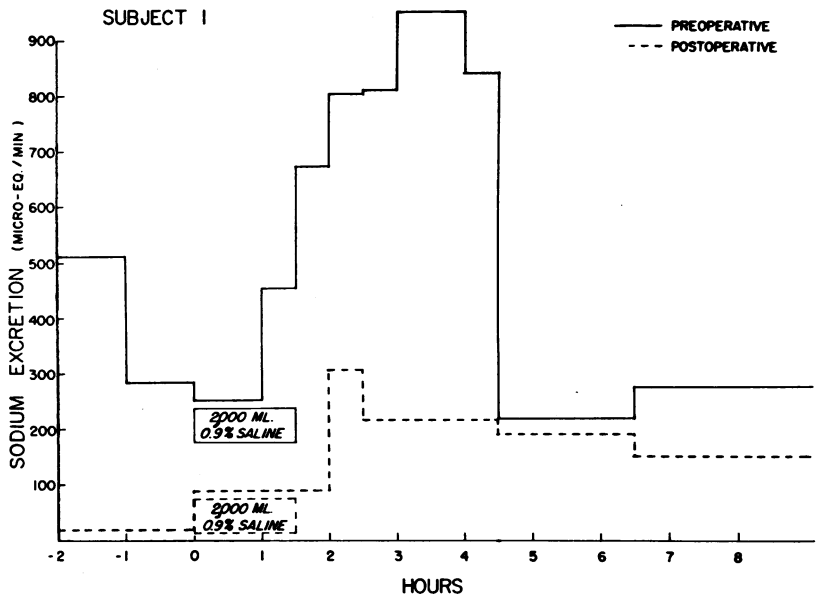

FIG. 1. PRE- AND POSTOPERATIVE NATRIURETIC RESPONSES TO THE CHALLENGING INFUSION OF SALINE IN PATIENT 1

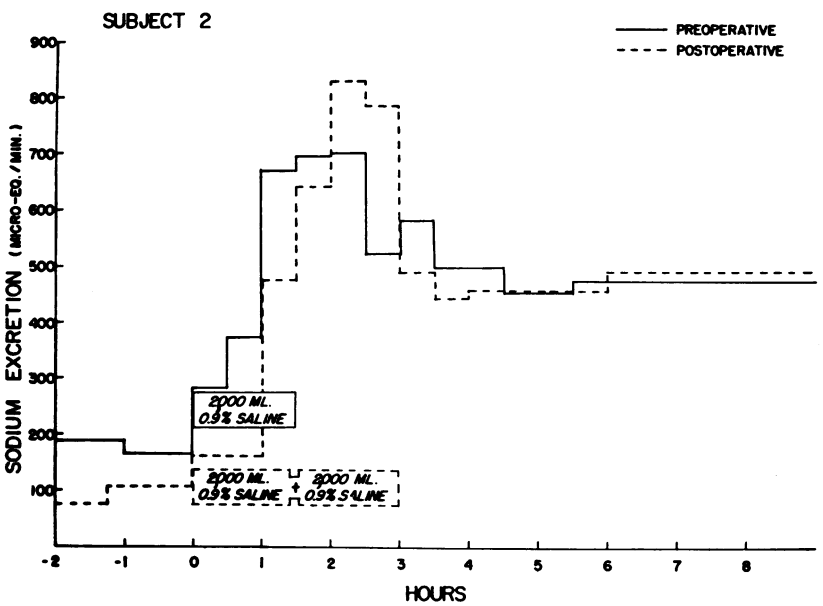

FIG. 2. PRE- AND POSTOPERATIVE NATRIURETIC RESPONSES TO THE CHALLENGING INFUSIONS OF SALINE IN PATIENT 2

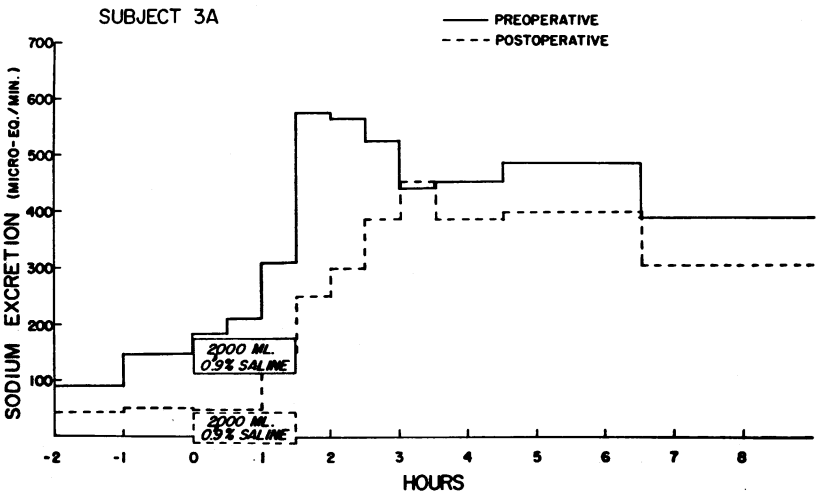

FIG. 3. PRE- AND POSTOPERATIVE NATRIURETIC RESPONSES TO THE CHALLENGING INFUSIONS OF SALINE IN PATIENT 3A

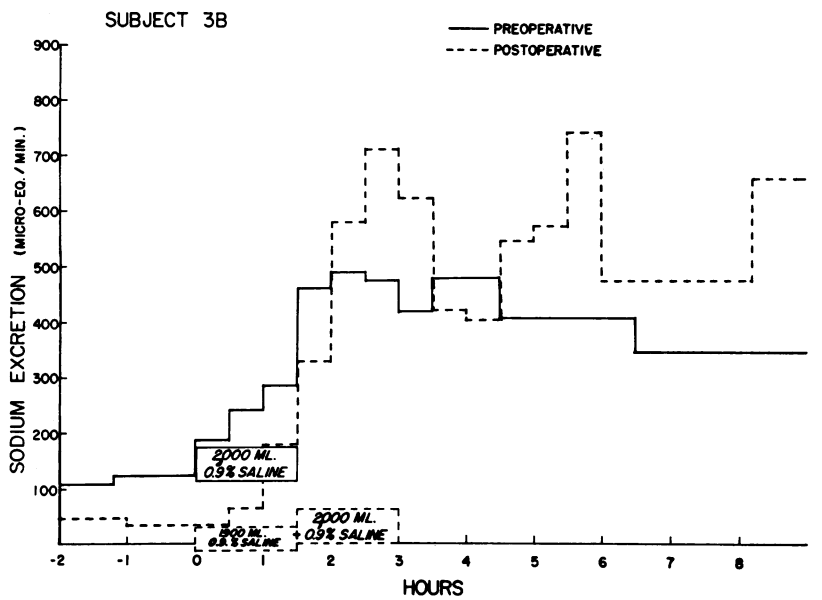

FIG. 4. PRE- AND POSTOPERATIVE NATRIURETIC RESPONSES TO THE CHALLENGING INFUSIONS OF SALINE IN PATIENT 3B

tive impairment in sodium excretion need not be related to decreased filtered load. Whether or not the decreased postoperative serum sodium concentration influences sodium excretion independent of filtered load remains unclear. While the precise mechanism of the observed postoperative increase in glomerular filtration rate noted in this and in other studies (35) is not known, it may be related to the reported influence of fever [8] upon glomerular filtration rate (34, 36).

In view of these observations, it seems reasonable to turn our attention to the possible role of enhanced renal tubular reabsorption of sodium in the impairment of sodium excretion in the post-

[8] Each patient had an oral temperature varying from 101 to 102° F. for one to three days following surgery.

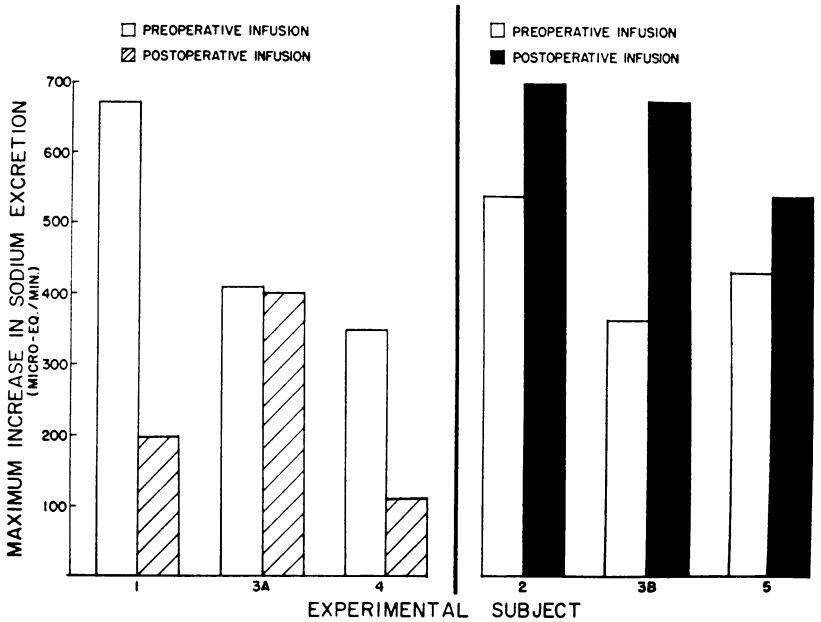

FIG. 5. COMPARISON OF THE INCREASE IN THE RATE OF SODIUM EXCRETION FROM THE PREINFUSION CONTROL PERIOD TO THE 60 MINUTE PERIOD OF MAXIMAL NATRIURESIS FOLLOWING THE CHALLENGING INFUSION OF SALINE

The cross-notched bars represent the response when only 2,000 ml. of saline was employed in the postoperative "test" infusion, while the solid black bars indicate the natriuretic response to the 2,000 ml. infusion when the rate of sodium excretion was *first* elevated to at least the preoperative "basal" level.

operative period. In attempting to determine the stimulus for any increased reabsorption, the normal stimuli for tubular conservation of sodium in man must be considered. Since the "effective" extracellular fluid volume is a major determinant of renal sodium excretion in the normal individual (19–21), a contraction of this portion of the body fluids might conceivably represent a significant physiological stimulus to postoperative sodium retention. In this regard various observations in animals and man undergoing surgery suggest that such a contraction in the effective extracellular fluid volume may indeed occur postoperatively. For example, sequestration of fluid and electrolytes occurs in and about traumatized tissues and surgical wounds (27, 37–45); fluid accumulates in the intestinal wall and lumen following manipulation during gastrointestinal tract surgery (38, 40, 41, 46–48), and in serous cavities (38) following thoracic and abdominal surgery. These collections of fluid may be as great as 4 to 5 per cent of body weight (37, 41, 42, 46), an amount probably sufficient to result in sodium retention in normal man. Numerous observations suggest that the *total* extracellular fluid volume may actually be enlarged postoperatively (13, 31, 32, 49–52), and indeed in the present study the inulin space, when measured, was increased after surgery.[4] However, such conclusions are based upon an increase in the volume of distribution of a variety of substances presumed to remain in the extracellular compartment, an assumption which may not apply to the same extent postoperatively as preoperatively. In any case, if the total extracellular fluid volume is expanded after surgery, this may well be the result of accumulation in the traumatized areas at the expense of the physiologically effective extracellular fluid volume (37, 41–44, 46). The operated patient may thus be likened to a patient with cirrhosis and ascites whose total extracellular fluid volume is expanded, but whose effective volume may well be contracted (53, 54).

While the mechanism of the decreased "basal" rate of sodium excretion postoperatively is not

[4] The volume of distribution of inulin was 16 to 38 per cent greater postoperatively than preoperatively.

clear, the possibility exists that it is a reflection of a contracted effective extracellular fluid volume. Indeed recent studies of Strauss, Lamdin, Smith and Bleifer have demonstrated that the renal excretion of sodium is altered by extremely small changes (1 per cent) in extracellular fluid volume (55). Consequently, the attempt was made to expand the effective extracellular fluid volume (in Patients 2, 3B and 5) with saline to the extent that the "basal" rate of sodium excretion postoperatively would be in the same range as in the preoperative values. Under these conditions the challenging infusion of saline evoked a greater natriuresis than in those instances without prior expansion of effective extracellular fluid volume. The fact that this natriuretic response following expansion of the extracellular fluid volume actually exceeded that of the preoperative response may be related to the fact that more saline was given prior to the challenging load than was actually required. This was in part due to the slight delay in determining the sodium content of the urine during which time the infusion of saline was continued, and to the fact that the peak natriuretic response to the expanding infusion had probably not yet been attained when the challenging infusion was begun.

If the sequestration of fluid following surgery accounts for the decreased natriuretic response to salt administration by producing a contraction of the effective extracellular fluid volume, it might be expected that restoration of this volume would prevent the diminished postoperative natriuretic response. On the other hand the fact that expansion of the extracellular fluid volume actually resulted in an increased natriuretic response in the postoperative period, does not constitute proof that the diminished rate of excretion was due to a contracted volume. It may well be that other stimuli for increased renal sodium reabsorption were in some way influenced, modified or overshadowed by extracellular fluid volume expansion. Nevertheless, in view of other observations, previously discussed, which suggest the possibility of decreased effective extracellular fluid volume postoperatively, the present studies may be considered consistent with the thesis that following major surgery, a contracted volume may play an important role in producing the observed limitation in sodium excretion. The manner in which such a volume stimulus is perceived and the pathways of mediation to the renal tubule remain unknown both in the surgical patient and in the normal subject (19–21). Regardless of the precise mechanisms involved, the data indicate that postoperative patients without hepatic, renal, cardiopulmonary or endocrine disease retain the ability to excrete large amounts of administered saline at a rate comparable to the preoperative period, if their "basal" rate of sodium excretion is first increased to the preoperative level by the administration of isotonic sodium chloride.

The increased adrenal activity (17-hydroxycorticosteroids and aldosterone) associated with major surgical procedures (4–13, 56) has been frequently implicated as causative of the sodium retention of the postoperative period (1, 3, 5, 10–13). There are important observations, however, which suggest that *increased* endogenous adrenal cortical activity is not essential to the postoperative abnormalities of sodium metabolism (14–18). In adrenalectomized animals and man, and in patients with Addison's disease, normal fluctuations in sodium excretion can occur in response to changes in volume (19, 26) or pathological conditions (57–59) despite a constant supply of adrenal hormones. Similarly, the response, insofar as sodium excretion is concerned, to standardized trauma in adrenalectomized animals receiving constant doses of adrenal cortical extract differs in no way from nonadrenalectomized animals experiencing similar trauma (14). Indeed, adrenalectomized animals kept alive with large salt intakes, but without adrenal cortical steroids, also show identical phenomena (18). In man, observations made immediately after bilateral adrenalectomy or after other surgical procedures in adrenalectomized patients have also revealed postoperative sodium retention (31, 60–62). This retention is of greatest significance in those studies in which hormonal dosage (and usually sodium intake as well) was kept constant (15–17). In the present study Patient No. 6, with Addison's disease, demonstrated marked and rapid renal sodium conservation while taking a diet low in sodium prior to the study reported here. In addition, both sodium retention and a diminished natriuretic response to saline administration were observed in this patient postoperatively, despite a constant supply of exogenous adrenal hormones

and the presumed absence of the endogenous secretion of either aldosterone or hydrocortisone. The possibility that surgery in some way altered the metabolic effects derived from the exogenous supply of hormone cannot, of course, be excluded, but it seems highly improbable that these effects would be enhanced.

While the increased plasma levels of 17-hydroxycorticosteroids, so frequently reported, on the day of surgery are perhaps in part due to decreased plasma clearance of these substances (63–66), it would be unlikely that diminished plasma clearance would account for significant plasma levels by the second postoperative day (67). Furthermore, the effect of hydrocorticosterone is not clearly that of producing increased tubular reabsorption of sodium, and in fact under certain circumstances there is evidence to suggest that such hormones may actually produce increased sodium excretion (68). It would appear that the increased aldosterone secretion associated with major surgical trauma (3, 69, 70) is not necessarily the prime mover in postoperative sodium retention, and almost certainly not in the adrenally insufficient subjects in whom sodium retention occurred despite all evidence indicating the complete lack of this hormone. Whether aldosterone plays any role in the production of altered sodium metabolism in the surgical subject with normal adrenal glands, remains unclear. Since a contraction of the volume has been shown to be a stimulus for aldosterone secretion (71), it is possible that if there is such a contraction postoperatively it may at least in part be responsible for the observed increase in urinary aldosterone. While both increased aldosterone secretion and decreased sodium excretion may be related to a contraction of the effective extracellular fluid volume, this does not imply any necessary causal relationship between these two effects.

The decreased potassium excretion that occurred following surgery in this study is in contrast to the observations reported by others (1–3). Since the intake of potassium was not strictly controlled, this decrease is probably accounted for by a reduced intake on the day of surgery and the first postoperative day.

The observation of decreased volumes of concentrated urine following surgery is similar to the observations reported by others (2, 3). This decreased excretion of water has been ascribed to increased antidiuretic hormone secretion (ADH) (3, 33, 72) which might well result from such factors as pain, emotion and a decreased effective extracellular fluid volume (21). While morphine and meperidine also result in decreased urine flow (73), this effect is probably independent of ADH secretion in man, as distinguished from its mechanism of action in animals (74, 75).

SUMMARY AND CONCLUSIONS

1. Postoperative and preoperative natriuretic responses to the intravenous administration of 2,000 ml. of 0.9 per cent saline were compared in five patients undergoing major orthopedic surgery. One patient was studied twice.

2. In all patients, the rate of sodium excretion prior to the infusions of saline was less in the postoperative experiments than preoperatively.

3. The diminished sodium excretion on the second postoperative day occurred despite a generally increased glomerular filtration rate, implying increased tubular reabsorption of sodium.

4. In two of three patients given the challenging infusion *without* prior expansion of the extracellular fluid volume postoperatively there was a strikingly smaller natriuretic response than preoperatively.

5. In each of three patients given the challenging infusion *with* prior isotonic expansion of the extracellular fluid volume postoperatively, the natriuretic response was at least as great as preoperatively.

6. One patient with Addison's disease, receiving a constant daily intake of hydrocortisone and saline, also demonstrated decreased sodium excretion and decreased natriuretic response to administered saline following major abdominal surgery.

7. These data are consistent with but do not prove the hypothesis that the postoperative limitation in sodium excretion, may to a significant extent, result from a contraction of the "effective" extracellular fluid volume.

8. Decreased postoperative sodium excretion, as well as the impaired natriuretic response to administered saline, apparently does not require enhanced adrenal cortical secretion.

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Dr. Arthur Ellison and other members of the Orthopedic and General Surgical Services for their cooperation during the study.

The technical assistance of the Misses Helen C. Alpert, Miriam Halpin, Barbara Murphy and Ellen Vaznelis is gratefully acknowledged.

Financial assistance for the procurement of reprints was provided by the Gray Pharmaceutical Company, Newton, Mass.

REFERENCES

1. Moore, F. D., and Ball, M. R. The Metabolic Response to Surgery. Springfield, Charles C Thomas, 1952.
2. Wilkinson, A. W. Body Fluids in Surgery. Edinburgh, E. & S. Livingstone, Ltd., 1955.
3. Le Quesne, L. P. Fluid Balance in Surgical Practice, 2nd ed. Chicago, Year Book Publishers, Inc., 1957.
4. Franksson, C., Gemzell, C. A., and von Euler, U. S. Cortical and medullary adrenal activity in surgical and allied conditions. J. clin. Endocr. 1954, **14**, 608.
5. Moore, F. D., Steenburg, R. W., Ball, M. R., Wilson, G. M., and Myrdon, J. A. Studies in surgical endocrinology. I. The urinary excretion of 17-hydroxycorticoids, and associated metabolic changes, in cases of soft tissue trauma of varying severity and in bone trauma. Ann. Surg. 1955, **141**, 145.
6. Jepson, R. P., Edwards, K. M., and Reece, M. W. Adrenocortical response to corticotrophin and operation. Clin. Sci. 1956, **15**, 603.
7. Jepson, R. P., Jordan, A., and Levell, M. J. Urinary steroid response to operation. Brit. J. Surg. 1956, **43**, 390.
8. Lefemine, A. A., Marks, L. J., Teter, J. G., Leftin, J. H., Leonard, M. P., and Baker, D. V. The adrenocortical response in surgical patients. Ann. Surg. 1957, **146**, 26.
9. Reece, M. W., Edwards, K. M., and Jepson, R. P. Adrenocortical response to surgery. Surgery 1957, **42**, 669.
10. Johnson, H. T., Conn, J. W., Iob, V., and Coller, F. A. Postoperative salt retention and its relation to increased adrenal cortical function. Ann. Surg. 1950, **132**, 374.
11. Hardy, J. D., and Ravdin, I. S. Some physiologic aspects of surgical trauma. Ann. Surg. 1952, **136**, 345.
12. MacPhee, I. W. Metabolic changes associated with operation. Brit. med. J. 1953, **1**, 1023.
13. De Cosse, J. J., Randall, H. T., Habif, D. V., and Roberts, K. E. The mechanism of hyponatremia and hypotonicity after surgical trauma. Surgery 1956, **40**, 27.
14. Ingle, D. J., Meeks, R. C., and Thomas, K. E. The effect of fractures upon urinary electrolytes in non-adrenalectomized rats and in adrenalectomized rats treated with adrenal cortex extract. Endocrinology 1951, **49**, 703.
15. Robson, J. S., Horn, D. B., Dudley, H. A., and Stewart, C. P. Metabolic response to adrenalectomy. Lancet 1955, **2**, 325.
16. Mason, A. S. Metabolic response to total adrenalectomy and hypophysectomy. Lancet 1955, **2**, 632.
17. Stewart, C. P. Aspects of recent work on electrolyte metabolism. Clin. Chem. 1957, **3**, 294.
18. Share, L., and Stadler, J. B. Alterations in sodium and potassium metabolism following hind leg fracture in the rat: Role of the adrenal cortex. Endocrinology 1958, **62**, 119.
19. Epstein, F. H. Renal excretion of sodium and the concept of a volume receptor *in* Essays in Metabolism, L. G. Welt, Ed. Boston, Little, Brown & Co., 1957, p. 282.
20. Smith, H. W. Salt and water volume receptors. Amer. J. Med. 1957, **23**, 623.
21. Strauss, M. B. Body Water in Man. The Acquisition and Maintenance of the Body Fluids. Boston, Little, Brown & Co., 1957.
22. Strauss, M. B., Davis, R. K., Rosenbaum, J. D., and Rossmeisl, E. C. "Water diuresis" produced during recumbency by the intravenous infusion of isotonic saline solution. J. clin. Invest. 1951, **30**, 862.
23. Reddy, W. J. Modification of the Reddy-Jenkins-Thorn method for the estimation of 17-hydroxycorticoids in urine. Metabolism 1954, **3**, 489.
24. Goldring, W., and Chasis, H. Hypertension and Hypertensive Disease. New York, The Commonwealth Fund, 1944, p. 203.
25. Young, M. K., Jr., and Raisz, L. G. An anthrone procedure for determination of inulin in biological fluids. Proc. Soc. exp. Biol. (N. Y.) 1952, **80**, 771.
26. Rosenbaum, J. D., Papper, S., and Ashley, M. M. Variations in renal excretion of sodium independent of change in adrenocortical hormone dosage in patients with Addison's Disease. J. clin. Endocr. 1955, **15**, 1459.
27. Moyer, C. A., Coller, F. A., Iob, V., Bryant, L., Vaughn, H., Kalder, N. B., and Berry, R. E. L. Some effects of an operation, anesthesia and composition of parenteral fluids upon the excretion of water and salt. Sth. Surg. 1949, **15**, 218.
28. Moyer, C. A. Acute temporary changes in renal function associated with major surgical procedures. Surgery 1950, **27**, 198.
29. Abbott, W. E., Krieger, H., Babb, L. I., Levey, S., and Holden, W. D. Metabolic alterations in surgical patients. I. The effect of altering the electrolyte, carbohydrate and amino acid intake. Ann. Surg. 1953, **138**, 434.
30. Drucker, W., Krieger, H., Babb, L. I., Levey, S., and Abbott, W. E. Metabolic alterations in surgical patients. II. The excretion of salt and water post-

operatively following the administration of various sodium-containing solutions. Surg. Forum 1953, 4, 544.
31. Martin, M. M., and Walker, G. Studies with Na^{22}—An assessment of sodium balance and distribution. Metabolism 1957, 6, 466.
32. Ariel, I. M., and Kremen, A. J. Compartmental distribution of sodium chloride in surgical patients pre- and postoperatively. Ann. Surg. 1950, 132, 1009.
33. Hayes, M. A., Williamson, R. J., and Heidenreich, W. F. Endocrine mechanisms involved in water and sodium metabolism during operation and convalescence. Surgery 1957, 41, 353.
34. Smith, H. W. The Kidney. Structure and Function in Health and Disease. New York, Oxford University Press, 1951.
35. Ariel, I. M., and Miller, F. The effects of abdominal surgery upon renal clearance. Surgery 1950, 28, 716.
36. Smith, H. W. The physiology of the renal circulation. Harvey Lect. 1939–40, 35, 166.
37. Blalock, A. Experimental shock; the cause of the low blood pressure produced by muscle injury. Arch. Surg. 1930, 20, 959.
38. Beard, J. W., and Blalock, A. Experimental shock. VIII. The composition of the fluid that escapes from the blood stream after mild trauma to an extremity, after trauma to the intestines and after burns. Arch. Surg. 1931, 22, 617.
39. Blalock, A. Shock; further studies with particular reference to the effects of hemorrhage. Arch. Surg. 1934, 29, 837.
40. Harkins, H. N., and Harmon, P. H. Plasma exudation; loss of plasma-like fluid in various conditions resembling surgical shock. Ann. Surg. 1937, 106, 1070.
41. Blalock, A. Principles of Surgical Care: Shock and Other Problems. St. Louis, C. V. Mosby Co., 1940.
42. Ricca, R. A., Fink, K., Steadman, L. T., and Warren, S. L. The distribution of body fluids of dogs in traumatic shock. J. clin. Invest. 1945, 24, 140.
43. Rosenthal, S. M., and Tabor, H. Electrolyte changes and chemotherapy in experimental burn and traumatic shock and hemorrhage. Arch. Surg. 1945, 51, 244.
44. Fox, C. L., Jr., and Baer, H. Redistribution of potassium, sodium and water in burns and trauma, and its relation to the phenomena of shock. Amer. J. Physiol. 1947, 151, 155.
45. Winfield, J. M., Fox, C. L., Jr., and Mersheimer, W. L. Etiologic factors in postoperative salt retention and its prevention. Ann. Surg. 1951, 134, 626.
46. Blalock, A. Trauma to the intestines. The importance of the local loss of fluid in the production of low blood pressure. Arch. Surg. 1931, 22, 314.
47. Beard, J. W., and Blalock, A. Intravenous injections. A study of the composition of the blood during continuous trauma to the intestines when no fluid is injected and when fluid is injected continuously. J. clin. Invest. 1932, 11, 249.
48. Crawford, N., and Brooke, B. N. Ileostomy chemistry. Lancet 1957, 1, 864.
49. Stewart, J. D., and Rourke, G. M. Changes in blood and interstitial fluid resulting from surgical operation and ether anesthesia. J. clin. Invest. 1938, 17, 413.
50. Lyon, R. P., Stanton, J. R., Freis, E. D., and Smithwick, R. H. Blood and "available fluid" (thiocyanate) volume studies in surgical patients. I. Normal patterns of response of the blood volume, available fluid, protein, chloride, and hematocrit in the postoperative surgical patient. Surg. Gynec. Obstet. 1949, 89, 9.
51. Aronstam, E. M., Schmidt, C. H., and Jenkins, E. Body fluid shifts, sodium and potassium metabolism in patients undergoing thoracic surgical procedures. Ann. Surg. 1953, 137, 316.
52. Roberts, K. E., De Cosse, J. J., and Randall, H. T. Fluid and electrolyte problems in surgery of the aged. Bull. N. Y. Acad. Med. 1956, 32, 180.
53. Strauss, M. B., Birchard, W. H., and Saxon, L. Correction of impaired water excretion in cirrhosis of the liver by alcohol ingestion or expansion of extracellular fluid volume: The role of the antidiuretic hormone. Trans. Ass. Amer. Phycns 1956, 69, 222.
54. Papper, S. The role of the kidney in Laennec's cirrhosis of the liver. Medicine. (In press.)
55. Strauss, M. B., Lamdin, E., Smith, W. P., and Bleifer, D. J. Surfeit and deficit of sodium: A kinetic concept of sodium excretion A.M.A Arch. intern. Med. (In press.)
56. Nelson, D. H., Egdahl, R. H., and Hume, D. M. Corticosteroid secretion in the adrenal vein of the non-stressed dog exposed to cold. Endocrinology 1956, 58, 309.
57. Davis, J. O., Howell, D. S., and Southworth, J. L. Mechanisms of fluid and electrolyte retention in experimental preparations in dogs. III. Effect of adrenalectomy and subsequent desoxycorticosterone acetate administration on ascites formation. Circulat. Res. 1953, 1, 260.
58. Marson, F. G. W. Total adrenalectomy in hepatic cirrhosis with ascites. Lancet 1954, 2, 847.
59. Giuseffi, J., Werk, E. E., Jr., Larson, P. U., Schiff, L., and Elliott, D. W. Effect of bilateral adrenalectomy in a patient with massive ascites and post necrotic cirrhosis. New Engl. J. Med. 1957, 257, 796.
60. Krieger, H., Abbott, W. E., Levey, S., and Babb, L. Bilateral total adrenalectomy in patients with metastatic carcinoma. Surg. Gynec. Obstet. 1953, 97, 569.
61. Graber, I. J., and Beaconsfield, P. Metabolic changes and therapeutic considerations in bilateral adrenalectomy. Brit. med. J. 1955, 2, 704.

62. Wilkinson, A. W. Adrenalectomy and the metabolic response to injury. Lancet 1956, 1, 184.
63. Sandberg, A. A., Eik-Nes, K., Samuels, L. T., and Tyler, F. H. The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man. J. clin. Invest. 1954, 33, 1509.
64. Tyler, F. H., Schmidt, C. D., Eik-Nes, K., Brown, H., and Samuels, L. T. The role of the liver and the adrenal in producing elevated plasma 17-hydroxycorticosteroid levels in surgery. J. clin. Invest. 1954, 33, 1517.
65. Steenburg, R. W., and Ganong, W. F. Observations on the influence of extra-adrenal factors on circulating 17-hydroxycorticoids in the surgically stressed, adrenalectomized animal. Surgery 1955, 38, 92.
66. Murray, J. O. S., Marks, L. J., Colombo, F. V., Josephs, B., Leftin, J. H., and Leonard, M. P. The effect of surgery on the plasma clearance of infused cortisol. Ann. Surg. (In press.)
67. Marks, L. J. Personal communication.
68. Raisz, L. G., McNeely, W. F., Saxon, L., and Rosenbaum, J. D. The effects of cortisone and hydrocortisone on water diuresis and renal function in man. J. clin. Invest. 1957, 36, 767.
69. Casey, J. H., Bickel, E. Y., and Zimmermann, B. The pattern and significance of aldosterone excretion by the postoperative surgical patient. Surg. Gynec. Obstet. 1957, 105, 179.
70. Llaurado, J. G., and Woodruff, M. F. Postoperative transient aldosteronism. Surgery 1957, 42, 313.
71. Bartter, F. C., Liddle, G. W., Duncan, L. E., Jr., Barber, J. K., and Delea, C. The regulation of aldosterone secretion in man: The role of fluid volume. J. clin. Invest. 1956, 35, 1306.
72. Eisen, V. D., and Lewis, A. A. G. Antidiuretic activity of human urine after surgical operations. Lancet 1954, 2, 361.
73. Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. McC., and Bradley, S. E. The renal and hepatic blood flow, glomerular filtration rate, and urinary output of electrolytes during cyclopropane, ether, and thiopental anesthesia, operation, and the immediate postoperative period. Surgery 1951, 30, 241.
74. Papper, S., Saxon, L., Burg, M. B., Seifer, H. W., and Rosenbaum, J. D. The effect of morphine sulfate upon the renal excretion of water and solute in man. J. Lab. clin. Med. 1957, 50, 692.
75. Papper, S., Belsky, J. L., Bleifer, K. H., and Smith, W. P. The effect of meperidine hydrochloride upon the renal excretion of water and solute in man. Clin. Res. 1958, 6, 289.