THE EFFECT OF ADRENOCORTICOTROPIC HORMONE IN PANHYPOPITUITARISM[1]

By FREDERIC C. BARTTER,[2] PAUL FOURMAN,[3] FULLER ALBRIGHT, ANNE P. FORBES, WILLIAM McK. JEFFERIES, GRACE GRISWOLD, ELEANOR DEMPSEY, DOROTHY BRYANT, AND EVELYN CARROLL

(From the Department of Medicine of the Harvard Medical School and the Medical Service of the Massachusetts General Hospital, Boston)

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A priori one would anticipate that the effects of a hormone would be most apparent when given to an individual lacking that hormone. To be sure, when the hormone acts through another gland, as does adrenocorticotropic hormone (ACTH), one might find the "target" gland unresponsive through atrophy. In panhypopituitarism, one is dealing not with a single deficiency, but with a deficiency of all "tropic" hormones. This may be advantageous for the study of any one of them, in that compensatory changes in the others cannot obscure the results. It may be disadvantageous in that some of the effects might not occur in the face of other deficiencies.

All in all, we decided to employ three patients with panhypopituitarism[4] for our first studies of the metabolic effects of ACTH. Preliminary reports of this work have appeared (1, 2). A number of other reports of the metabolic effects of ACTH are now available (3–9).

CASE SUMMARIES

(*1*) *Patient M.W.*, female aged 43, M.G.H. No. 160,451, had a severe postpartum haemorrhage 17 years before the study. After delivery she did not lactate and her periods did not return. She remained weak and had an anemia resistant to iron treatment. On six subsequent occasions she had to be treated for Addisonian crisis precipitated by mild infections. Sixteen months before the present study treatment was begun with thyroid extract by mouth and with testosterone and desoxycorticosterone acetate by pellet implantation, and she remained symptom free thereafter. She continued to take thyroid during the study.

She had a facies suggestive of myxedema, thin skin, absent axillary and very scant pubic hair, and a normal-sized thyroid. The blood pressure was 108/58.

X-rays revealed a small sella turcica. The basal metabolic rate had been minus 38 before thyroid therapy. The following serum values were obtained: sodium 141 m.eq./L; chloride 100 m.eq./L; potassium 4.6 m.eq./L; carbon dioxide content 28.8 m.eq./L; glucose 88 mg. per 100 ml.; non-protein nitrogen 30 mg. per 100 ml.; total protein 7.1 gm. per 100 ml.; calcium 9.4 mg. per 100 ml.; inorganic phosphorus 3.6 mg. per 100 ml.; alkaline phosphatase 2.0 Bodansky units; cholesterol 278 mg. per 100 ml. The hemoglobin was 10 gm. per 100 ml.

Twenty-four hour urine specimens contained less than 0.5 mg. of 17-ketosteroids (before testosterone therapy), more than 3 but less than 6 mouse units of follicle stimulating hormone, 0.06 to 0.18 mg. of "11-oxysteroids,"[5] and less than 3 mouse units of "cortin."[6] A Cutler-Power-Wilder test (four months after implantation of one 75 mg. "DOCA" pellet) showed normal four-hour urinary chloride concentration, but produced a fall in serum sodium to 134 m.eq./L.

(*2*) *Patient H.J.*, male aged 41, M.G.H. No. 550,872, complained of failing vision for four years, and lassitude and loss of libido for two years.

He presented the facies of myxedema, scant axillary and pubic hair, soft testes, no palpable prostatic tissue, a thyroid normal to palpation, a blood pressure of 120/78, pale optic discs and a bitemporal hemianopsia.

The basal metabolic rate was minus 31. X-rays revealed an enlarged sella turcica. The following serum

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[2] Surgeon, U.S.P.H.S., on detail from National Heart Institute.

[3] Rockefeller Traveling Fellow.

[4] By panhypopituitarism we mean a deficiency, (not necessarily an absence) of all functions of the anterior pituitary. In case 2, (vide infra) in spite of the presence of Leydig cells, there was obviously hypoleydigism.

[5] Method of Talbot and his associates (10). The test depends on the reduction of alkaline copper tartrate. Normal subjects excrete between 0.10 and 0.44 mg. per 24 hours (11).

[6] By "cortin" we mean urinary corticoids assayed biologically (12). The test depends on the amount of glycogen formed in the livers of fasting, adrenalectomized mice. Normal subjects excrete more than 3 and less than 24 mouse units per 24 hours.

values were obtained: sodium 146 m.eq./L; chloride 103 m.eq./L; potassium 4.8 m.eq./L; carbon dioxide content 32 m.eq./L; glucose 93 mg. per 100 ml.; non-protein nitrogen 25 mg. per 100 ml.; total protein 7.0 gm. per 100 ml.; calcium 9.5 mg. per 100 ml.; inorganic phosphorus 4.3 mg. per 100 ml.; alkaline phosphatase 2.7 Bodansky units; cholesterol 284 mg. per 100 ml.; protein bound iodine 3.5 micrograms per 100 ml. The hemoglobin was 12.4 gm. per 100 ml.

Twenty-four hour urine specimens contained 1.7 mg. of 17-ketosteroids, more than 3 but less than 6.5 mouse units of follicle stimulating hormone, 0.1 mg. of "11-oxysteroids" and less than 1.5 mouse units of "cortin."

Two insulin tolerance tests showed hypoglycemia unresponsiveness. A testicular biopsy was interpreted by Dr. Ronald S. Sniffen as follows: "The testis has tubules in all stages of activity from normal to those lined solely by a thickened tunica propria which is peppered with granules. The Leydig cells are present in normal numbers; most of them are solid, but a few contain vacuoles, crystalloids or pigment."

Following unsuccessful X-ray therapy, a chromophobe adenoma was partially removed by trans-sphenoidal approach. The first metabolic study preceded, the second and third followed this operation.

(*3*) *Patient M.H.*, female aged 56, M.G.H. No. 568,954, complained of loss of energy for five years, dry hair for four years, cold sensitivity for two years, and episodes of weakness or dizziness, occurring in mid-morning, for one year. Menses had ceased 13 years previously without hot flashes.

She showed the facies of myxedema, dry thin skin, absent axillary and scant pubic and eyebrow hair, a slightly enlarged tongue, a very small thyroid, and a blood pressure of 190/95.

X-rays revealed a normal sella turcica. The basal metabolic rate was minus 37. The following serum values were obtained: sodium 108 m.eq./L; chloride 82 m.eq./L; potassium 5.7 m.eq./L; carbon dioxide content 27.2 m.eq./L; glucose 116 mg. per 100 ml.; non-protein nitrogen 24 mg. per 100 ml.; total protein 8.2 gm. per 100 ml.; calcium 9.1 mg. per 100 ml.; inorganic phosphorus 3.5 mg. per 100 ml.; alkaline phosphatase 3.5 Bodansky units; cholesterol 451 mg. per 100 ml.; protein bound iodine 1.0 microgram per 100 ml. The hemoglobin was 9.4 gm. per 100 ml.

Twenty-four hour urine specimens contained 1.0 mg. of 17-ketosteroids, more than 6.5 but less than 13 mouse units of follicle stimulating hormone (very low for the post-menopausal state). Two insulin tolerance tests showed hypoglycemia unresponsiveness. A Kepler water test gave an abnormal result and the calculated "index," A, was 19.

PROCEDURE

Five balance studies (13) were carried out. In these the effects of ACTH (Armour[7]) were observed and

[7] We wish to express our gratitude for the generous grants of ACTH made available to us by Dr. John Mote of Armour and Company. We are indebted to Dr.

TABLE I

Sequence, duration, and dosage of treatments in five balance studies

Period	1 (Jan. 1947) M. W. female see Table IV		2 (Jan. 1947) H. J. male see Table V (Figs. 1 and 2)		3 (May 1947) M. H. female see Table VI (Figs. 3 and 4)		4 (June 1947) H. J. male see Table VII (Figs. 5 and 6)		5 (Oct. 1947) H. J. male see Table VIII (Figs. 7, 8, and 9)	
	Days treatment	Daily dose in 3 divided doses 8 a.m., 2 p.m., 8 p.m.	Days treatment	Daily dose in 3 divided doses 8 a.m., 2 p.m., 8 p.m.	Days treatment	Daily dose in 3 divided doses 8 a.m., 2 p.m., 8 p.m.	Days treatment	Daily dose in 4, 6-hourly doses	Days treatment	Daily dose in 4, 6-hourly doses
Control	10	0	24	0	6	0	8	0	18	0
ACTH* (Armour)	10	10–15 mg.†	18	15 mg.†	5	43 mg.§ (interrupted see Fig. 3)	13	43 mg.§	6	98 mg.§
Recovery	6	0	12	0	2	0	7	0	6	0
ACTH* (Armour)	4	10–15 mg.‡	4	15 mg.‡	7	43 mg.§			7	98 mg.§
Recovery	8	0	4	0	9	0			10	0
Additional treatment (1)					7	Pitressin 6–24 u			6	60 mg. Li and Evans' ACTH‖
Recovery					6	0			8	0
Additional treatment (2)					6	Prolactin 200 u			7	30 mg. DOCG
Recovery					3	0			7	0

* Dissolved in physiological saline or distilled water according to solubility and pH adjusted for complete solution.
† Amount sufficient for the period dissolved at the beginning of the period, filtered through sintered glass and kept at 4 C° until used.
‡ As in previous footnote, but kept frozen until used.
§ Each dose dissolved immediately prior to use and not filtered.
‖ As in above footnote (†) but not filtered.

TABLE II

Properties of ACTH Armour used in these experiments*

Experiment No.	Lot No.	Strength† relative to Armour Standard LA 1 A	Units per mg.		
			Oxytocin‡	Pitressin§	Prolactin‖
1 and 2	21 B	102±8%	0.12	0.1–0.2	0.75–2.0
3 and 4	32 D	71±9%	0.05	0.1	1.8±.15
5	37 KF	41.5±12%	.0025	.005	0.5

* All these tests were done by the Armour Laboratories.
† Based on the rat adrenal ascorbic acid depletion test of Sayers and Sayers (23).
‡ Method of Thompson (24).
§ Modification of method of Hogben, Schlapp and MacDonald (25).
‖ Method of Riddle and Bates (26).

compared with the effects of electrophoretically pure ACTH (Li and Evans), pitressin (Parke-Davis), prolactin (Schering) and desoxycorticosterone glucoside (Ciba). All injections were intramuscular. The sequence, duration and dosage of the treatments in each balance study are shown in Table I. In this table the doses of Armour ACTH are expressed as the equivalent weights of Armour standard, lot LA 1A. The actual weights of the different lots of Armour ACTH given and the estimated content of impurities are shown in Table II.

The approximate protein, fat and carbohydrate content of the diet for each experiment is shown in Table III. A sample diet was analysed for mineral and nitrogen content in each experiment except the first. Urinary excretion of N, P, Ca, K, Cl, Na and 17-ketosteroids was measured in all experiments and of "11-oxycorticosteroids," "cortin," creatinine [8] and creatine [8] in some. Glucose was not measured. Fecal excretion of N, P, Ca and K was measured; fecal excretion of Na was assumed to be 2 per cent of intake.

Blood samples on a given day were taken before food or treatment had been given.

Choh Hao Li for the Li and Evans ACTH, to Dr. Richard Tislow of Schering Corporation for the prolactin, to Drs. George Thorn and Peter Forsham for the DOCG.

[8] These results are not discussed.

TABLE III

Composition of diets

Experiment No.	Carbohydrate	Protein	Fat	Calories
	gm.	*gm.*	*gm.*	
1	220.8	60.2	67.2	1730
2	256.8	79.3	71	1985
3	161.2	54.4	44.8	1265
4 and 5	311.2	79.8	71.3	2205

RESULTS

The results are given in Tables IV–VIII, and are shown graphically in Figures 1–12.

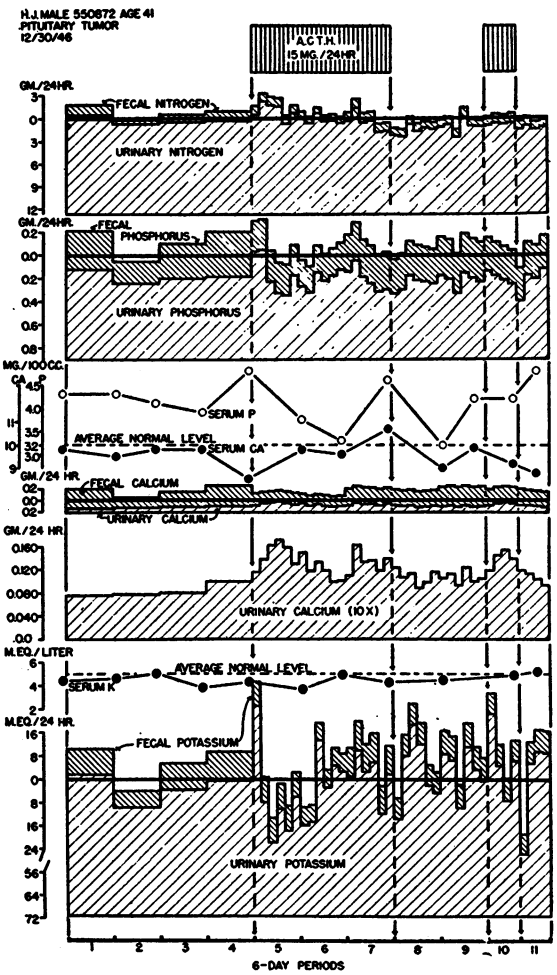

FIG. 1. PATIENT H.J., M.G.H. No. 550,872. EXPERIMENT 2. EFFECT OF ACTH ON N, P, CA, AND K BALANCES AND ON SERUM P, CA, AND K

Metabolic data in this and other figures are arranged according to the following scheme. There is a horizontal base line; intake is charted downward from this base line; the urinary and fecal excretions are then measured upward from the intake line towards the base line. If the output (fecal and urinary) exceeds the intake, the final level will be above the base line: if it does not, the final level will be below the base line. Thus a negative balance is indicated by a shaded area above the base line, and a positive balance by a clear area below the base line. The scales for N, P, Ca, and K metabolism are so chosen that (for changes in protoplasm and bone) the area representing P balance should equal the sum of the corresponding areas for N and Ca; and that representing K balance should equal that for N.

a) Nitrogen metabolism

In all our experiments except the first, in which the dosage was small and our technique of preparation not optimal, ACTH caused an increase in urine N excretion and a negative N balance by the second day. N excretion after the second day apparently depended on the dose of ACTH; thus in patient H.J. it fell off on 15 mg. a day (see Figure 1), remained the same on 43 mg. a day (see Figure 5) and rose on 98 mg. a day (see Figure 7). In all experiments there was a fall in N excretion after stopping ACTH. This tended to bring the patient into positive balance. Retention of N in the recovery period was not as rapid as the loss during treatment, and usually lasted throughout the period of observation after treatment.

The changes in N balance during and after ACTH are taken to represent loss and restoration of protoplasm and may be attributed to secretion of "sugar" hormone from the adrenal cortex. This hormone is thought (14) to inhibit anabolism of protoplasm (glyconeogenesis effect).

b) Calcium metabolism

There was a rise in the urinary Ca excretion in nine of the ten courses of ACTH given; there was a fall after stopping treatment in all ten. In some the rise was abrupt; in others it was step-like. For example, in experiment 3 (Figure 3, seventh day) the urinary Ca rose from 109 mg. to 195 mg. in one day, whereas in experiment 4 (Figure 5, days 9 through 18) it rose from 97 to 221 mg. in ten days. There was no consistent change in serum Ca or alkaline phosphatase [9] with therapy.

[9] In later studies on patients with elevated serum phosphatase, ACTH produced a fall in serum phosphatase, consistent with diminished bone formation.

TABLE IV

Metabolic data for experiment 1

Periods	Date 1947	Urine vol.	Wt. of pt.*	Urinary excretion						Serum values*				Treatment*†
				Calcium	Phosphorus	Nitrogen	Potassium	17-Ketosteroids	11-Oxysteroids	Cl	K	CO_2	Glucose	
		L	*kg.*	*mg./24 hr.*	*mg./24 hr.*	*gm./24 hr.*	*m.eq./24 hr.*	*mg./24 hr.*	*mg./24 hr.*	*m.eq./L.*	*m.eq./L.*	*m.eq./L.*	*mg.%*	
1	Jan. 28–30	2.5	58.7I	33	624	9.49	47.9	0.0	0.06					
2	Feb. 30–1	2.7	58.6I	36	659	9.44	54.3	0.1	0.06	100I	4.6I	28.8I	88I	
3	1–3	2.8	58.2I	40	671	9.50	58.8	0.4	0.09					
4	3–5	2.4	57.9I	38	645	9.82	62.3	0.0	0.08	104I	4.7I	30.6I	92I	
5	5–7	2.4	57.8I	47	622	9.70	47.2	0.0	0.05					
6	7–9	2.1	57.8I	58	673	9.85	61.6	1.8	0.08	110I	3.7I	27.5I	82I	ACTH 15 *mg./24 hr.*
7	9–11	2.5	58.1I	56	636	9.91	58.5	0.4	0.28	106II	4.0II	28.7II	96II	ACTH 15 *mg./24 hr.*
8	11–13	2.0	57.7I	50	612	9.19	57.7	0.0	0.06					ACTH 15 *mg./24 hr.*
9	13–15	2.6	57.7I	55	604	10.09	52.2	0.2	0.11	104I	4.3I	29.0I	67I	ACTH 15 *mg./24 hr.*
10	15–17	3.5	58.0I	44	606	10.02	41.7	0.3	0.07					ACTH 15 *mg./24 hr.*I ACTH 10 *mg./24 hr.*II
11	17–19	2.9	57.3I	26	503	7.69	41.1	0.4	—	107I	4.6I	30.0I	72I	
12	20–21	1.6	57.4I	31	524	9.09	53.0	0.5	—					
13	21–23	3.3	57.5I	32	535	9.28	58.8	0.4	0.12	107II	4.4II	30.4II	100II	
14	23–25	2.0	57.2I	49	632	8.85	60.6	0.5	0.09					ACTH 15 *mg./24 hr.*
15	25–27	3.8	57.8I	62	749	10.27	55.3	1.2	0.10	104I	4.7I	27.9	92I	ACTH 15 *mg./24 hr.*I ACTH 10 *mg./24 hr.*II
16	27–28 March	1.5	57.0	45	482	8.26	35.8	0.8	0.08					
17	28–1	1.3	—	34	517	8.34	46.9							
18	1–3	3.2	56.8I	39	568	8.95	50.5	1.0	0.07	100I	5.0I	31.8I	103I	
19	3–5	2.8	56.8I	35	500	8.07	50.4	0.5	—					
20	5–7	4.5	56.7I	35	541	8.98	62.2	0.4	0.05	85II		29.4II	103II	

* Roman numerals indicate day of period to which values pertain.
† Expressed as equivalent of Armour Standard LA 1A.

The changes in Ca are taken to represent changes in bone, and one might anticipate corresponding changes in P (13). Whether these changes in calcium excretion are to be attributed to ACTH or to the contaminating pitressin is not clear since there were similar changes when pitressin was given alone (Figure 3). On the other hand, the electrophoretically pure ACTH of Li and Evans reproduced the loss of Ca. Furthermore, in Cushing's syndrome, which is thought to be due to an overproduction of sugar hormone (14), osteoporosis (15) is a prominent feature. While osteoporosis is developing one expects hypercalcuria due to decreased bone formation in the presence of continued bone resorption. Characteristically, the serum Ca, P and alkaline phos-

TABLE V

Metabolic data for experiment 2

Period*	Date	Urine vol.	Wt. of pt.	Calcium mg./24 hr.			Phosphorus mg./24 hr.			Nitrogen gm./24 hr.			Sodium m.eq./24 hr.		Potassium m.eq./24 hr.		
				Urine	Fecal	Balance†	Urine	Fecal	Balance†	Urine	Fecal	Balance†	Urine	Balance†‡	Urine	Fecal	Balance†
		L	*kg.*														
1	12/30–1/5/47	11.1	77.0	76	336	−201	780	329	−210	13.08	1.28	−1.60	—		72.90	8.88	−10.6
2	1/5–1/11	10.2	76.5	78	173	− 49	662	186	+ 51	11.91	0.68	+0.16	59.8	+19.6	61.54	5.74	+ 3.9
3	1/11–1/17	11.5	76.7	79	274	−151	706	292	− 99	12.21	0.99	−0.45	68.9	+10.5	67.34	9.03	− 5.2
4	1/17–1/23	11.7	76.4	99	364	−261	720	387	−208	12.34	1.32	−0.90	67.6	+11.8	70.41	9.91	− 9.1
5 I	1/23–1/24	1.3	76.2	116	222	−136	935	263	−298	13.14	1.08	−1.46	84.3	− 4.9	95.92	8.54	−33.3
5 II	1/24–1/25	1.8	76.8	137	222	−157	956	263	−320	14.92	1.08	−3.25	65.8	+13.6	63.50	8.54	− 0.8
5 III	1/25–1/26	2.3	76.9	162	222	−182	677	263	− 41	14.48	1.08	−2.81	80.7	− 1.3	49.19	8.54	+13.5
5 IV	1/26–1/27	2.4	76.6	171	222	−191	577	263	+ 59	14.26	1.08	−2.58	84.0	− 4.6	61.06	8.54	+ 1.6
5 V	1/27–1/28	2.3	75.8	159	222	−179	558	263	+ 78	12.10	1.08	−0.42	106.9	−27.5	53.58	8.54	+ 9.1
5 VI	1/28–1/29	2.2	75.6	130	222	−150	727	230	− 91	13.43	1.08	−1.75	112.6	−33.2	65.18	8.54	− 2.5
6 I	1/29–1/30	2.2	75.4	150	189	−137	638	230	+ 31	12.85	0.69	−0.78	89.3	− 9.9	55.50	5.98	+ 9.7
6 II	1/30–1/31	1.4	75.2	117	189	−104	582	230	+ 87	12.12	0.69	−0.06	69.3	+10.1	56.33	5.98	+ 8.9
6 III	1/31–2/1	1.9	75.3	133	189	−120	755	230	− 86	13.35	0.69	−1.28	91.2	−11.8	84.50	5.98	−19.3
6 IV	2/1–2/2	1.6	75.0	118	189	−105	680	230	− 11	12.28	0.69	−0.22	79.8	− 0.5	68.53	5.98	− 3.3
6 V	2/2–2/3	1.5	75.1	99	189	− 86	714	230	− 45	12.35	0.69	−0.28	64.0	+15.4	76.02	5.98	−10.8
6 VI	2/3–2/4	1.5	75.1	101	189	− 88	776	230	−107	12.15	0.69	−0.08	50.9	+28.5	73.87	5.98	− 8.7
7 I	2/4–2/5	1.5	75.7	112	296	−206	762	320	−183	12.44	1.06	−0.74	71.2	+ 8.2	72.22	9.75	−10.8
7 II	2/5–2/6	2.7	75.4	163	296	−257	860	320	−281	13.95	1.06	−2.25	118.7	−39.3	81.12	9.75	−19.7
7 III	2/6–2/7	1.6	75.1	134	296	−228	717	320	−138	12.10	1.06	−0.40	66.8	+12.6	73.30	9.75	−11.9
7 IV	2/7–2/8	1.6	75.1	136	296	−230	661	320	− 82	12.44	1.06	−0.74	58.2	+21.2	77.04	9.75	−15.6
7 V	2/8–2/9	1.1	75.3	117	296	−211	585	320	− 6	10.91	1.06	+0.79	34.1	+45.3	59.01	9.75	+ 2.4
7 VI	2/9–2/10	1.4	75.4	140	296	−234	606	320	− 27	11.10	1.06	+0.60	59.5	+19.9	72.64	9.75	−11.2
8 I	2/10–2/11	1.6	75.4	122	277	−197	566	299	+ 34	10.54	0.94	+1.28	43.0	+36.4	57.47	7.34	+ 6.4
8 II	2/11–2/12	1.2	75.3	105	277	−180	605	299	− 5	10.44	0.94	+1.38	45.7	+33.7	79.17	7.34	−15.3
8 III	2/12–2/13	1.7	75.7	113	277	−188	724	299	−124	12.03	0.94	−0.21	57.4	+22.0	89.51	7.34	−25.7
8 IV	2/13–2/14	1.3	75.6	89	277	−164	684	299	− 84	11.01	0.94	+0.81	57.0	+22.4	83.20	7.34	−19.3
8 V	2/14–2/15	1.6	75.8	99	277	−174	675	299	− 75	11.56	0.94	+0.26	57.4	+22.0	69.00	7.34	− 5.1
8 VI	2/15–2/16	1.6	75.7	116	277	−191	653	299	− 53	11.35	0.94	+0.47	67.8	+11.6	66.60	7.34	− 2.7
9 I	2/16–2/17	1.5	75.9	107	337	−242	721	339	−161	11.58	1.02	+0.16	55.1	+24.3	79.83	7.92	−16.6
9 II	2/17–2/18	1.8	75.7	112	337	−247	693	339	−133	11.95	1.02	−0.21	66.3	+13.1	78.25	7.92	−15.0
9 III	2/18–2/19	1.3	75.8	92	337	−227	571	339	− 11	10.24	1.02	+1.51	55.2	+24.2	61.33	7.92	+ 1.9
9 IV	2/19–2/20	2.0	75.9	123	337	−258	750	339	−190	13.09	1.02	−1.35	84.5	− 5.1	82.55	7.92	−19.3
9 V	2/20–2/21	1.5	75.8	100	337	−235	702	339	−142	11.72	1.02	+0.02	52.8	+26.6	74.59	7.92	−11.3
9 VI	2/21–2/22	1.7	76.0	105	337	−240	674	339	−114	11.56	1.02	+0.08	79.9	− 0.5	71.00	7.92	− 7.7
10 I	2/22–2/23	1.4	75.9	119	281	−198	775	284	−160	11.81	1.05	−0.10	86.4	− 7.0	93.36	7.24	−29.4
10 II	2/23–2/24	1.6	76.2	144	281	−223	722	284	−107	12.11	1.05	−0.41	88.8	− 9.4	76.01	7.24	−12.1
10 III	2/24–2/25	1.8	76.3	154	281	−233	689	284	− 74	12.04	1.05	−0.34	77.4	+ 2.0	64.10	7.24	− 0.1
10 IV	2/25–2/26	2.0	75.9	140	281	−219	656	284	− 41	12.08	1.05	−0.38	85.7	− 6.3	77.20	7.24	−13.2
11 I	2/26–2/27	1.6	75.6	118	281	−197	504	284	+111	11.06	1.05	+0.65	52.7	+26.7	45.15	7.24	+18.8
11 II	2/27–2/28	1.7	75.7	113	281	−192	724	284	−109	11.71	1.05	−0.01	71.6	+ 7.8	76.71	7.24	−12.8
11 III	2/28–3/1	1.6	—	104	281	−183	694	284	− 79	11.13	1.05	+0.58	75.2	+ 4.2	80.71	7.24	−16.8
11 IV	3/1–3/2	1.6	75.9	94	281	−173	780	284	−165	11.51	1.05	+0.19	70.7	+ 8.7	80.55	7.24	−16.6

* Roman numerals indicate day of period to which values pertain.

† Intakes per 24 hr. were as follows for all periods save period 1: Ca 202 mg.; P 899 mg.; N 12.76 gm.; Na 81.0 m.eq.; K 71.2 m.eq. In period 1, Ca intake was 211 mg. per 24 hr.; Na intake was not measured.

TABLE V—*Continued*

Period	Urinary excretion				Serum values*								Treatment
	Chloride	17-Keto-steroids	11-Oxy-steroids	Biol. cortin	Ca	P	P'tase	Cl	K	Na	CO_2	Glucose	
	m.eq./24 hr.	*mg./24 hr.*	*mg./24 hr.*	*Mouse units/ 24 hr.*	*mg.%*	*mg.%*	*B.U.*	*m.eq./L*	*m.eq./L*	*m.eq./L*			
1		1.0	0.04	<1.5	9.8[I]	4.3[I]	1.7[I]	103[I]	4.4[I]	135.6[I]	30.2[I]		
2	75.93	1.7	0.11	<1.5	9.5[II]	4.5[II]	2.7[II]	103[II]	4.6[II]	139.0[II]	31.9[II]		
3	83.65	1.5	0.05	<1.5	9.8[I]	4.1[I]	2.3[I]	105[I]	5.0[I]	139.8[I]	34.0[I]		
4	82.08	0.7	0.14	<1.5	9.8[I]	3.9[I]	3.3[I]	109[I]	3.8[I]	145[I]	31.1[I]	110[I]	
5 I	67.86				7.7	4.8	1.6	103	4.3	141.8	28.6	86	
5 II	89.87												
5 III	100.39	2.5	0.42	>1.5									
5 IV	117.98												
5 V	116.05												
5 VI	110.36												
6 I	84.28				9.8	3.8	2.2	97	3.7	139.1	33.2	84	
6 II	68.47		0.28										
6 III	87.31	1.8		<1.5									ACTH§
6 IV	76.33												*15 mg./d.*
6 V	65.67		0.14										
6 VI	50.4												
7 I	54.3				9.6	3.3	2.9	103	4.9	137.5	33.3	82	
7 II	117.5		0.14										
7 III	68.8	3.0		<1.5									
7 IV	61.2												
7 V	45.0		0.12										
7 VI	64.2												
8 I	50.1				10.7	4.6	1.8	103	4.3		32	95	
8 II	61.0		0.18										
8 III	62.5	1.5		<1.5						145.6			
8 IV	62.0												
8 V	60.8		0.16										
8 VI	71.1												
9 I	70.6												
9 II	73.6				9.0	3.9	2.9	105	4.5	143	32.5	84	
9 III	70.4												
9 IV	84.1	1.3											
9 V	69.7		0.17										
9 VI	75.2				9.9	4.2	2.4	107			31.0	99	
10 I	82.6												
10 II	81.4	2.0	0.15	<3.0									ACTH§
10 III	87.4											99	*15 mg./d.*
10 IV	99.7												
11 I	75.9				9.2	4.2	2.8	97	4.9	142.5	30.9	95	
11 II	85.9	2.8	0.08	<3.0		4							
11 III	74.2												
11 IV	67.9				8.8	4.8	3.4	103	5.2	140.4	33.5	95	

‡ Fecal Na assumed to be 2 per cent of intake.
§ Expressed as equivalent of Armour Standard LA 1A.

phatase are within normal limits. An increased excretion of Ca with ACTH would be consistent with the findings in Cushing's syndrome.

c) Phosphorus metabolism

One might have expected (13) that the changes in P metabolism would be explained by the changes in N and Ca alone. Such was not the case. Thus, there was a slight rise in P excretion on the first day of giving ACTH—when there were no notable changes in N or Ca—and then there was either little change in P balance or actual retention—while N and Ca were lost—(Figure 3, days 17 through 19, and Figure 7, days 33 through 37 and 50 through 53). In the recovery periods the reverse changes in P occurred, at first retention then loss.

The serum P fell with ACTH.[10]

[10] Although the serum P is consistently high in acromegaly, we have not found it low in panhypopituitarism. Possibly the lack of ACTH in this disease counteracts the lack of growth hormone, so that normal values result.

Phosphorus is the main anion of intracellular fluid, and one must conclude that with ACTH there are changes in intracellular fluid volume independent of protoplasmic changes. This conclusion gains support from the data for K metabolism (see below).

d) Sodium and chloride metabolism

The effect of ACTH on Na and Cl metabolism apparently varied with the dose and the length of the course. The results were also probably affected by pitressin contaminating the ACTH. Thus pitressin itself caused a transient loss of Na followed by a retention during the recovery period (Figure 4). With a dose of 15 mg. (experiments 1 and 2, Figure 2) ACTH had no consistent effect on Na. With the larger doses *1*) Na was lost on the first day (possibly a pitressin effect); then *2*) Na was retained for several days (experiment 5, Figure 8); but *3*) Na was lost again if the administration of ACTH was continued after the seventh or eighth day (Figures 4 and 6). At this time the serum Na level fell. We have been able to confirm this late loss of Na in other experiments with ACTH (16). It sometimes took longer to appear.

Changes in Na were accompanied by relatively smaller changes in Cl. If changes in Cl are a

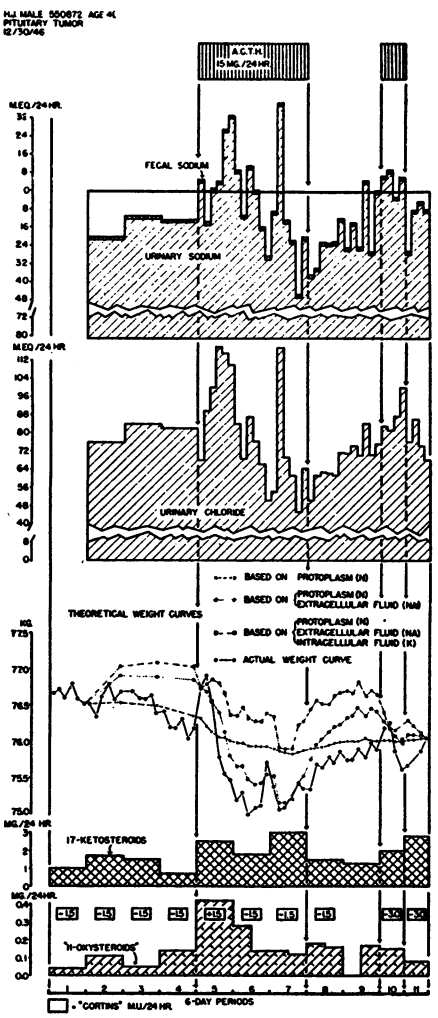

FIG. 2. EXPERIMENT 2, CONTINUED. EFFECT OF ACTH ON NA BALANCE, URINARY CL, 17-KETOSTEROIDS, "11-OXYSTEROIDS" AND "CORTIN," AND ON THE ACTUAL AND "THEORETICAL" WEIGHT CURVES

"Cortin" is expressed in "mouse units per 24-hours" (for '—', read 'less than'; for '+' read 'more than'). For method of plotting theoretical weight curves see (13).

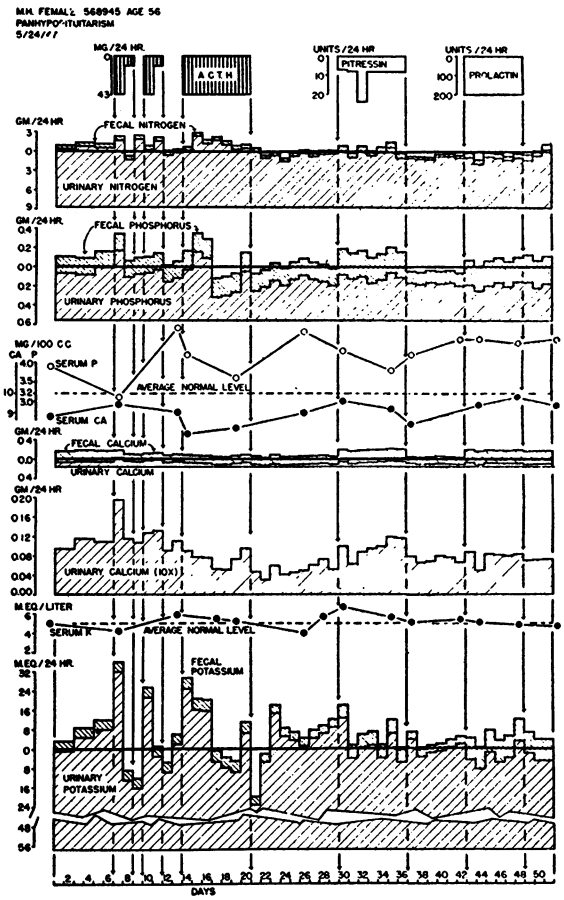

FIG. 3. PATIENT M.H., M.G.H. NO. 568,945. EXPERIMENT 3. EFFECT OF ACTH, PITRESSIN, AND PROLACTIN ON N, P, CA, AND K BALANCES AND ON SERUM P, CA, AND K

measure of changes in extracellular fluid (ECF), then the changes in Na due to changes in ECF

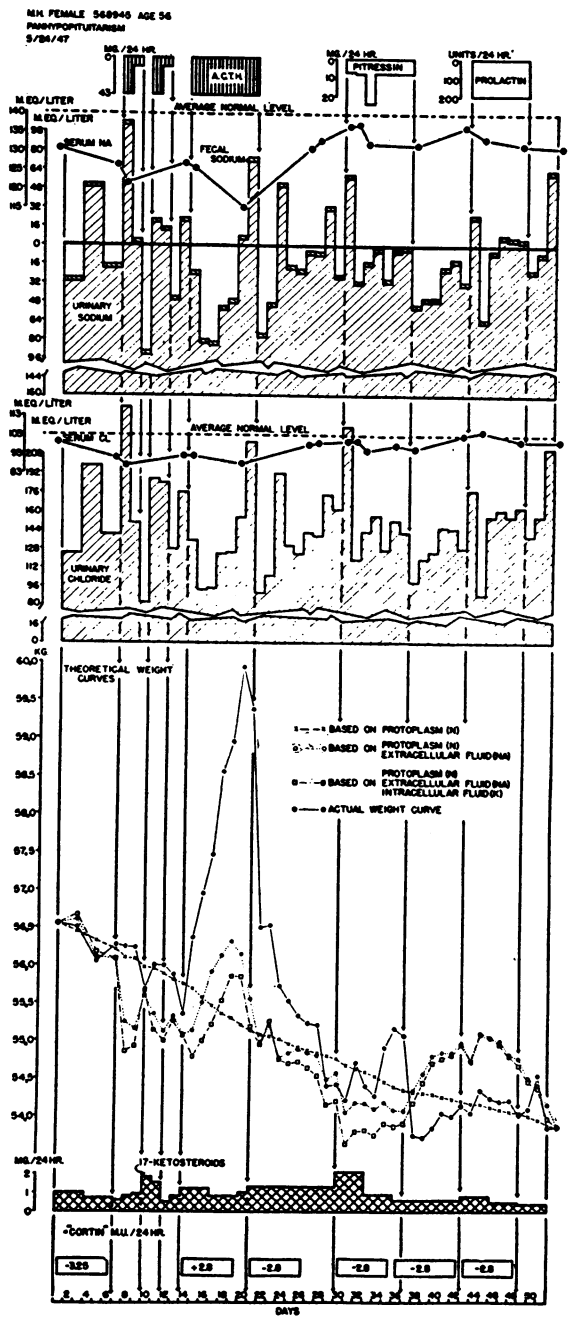

FIG. 4. EXPERIMENT 3, CONTINUED. EFFECT OF ACTH, PITRESSIN, AND PROLACTIN ON NA BALANCE, URINARY CL, 17-KETOSTEROIDS, AND "CORTIN," ON THE ACTUAL AND "THEORETICAL" WEIGHT CURVES, AND ON SERUM NA AND CL

"Cortin" is expressed in "mouse units per 24 hours" (for '—' read 'less than'; for '+' read 'more than').

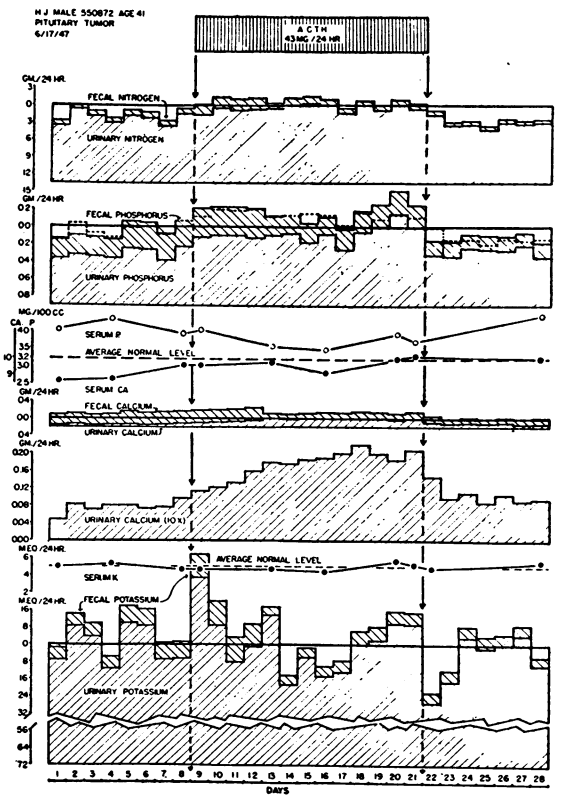

FIG. 5. PATIENT H.J., M.G.H. NO. 550,872. EXPERIMENT 4. EFFECT OF ACTH ON N, P, CA, AND K BALANCES, AND ON SERUM P, CA, AND K

would be given by the equation:

$$\text{Na (ECF)} = \frac{\text{Na (serum)} \times .97}{\text{Cl (serum)} \times 1.04} \times \text{Cl.}$$

Na changes in excess of those due to ECF would represent shifts in intracellular Na (17).

In Figures 10–B and 11–B are plotted for experiments 3 and 5 the theoretical changes in intracellular Na. It apparently entered the cells when ACTH was given and left the cells during the recovery periods. A similar effect has been reported by Prunty, Forsham and Thorn (8).

e) Potassium metabolism

In some of the experiments there was an apparent negative K balance throughout the study (Figures 1 and 7). Therefore, K changes during treatment and recovery periods should be evaluated from the data in the control periods.

With ACTH there was always a large, immediate loss of K within 24 hours of the beginning of treatment and a corresponding retention of K

TABLE VI

Metabolic data for experiment 3

Day	Date	Urine vol.	Wt. of Pt.	Calcium* mg./24 hr.			Phosphorus* mg./24 hr.			Nitrogen* gm./24 hr.			Sodium*† m.eq./24 hr.		Potassium* m.eq./24 hr.		
				Urine	Fecal	Balance	Urine	Fecal	Balance	Urine	Fecal	Balance	Urine	Balance	Urine	Fecal	Balance
	1947	*L.*	*kg.*														
	May																
1&2	24–26	3.5	56.5	94	225	−165	432	226	− 99	8.93	0.70	−0.94	127.5	+ 28.1	55.99	4.92	− 3.13
3&4	26–28	4.9	56.5	117	225	−188	419	226	− 86	9.37	0.70	−1.38	207.3	− 51.7	61.53	4.92	− 8.67
5&6	28–30	4.1	56.0	109	225	−180	495	226	−162	9.15	0.70	−1.16	139.6	+ 16.6	64.83	4.92	−11.97
7	30–31	1.8	56.3	195	145	−186	727	169	−337	10.52	0.59	−2.42	260.6	−105.0	89.48	4.14	−35.84
	June																
8	31–1	1.4	56.2	115	145	−106	449	169	− 59	7.37	0.59	+0.73	160.6	− 5.0	44.82	4.14	+ 8.82
9	1–2	2.3	56.2	107	145	− 98	486	169	− 96	10.56	0.59	−2.46	65.7	+ 89.9	41.30	4.14	+12.34
10	2–3	1.3	55.8	127	145	−118	489	169	− 99	9.01	0.59	−0.91	161.0	− 22.5	78.98	4.14	−25.34
11	3–4	2.1	56.0	131	145	−122	529	169	−139	10.26	0.59	−2.16	170.3	− 14.7	54.55	4.14	− 0.91
12	4–5	2.1	56.0	90	145	− 81	406	169	− 16	8.13	0.59	−0.04	112.1	+ 43.5	47.92	4.14	+ 5.72
13	5–6	2.5	55.8	110	145	−101	444	169	− 54	8.46	0.59	−0.36	178.2	− 22.6	59.23	4.14	− 5.59
14	6–7	1.1	55.4	90	174	−110	524	200	−165	8.86	0.54	−0.71	134.1	+ 21.5	82.83	4.48	−29.53
15	7–8	.9	56.4	77	174	− 97	711	200	−352	11.06	0.54	−2.91	76.1	+ 79.5	74.12	4.48	−20.82
16	8–9	.8	57.0	76	174	− 96	650	200	−291	9.98	0.54	−1.83	74.3	+ 81.3	73.76	4.48	−20.46
17	9–10	.8	57.5	52	174	− 72	241	200	+118	10.40	0.54	−2.25	103.3	+ 52.3	53.22	4.48	+ 0.08
18	10–11	.9	58.6	50	174	− 70	260	200	+ 99	9.76	0.54	−1.61	109.2	+ 46.4	49.87	4.48	+ 3.43
19	11–12	1.1	59.0	73	174	− 93	294	200	+ 65	9.08	0.54	−0.93	163.6	− 8.0	48.24	4.48	+ 5.06
20	12–13	2.4	59.9	94	174	−114	513	200	−154	9.30	0.54	−1.15	230.2	− 74.6	64.30	4.48	−11.00
21	13–14	4.7	59.4	47	167	− 60	313	178	+ 68	8.75	0.45	−0.51	80.9	+ 74.7	34.50	3.37	+19.91
22	14–15	2.0	56.5	30	167	− 43	351	178	+ 30	7.70	0.45	+0.54	106.4	+ 49.2	52.28	3.37	+ 2.13
23	15–16	2.5	56.5	60	167	− 95	418	178	− 56	7.47	0.45	+0.24	206.3	− 53.1	67.79	3.37	−18.19
24	16–17	2.3	55.7	41	167	− 54	369	178	+ 12	7.18	0.45	+1.06	138.3	+ 17.3	63.06	3.37	− 8.65
25	17–18	2.0	55.5	46	167	− 59	430	178	− 49	8.00	0.45	+0.24	135.3	+ 20.3	61.50	3.37	− 7.09
26	18–19	2.5	55.3	50	167	− 63	470	178	− 89	8.41	0.45	−0.17	151.2	+ 4.4	59.07	3.37	− 4.66
27	19–20	2.0	55.0	61	167	− 74	430	178	− 49	7.88	0.45	+0.36	150.7	+ 4.9	62.19	3.37	− 7.78
28	20–21	2.2	55.0	73	167	− 86	411	178	− 30	8.30	0.45	−0.06	189.2	− 33.6	64.07	3.37	− 9.66
29	21–22	2.0	54.4	52	167	− 65	366	178	+ 15	8.08	0.45	−0.16	130.7	+ 24.9	66.69	3.37	−12.28
30	22–23	1.8	54.4	99	252	−197	483	268	−192	8.83	0.77	−0.91	216.1	− 60.5	70.29	5.46	−17.97
31	23–24	1.3	54.2	63	252	−161	435	268	−144	7.79	0.77	+0.13	126.1	+ 29.5	53.75	5.46	− 1.43
32	24–25	1.8	54.7	87	252	−185	467	268	−176	8.83	0.77	−0.91	142.1	+ 13.5	58.38	5.46	− 6.06
33	25–26	1.5	54.4	94	252	−192	391	268	−100	8.16	0.77	−0.23	153.7	+ 1.9	59.25	5.46	− 6.93
34	26–27	1.1	54.3	98	252	−196	430	268	−139	8.72	0.77	−0.79	127.6	+ 28.0	53.97	5.46	− 1.65
35	27–28	1.3	54.9	119	252	−217	502	268	−211	9.38	0.77	−1.45	153.1	+ 2.5	64.38	5.46	−12.06
36	28–29	1.3	55.2	116	252	−214	471	268	−180	7.79	0.77	+0.13	154.6	+ 1.0	52.03	5.46	+ 0.29
37	29–30	2.8	55.1	79	124	− 49	388	129	+ 42	7.59	0.37	+0.72	105.2	+ 50.4	61.67	3.06	− 6.95
	July																
38	30–1	2.0	53.8	66	124	− 36	374	129	+ 56	7.55	0.37	+0.77	111.8	+ 43.8	54.58	3.06	+ 0.14
39	1–2	1.8	53.7	69	124	− 39	393	129	+ 37	7.44	0.37	+0.88	112.0	+ 43.6	55.92	3.06	− 1.20
40	2–3	2.1	53.2	80	124	− 50	387	129	+ 43	7.84	0.37	+0.43	137.5	+ 18.1	56.71	3.06	− 1.99
41	3–4	2.4	54.0	77	124	− 47	390	129	+ 40	7.94	0.37	+0.37	144.9	+ 10.7	58.39	3.06	− 3.67
42	4–5	2.0	54.0	66	124	− 36	366	129	+ 64	7.70	0.37	+0.62	126.0	+ 29.6	59.64	3.06	− 4.92
43	5–6	2.3	54.1	88	260	−194	365	260	− 66	7.82	0.66	+0.21	182.2	− 26.6	53.17	8.82	− 4.21
44	6–7	1.5	54.1	49	260	−155	305	260	− 6	6.76	0.66	+1.27	94.0	+ 61.6	49.25	8.82	− 0.29
45	7–8	2.0	54.3	84	260	−190	358	260	− 59	7.86	0.66	+0.17	151.4	+ 4.2	56.42	8.82	− 7.46
46	8–9	1.8	54.2	82	260	−188	386	260	− 87	7.71	0.66	+0.32	164.5	− 8.9	52.29	8.82	− 3.33
47	9–10	1.8	54.2	80	260	−186	351	260	− 52	7.30	0.66	+0.73	163.1	− 7.5	54.06	8.82	− 5.10
48	10–11	2.4	54.2	83	260	−189	392	260	− 93	7.75	0.66	+0.29	161.9	− 6.3	61.09	8.82	−12.13
49	11–12	2.1	54.0	70	265	−181	383	286	−110	7.36	0.80	+0.53	135.5	+ 20.1	57.89	6.70	− 6.81
50	12–13	1.6	54.1	72	265	−183	334	286	− 61	8.03	0.80	−0.14	150.2	+ 5.4	54.89	6.70	− 3.81
51	13–14	3.1	54.6	73	265	184	378	286	−105	8.93	0.80	−1.04	220.0	− 64.4	54.89	6.70	− 3.81
52	14–15	lost	53.9		265			286			0.80					6.70	

* Intakes per 24 hr. were as follows for all days save day 23: Ca 154 mg.; P 559 mg.; N 8.69 gm.; Na 158.8 m.eq.; K 57.8. On day 23, intake was: Ca 132 mg.; P 540 mg.; N 8.16 gm.; Na 156.4 m.eq.; K 53.0 m.eq.

† Fecal Na assumed to be 2 per cent of intake.

‡ Expressed as equivalent of Armour Standard LA 1A.

TABLE VI—*Continued*

Day	Urinary excretion				Serum values								Treatment
	Chloride	17-Keto-steroids	11-Oxy-steriods	Biol. cortin	Ca	P	P'tase	Cl	K	CO_2	Na	Glucose	
	m.eq./24 hr.	*mg./24 hr.*	*mg./24 hr.*	*Mouse units /24 hr.*	*mg.%*	*mg.%*	*Units %*	*m.eq./L*	*m.eq./L*	*m.eq./L*	*m.eq./L*	*mg.%*	
1&2	123.7	1.0	0.48	<3.25	8.8	3.9		99	5.0	28.1	130.5	89	
3&4	198.2												
5&6	140.6	0.7	1.17					91		25.4	126.6	89	
7	255.2	0.6	0.48		9.4	3.1		87	4.2	24.2	121.4	106	ACTH§ *43 mg.*
8	149.5	0.8	0.32										ACTH *11 mg.*
9	82.4	0.9	0.27										
10	187.4	1.8	0.58										ACTH *43 mg.*
11	183.8	1.5	0.34										ACTH *11 mg.*
12	127.5	0.5	0.17										
13	17.63	0.8			9.0	4.9	2.9	92	5.9	29.0	126.8	95	
14	135.3												
15	93.2	1.2	0.37		7.6	4.2	5.0	92		23.9	125.6	95	
16	93.6												ACTH
17	124.2			>2.8					5.5				*43 mg.*
18	124.9	0.8	—										*/24 hr.*
19	154.8				8.2	3.6	3.6	88	5.2	26.9	115.1	100	
20	218.3	1.0	0.56										
21	90.8												
22	105.7	1.3											
23	191.7			<2.8									
24	130.6												
25	123.8	1.3	0.04										
26	141.8				9.0	4.8	3.0	99	4.0	26.0	130.8	83	
27	139.1							98			133.0		
28	174.9	1.3							5.7				
29	162.3												Pitressin
30	239.6				9.6	4.3	3.3	100	6.7	27.3	136.8	85	7 u.
31	119.5	2.1	3.40					100			137.2		8 u.
32	142.3			<2.8				95			132.2		24 u.
33	156.3												8 u.
34	127.3	0.9	0.75										8 u.
35	152.2				9.2	3.8	4.4	98	5.6	26.5	127.7	86	8 u.
36	141.7												
37	99.6	0.6	—		8.4	4.2	2.2	96	5.1	25.7	131.7	108	
38	119.7			<2.8									
39	125.4												
40	146.2	0.6											
41	145.2		2.00										
42	128.4					4.6	4.0	103	5.4	26.3	137.5	83	
43	177.2	0.8											Prolactin 200 u.
44	89.1		2.24		9.4	4.6	3.8	105	5.1	24.9		120	200 u.
45	155.3		2.24										200 u.
46	160.4			<2.8									200 u.
47	155.3	0.5	1.83										200 u.
48	162.4				9.8	4.5	4.1	100	4.9	29.6	131.7	107	200 u.
49	138.9												
50	155.5	0.4	1.00										
51	212.6												
52					9.4	4.6	3.2	100	4.7	27.8	131.2	93	

at the beginning of the recovery period. These changes were out of proportion to the changes in N and P, the other constituents of ICF measured. Apart from this, K balances were little affected by ACTH.

With K then, as with P, the changes were not those to be expected from the changes in N. In Figures 10–A and 11–A are shown for experiments 3 and 5, respectively, *1*) the difference between the K values found and the K values expected

from changes in protoplasm and ECF (solid lines) and *2*) the difference between the P values found and the P values expected from changes in protoplasm, ECF and bone (broken lines).[11] Both K and P are expressed in milliequivalents, P being given a "valence" of 2.[12] The fluctuations in K and P beyond those expected from the changes in

[11] For factors used see legend to Figure 10.

[12] At the pH of body fluids, 1 mM of P would combine with 1.8 m.eq. of cation, giving P a "valence" of 1.8.

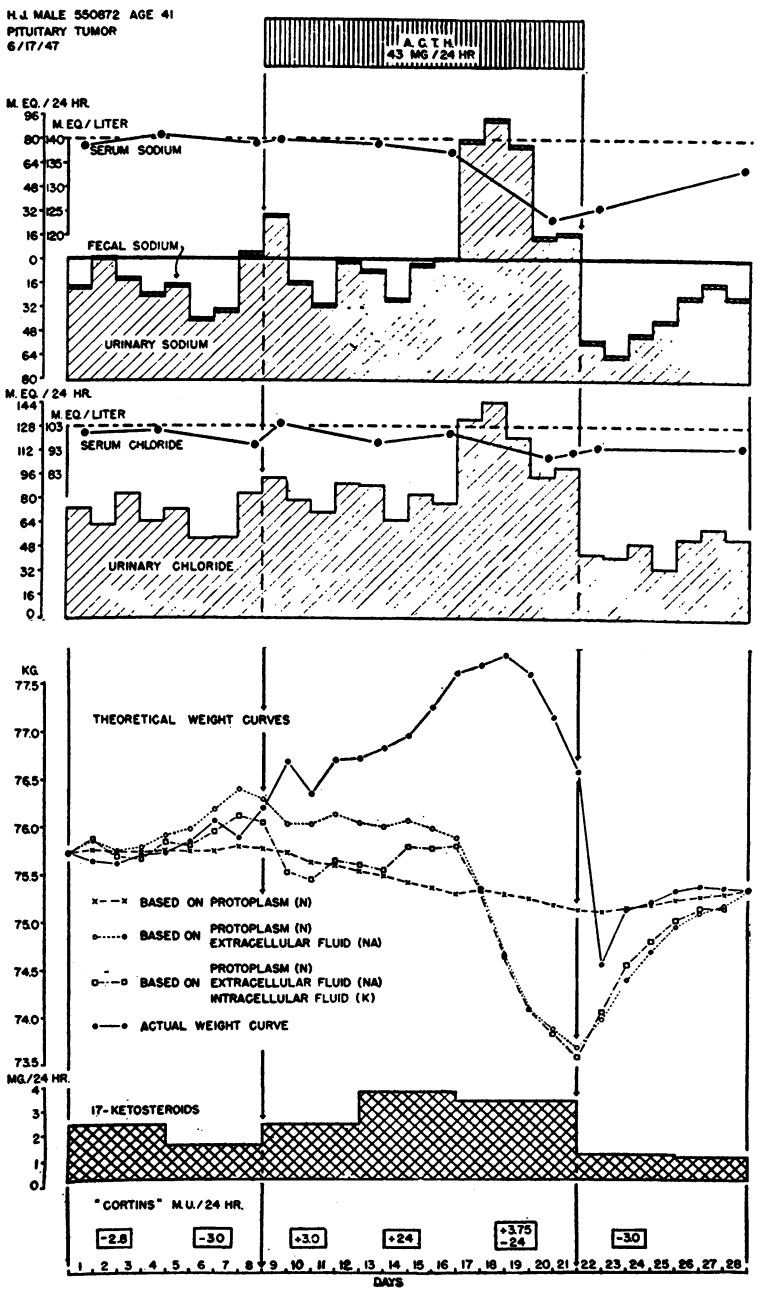

FIG. 6. EXPERIMENT 4, CONTINUED. EFFECT OF ACTH ON NA BALANCE, URINARY CL, 17-KETOSTEROIDS, AND "CORTIN" ON THE ACTUAL AND "THEORETICAL" WEIGHT CURVES, AND ON THE SERUM NA AND CL

"Cortin" is expressed in "mouse units per 24 hours" (for '—' read 'less than'; for '+' read 'more than').

N, Ca and Cl are highly correlated, and their relation to each other is roughly that of K to P in ICF.[18]

From the changes shown, one may conclude that, independently of the protoplasm changes, ICF is retained with ACTH, to be lost again during the recovery period. This may be due to glycogen deposition with ACTH (18, 19) for, when glycogen is formed, P and K are retained (20). In patients with hypopituitarism, in whom the stores of glycogen are depleted, this effect might be all the more marked.

There remains to be discussed the sharp loss of K on starting ACTH with corresponding retention at the beginning of recovery. These changes are not accompanied by commensurate changes in P values, but are inversely related to changes in intracellular Na (Figures 10–B and 11–B). They presumably represent changes in ICF composition rather than in ICF volume.

[18] See appendix.

Desoxycorticosterone glucoside apparently had a similar effect on ICF composition (Figure 11), but since 17-hydroxycorticosterone, a substance with sugar hormone activity, also had this effect (21), there is no need to postulate that a separate desoxycorticosterone-like substance is liberated with ACTH.

f) Body weight and water balance

As reported elsewhere (13) one may pro-rate the changes in body weight contributed by protoplasm, extracellular fluid, and intracellular fluid by constructing "theoretical weight curves" in which the actual fluctuations are plotted against the theoretical fluctuations expected from the N, Na and K balances.

"Theoretical weight curves" for experiments 2, 3, 4 and 5 are shown in Figures 2, 4, 6 and 8, respectively. The actual weight curves should be compared with the theoretical weight curves based on (N + Na + K). In experiment 5 (Figure 8),

TABLE VII

Metabolic data for experiment 4

Day	Date	Urine volume	Wt. of pt.	Calcium* *mg./24 hr.*			Phosphorus* *mg./24 hr.*			Nitrogen* *gm./24 hr.*			Sodium*† *m.eq./24 hr.*	
				Urine	Fecal	Balance	Urine	Fecal	Balance	Urine	Fecal	Balance	Urine	Balance
	1947 June	*L*	*kg.*											
1	17–18	.8	75.5	53	250	− 90	539	234	+132	10.04	0.71	+2.73	61.7	+18.0
2	18–19	1.5	75.7	83	250	−120	592	234	+ 79	12.56	0.71	+0.21	80.5	− 0.8
3	19–20	1.3	75.6	71	250	−108	570	234	+101	11.42	0.71	+1.35	67.0	+12.7
4	20–21	1.4	75.6	79	250	−116	546	234	+125	10.44	0.71	+2.33	56.6	+23.1
5	21–22	1.1	75.7	79	314	−180	637	313	− 45	11.51	0.96	+1.01	62.7	+17.0
6	22–23	1.1	75.7	72	314	−173	620	313	− 28	11.18	0.96	+1.34	40.6	+39.1
7	23–24	.8	75.9	75	314	−176	512	313	+ 80	9.90	0.96	+2.62	46.1	+33.6
8	24–25	1.8	76.1	97	314	−198	651	313	− 59	11.92	0.96	+0.60	84.1	+ 4.4
9	25–26	1.0	75.8	110	330	−227	771	345	−211	11.76	1.76	−0.04	109.0	−29.3
10	26–27	.8	76.2	119	330	−236	778	345	−218	12.69	1.76	−0.97	64.6	+15.1
11	27–28	.8	76.7	133	330	−250	778	345	−218	12.52	1.76	−0.79	49.5	+30.2
12	28–29	.8	76.4	159	330	−276	760	345	−200	12.52	1.76	−0.80	78.7	+ 1.0
13	29–30	1.0	76.7	175	190	−152	785	240	−120	13.00	0.88	−0.40	72.7	+ 7.0
	July													
14	30–1	1.0	76.7	173	190	−150	816	240	−151	13.72	0.88	−1.12	53.4	+26.3
15	1–2	.9	77.0	185	190	−162	717	240	− 52	13.89	0.88	−1.29	76.5	+ 3.2
16	2–3	.9	77.3	189	190	−166	790	240	−125	13.60	0.88	−1.00	80.6	− 0.9
17	3–4	1.3	77.6	199	178	−164	632	247	+ 26	12.00	0.85	+0.63	149.6	−69.9
18	4–5	1.4	77.5	221	178	−186	833	247	−175	13.44	0.85	−0.81	173.1	−93.4
19	5–6	1.4	77.8	202	178	−167	923	247	−265	12.52	0.85	+0.11	155.8	−76.1
20	6–7	1.8	77.6	186	178	−151	1059	247	−401	13.60	0.85	−0.97	95.1	−15.4
21	7–8	2.3	77.2	206	178	−171	901	247	−243	12.99	0.85	−0.36	97.6	−17.9
22	8–9	3.5	76.6	142	137	− 66	544	176	+185	12.17	0.52	+0.79	25.5	+54.2
23	9–10	1.1	74.6	97	137	− 21	536	176	+193	10.31	0.52	+2.65	16.0	+63.7
24	10–11	1.4	75.1	105	137	− 29	627	176	+102	10.47	0.52	+2.49	31.7	+49.0
25	11–12	1.2	75.2	89	137	− 13	620	176	+109	9.43	0.52	+3.53	39.8	+39.9
26	12–13	1.4	75.3	104	137	− 28	618	176	+111	10.60	0.52	+2.36	55.4	+24.3
27	13–14	1.4	75.4	93	137	− 17	655	176	+ 74	10.35	0.52	+2.61	64.6	+15.1
28	14–15	.9	75.3	97	137	− 21	607	176	+122	10.49	0.52	+2.47	55.5	+24.2

TABLE VII—*Continued*

Day	Potassium* m.eq./24 hr.			Urinary excretion				Serum values						Treatment
	Urine	Fecal	Balance	Chloride	17-Keto-steroids	Biol. cortin	Creatinine	Ca	P	Cl	K	CO_2	Na	
				m.eq./24 hr.	mg./24 hr.	Mouse units/ 24 hr.	gm./24 hr.	mg.%	mg.%	m.eq./L	m.eq./L	m.eq./L	m.eq./L	
1	65.78	5.41	+ 1.58	72.85			1.10							
2	81.70	5.41	−14.34	61.61	2.4	<2.8	0.99	8.7	4.0	100	5.1	33.1		
3	76.98	5.41	− 9.62	82.52			1.03							
4	61.89	5.41	+ 5.47	64.16			0.98							
5	83.56	7.18	−17.97	71.15			1.12	8.9	4.3	100	5.2	33.1	140.7	
6	81.63	7.18	−16.04	54.77	1.5	<3.0	1.20							
7	66.78	7.18	− 1.19	55.24			1.25							
8	66.89	7.18	− 1.30	82.78			1.20							
9	102.78	11.12	−41.13	92.82			1.30	9.6	3.9	95	4.8	32.3	139.0	ACTH 43‡ mg./ 24 hr.
10	81.10	11.12	−19.45	77.80	2.4	≥3.0	1.35	9.6	4.0	104	4.7	26.1	139.7	
11	56.54	11.12	+ 5.11	69.77			1.16							
12	62.93	11.12	− 1.28	89.33			1.37							
13	77.07	4.86	− 9.16	87.65			1.33							
14	53.05	4.86	+14.86	64.78	3.8	≥24	1.26	9.9	3.6	96	4.6	28.8	139.0	
15	65.98	4.86	+ 1.93	81.82			—							
16	57.53	4.86	+10.38	75.77			1.18	9.2	3.5	100	4.1	29.5	137.2	
17	59.74	5.79	+ 7.24	132.41										
18	73.01	5.79	− 6.03	144.28										
19	74.25	5.79	− 7.27	121.69	3.4	≥3.75 <24	1.23							
20	81.74	5.79	−14.47	93.98										
21	81.07	5.79	−14.09	99.90			1.24	10.0	3.9	90	5.6	30.0	128.2	
22	45.66	4.71	+22.40	42.53			1.28	10.2	3.7	92	5.1	31.0	125.1	
23	55.69	4.71	+12.37	40.96	1.1	<2.8	1.31			94	4.9		125.0	
24	75.43	4.71	− 7.37	49.40			—							
25	71.02	4.71	− 2.96	33.90			1.32							
26	72.59	4.71	− 4.53	52.70			1.45							
27	76.93	4.71	− 8.87	60.22	1.0		1.37							
28	62.63	4.71	+ 5.43	53.45			1.39							

* Intakes per 24 hr. were as follows: Ca 213 mg.; P 905 mg.; N 13.48 gm.; Na 81.3 m.eq.; K 72.77 m.eq.
† Fecal Na assumed to be 2 per cent of ntake.
‡ Expressed as equivalent of Armour Standard LA 1A.

in which the ACTH contained little pitressin, the correlation was good. In experiments 2, 3 and 4 the ACTH produced a gain of weight not explained by N, Na and K (Figure 2, periods 5 and 10; Figure 4, days 14 through 20; Figure 6, days 9 through 21). This was probably due to water retention without sodium and may have been a pitressin effect, since a similar discrepancy was produced in the experiment with pitressin (Figure 4, days 30 through 36).

g) Urinary corticoids

ACTH caused a rise in "cortin" [6] in the three experiments (2, 3 and 4, Figures 2, 4 and 6) in which it was assayed. In the control periods the values were below normal, as one would expect in panhypopituitarism. With ACTH there was a rise to values of *at least* 1.5 (experiment 2), 2.8 (experiment 3) and 24 (experiment 4) mouse units per 24 hours. The last value is above the normal range. Upon stopping ACTH "cortin" excretion fell to the control levels.

In the three experiments [14] (1, 2 and 5, Figures 2 and 9) in which "11-oxysteroid" excretion could be determined chemically [15] ACTH produced a rise from low normal values to normal values (experiments 1 and 2) or, when larger doses were given, to values greatly above normal. In experiment 5, where the highest doses of ACTH were used, the rise (Figure 9) was to 2.41 mg. per 24 hours, a value within the range found in Cushing's syndrome.

Thus in all experiments urinary corticoid values indicated an increased output of sugar hormone with ACTH.

[14] In experiments 3 and 4, determinations of "11-oxysteroids" were carried out, but all determinations done at that time were later found to be unreliable due to technical difficulties.

[15] These determinations were done for us by Dr. Nathan Talbot, to whom the authors are indebted.

h) Urinary 17-ketosteroids

Most workers, including ourselves have found in subjects with intact pituitaries a rise in 17-ketosteroid excretion after giving ACTH. On the other hand, only one of these three patients with panhypopituitarism showed a significant rise (H.J., experiments 2, 4, 5; Figures 2, 6, 9), and he was certainly not totally lacking in pituitary function. Thus, there were many mature Leydig cells in the testicular biopsy as evidence that the luteinizing hormone (L.H.) was being produced, albeit not sufficiently to prevent hypoleydigism.

In M. W. (experiment 1), given about the same dose of ACTH that H. J. received in experiment 2, and in M.H. (experiment 3), given the same dose of ACTH that H.J. received in experiment 2, and in M.H (experiment 3), given the same dose that H. J. received in experiment 4, there was no significant rise in 17-ketosteroids. In each case, however, there was a rise in corticoids, and in the latter the other metabolic effects of ACTH were produced.

These observations suggest that ACTH produces less rise in 17-ketosteroids in patients with panhypopituitarism than in others, possibly because a second pituitary hormone is required. The second hormone might, for example, be L.H. The normal child, whose output of sugar hormone, and therefore of ACTH, is presumably normal, does not excrete appreciable amounts of 17-keto-

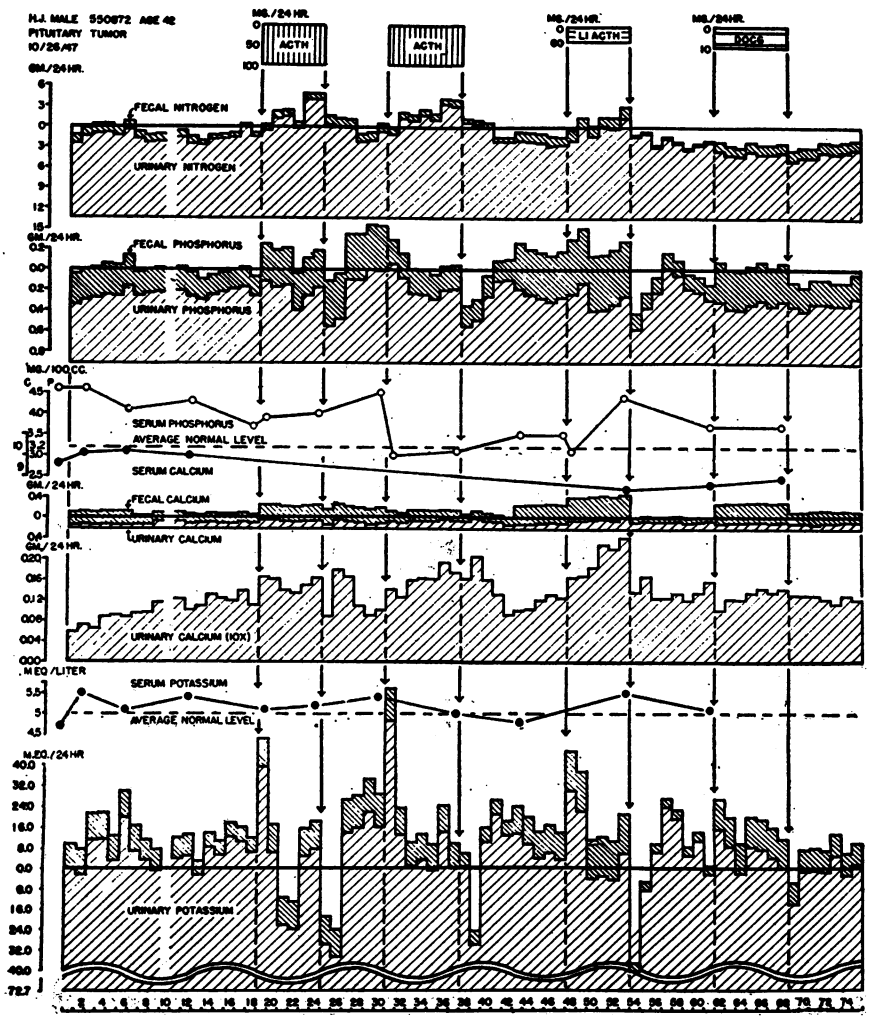

FIG. 7. PATIENT H.J., M.G.H. NO. 550,872. EXPERIMENT 5. EFFECT OF ACTH AND DESOXYCORTICOSTERONE GLUCOSIDE (DOCG) ON N, P, CA, AND K BALANCES, AND ON SERUM P, CA, AND K

TABLE VIII—*Metabolic data for experiment 5*

Day	Date	Urine Vol.	Wt. of Pt.	Calcium* mg./24 hr.			Phosphorus* mg./24 hr.			Nitrogen* gm./24 hr.			Sodium*† m.eq./24 hr.		Potassium* m.eq./24 hr.		
				Urine	Fecal	Balance	Urine	Fecal	Balance	Urine	Fecal	Balance	Urine	Balance	Urine	Fecal	Balance
		L.	*kg.*														
	Oct. 1947																
1	26–27	.9	75.9	58	251	− 96	557	303	+ 45	10.94	1.23	+1.30	47.9	+ 31.8	72.79	9.88	− 9.9
2	27–28	1.2	76.1	71	251	−109	601	303	+ 1	12.01	1.23	+0.24	44.4	+ 35.3	70.32	9.88	− 7.4
3	28–29	1.4	76.3	64	251	−102	621	303	− 19	12.47	1.23	−0.23	50.8	+ 28.9	83.07	9.88	−17.2
4	29–30	1.6	76.3	87	251	−125	650	303	− 48	12.58	1.23	−0.34	71.0	+ 8.7	84.55	9.88	−21.7
5	30–31	1.8	76.3	90	251	−128	640	303	− 38	12.17	1.23	+0.08	81.0	− 1.3	75.90	9.88	−13.0
	Nov.																
6	31–1	1.8	76.2	87	251	−125	754	303	−152	12.99	1.23	−0.74	78.5	+ 1.2	92.93	9.88	−30.0
7	1–2	1.3	76.2	94	189	− 70	663	228	+ 14	11.74	1.01	+0.73	59.0	+ 20.7	80.14	8.14	−15.5
8	2–3	1.2	76.2	96	189	− 72	675	228	+ 2	11.15	1.01	+1.32	63.8	+ 15.9	76.46	8.14	−11.8
9	3–4	1.3	76.3	115	189	− 91	693	228	− 16	11.38	1.01	+1.09	77.6	+ 2.1	72.05	8.14	− 7.4
10	4–5	—	76.3	—	189	—	—	228	—	—	1.01	—	—	—	—	8.14	—
11	5–6	1.5	76.3	122	189	− 98	695	228	− 18	11.88	1.01	+0.59	81.9	− 2.2	77.01	8.14	−12.4
12	6–7	1.2	76.3	101	189	− 77	648	228	+ 29	10.74	1.01	+1.73	59.0	+ 20.7	78.03	8.14	−13.4
13	7–8	1.2	76.4	108	163	− 58	616	189	+100	10.86	0.59	+2.03	70.0	+ 9.7	69.91	5.23	− 1.4
14	8–9	1.3	76.4	130	163	− 80	657	189	+ 59	11.61	0.59	+1.28	78.8	+ 0.9	81.61	5.23	−14.1
15	9–10	1.3	76.4	123	163	− 73	687	189	+ 29	11.71	0.59	+1.17	71.6	+ 8.1	78.53	5.23	−11.0
16	10–11	1.4	76.5	118	163	− 68	712	189	+ 4	11.98	0.59	+0.91	59.9	+ 19.8	85.44	5.23	−17.9
17	11–12	1.3	76.6	137	163	− 87	733	189	− 17	13.30	0.59	−0.41	74.9	+ 4.8	83.75	5.23	−16.2
18	12–13	1.5	76.6	110	163	− 60	647	189	+ 69	11.96	0.59	+0.92	78.0	+ 1.7	79.60	5.23	−12.1
19	13–14	1.2	76.6	164	301	−252	801	367	−263	12.85	1.01	−0.38	93.1	− 13.4	122.40	10.66	−60.3
20	14–15	1.1	76.9	160	301	−248	741	367	−203	14.91	1.01	−2.44	42.8	+ 36.9	79.41	10.66	−17.3
21	15–16	1.7	77.0	139	301	−227	758	367	−220	15.01	1.01	−2.54	27.2	+ 52.5	61.50	10.66	+ 0.6
22	16–17	.7	76.3	135	301	−223	508	367	+ 30	13.20	1.01	−0.73	22.5	+ 57.2	55.95	10.66	+ 2.2
23	17–18	.8	76.7	147	301	−235	658	367	−120	17.39	1.01	−4.92	31.7	+ 48.0	78.21	10.66	−16.1
24	18–19	.9	77.1	163	301	−251	737	367	−199	17.46	1.01	−4.99	40.6	+ 39.1	80.69	10.66	−18.6
25	19–20	1.0	77.5	89	299	−175	361	440	+104	13.79	1.30	−1.61	23.0	+ 56.7	42.84	12.50	+17.4
26	20–21	1.7	77.7	178	299	−264	430	440	+ 35	13.41	1.30	−1.23	188.6	−108.9	38.42	12.50	+21.9
27	21–22	2.2	77.0	165	299	−251	812	440	−347	13.22	1.30	−1.04	228.9	−149.2	87.10	12.50	−26.8
28	22–23	1.4	76.2	108	299	−194	813	440	−348	11.04	1.30	+1.14	127.0	− 47.3	88.81	12.50	−28.5
29	23–24	1.0	75.8	90	299	−176	908	440	−443	11.37	1.30	+0.80	95.6	− 15.9	95.08	12.50	−34.8
30	24–25	1.7	75.6	101	299	−187	905	440	−440	12.74	1.30	−0.57	98.0	− 18.3	89.41	12.50	−29.1
31	25–26	1.2	75.3	142	203	−132	966	243	−304	12.28	0.94	+0.26	95.0	− 15.3	129.35	10.29	−66.9
32	26–27	1.2	75.1	124	203	−114	830	243	−168	14.72	0.94	−2.18	26.5	+ 53.2	86.27	10.29	−23.8
33	27–28	.7	74.9	158	203	−148	683	243	− 21	14.32	0.94	−1.78	14.4	+ 65.3	73.07	10.29	−10.6
34	28–29	.7	75.1	162	203	−152	679	243	− 17	15.08	0.94	−2.54	13.7	+ 66.0	76.52	10.29	−14.0
35	29–30	.6	75.6	161	203	−151	628	243	+ 34	14.53	0.94	−1.99	13.6	+ 66.1	71.35	10.29	− 8.9
	Dec.																
36	30–1	.7	75.6	192	203	−182	705	243	− 43	16.85	0.94	−4.31	26.0	+ 53.7	87.58	10.29	−25.1
37	1–2	.7	76.1	174	203	−164	729	243	− 67	16.54	0.94	−3.99	25.3	+ 54.4	72.63	10.29	−10.2
38	2–3	.8	76.6	163	142	− 92	375	206	+324	14.06	0.60	−1.19	39.5	+ 40.2	73.42	5.42	− 6.1
39	3–4	1.8	76.9	204	142	−133	431	206	+268	13.91	0.60	−1.03	246.3	−166.6	42.96	5.42	+24.4
40	4–5	2.1	75.7	160	142	− 89	660	206	+ 39	13.53	0.60	−0.65	225.1	−145.4	85.45	5.42	−18.1
41	5–6	1.5	75.0	131	142	− 60	814	206	−115	11.25	0.60	+1.63	128.6	− 48.9	94.00	5.42	−26.7
42	6–7	1.2	74.9	94	142	− 23	826	206	−127	11.28	0.60	+1.59	80.9	− 1.2	85.81	5.42	−18.5
43	7–8	1.0	74.7	100	356	−243	739	457	−291	11.58	1.25	+0.64	54.7	+ 25.0	86.62	10.54	−24.4
44	8–9	1.1	74.9	104	356	−247	671	457	−223	11.53	1.25	+0.70	48.6	+ 31.1	82.44	10.54	−20.2
45	9–10	1.0	74.8	120	356	−263	645	457	−197	11.29	1.25	+0.93	48.6	+ 31.1	77.00	10.54	−14.8
46	10–11	1.2	74.5	131	356	−274	613	457	−165	11.02	1.25	+1.21	57.5	+ 22.2	79.00	10.54	−16.8
47	11–12	1.2	75.0	126	356	−269	639	457	−191	10.97	1.25	+1.26	62.2	+ 17.5	76.13	10.54	−13.9
48	12–13	1.4	75.1	164	445	−396	684	544	−323	11.54	1.65	+0.29	83.4	− 3.7	103.12	15.11	−45.5
49	13–14	1.3	75.4	169	445	−401	790	544	−429	13.29	1.65	−1.46	52.3	+ 27.4	95.15	15.11	−37.5
50	14–15	1.0	74.9	184	445	−416	526	544	−165	12.15	1.65	−0.33	31.6	+ 48.1	68.76	15.11	−11.1
51	15–16	1.0	75.2	195	445	−427	531	544	−170	13.55	1.65	−1.72	34.7	+ 45.0	69.63	15.11	−12.0
52	16–17	1.0	75.2	187	445	−419	580	544	−219	13.28	1.65	−1.45	36.7	+ 43.0	68.38	15.11	−10.7
53	17–18	1.3	75.7	202	445	−434	666	544	−305	14.88	1.65	−3.05	50.3	+ 29.4	77.57	15.11	−19.9
54	18–19	1.1	75.8	141	96	− 24	320	105	+408	12.23	0.34	+0.91	42.9	+ 36.8	31.80	3.20	+37.8
55	19–20	1.7	76.1	167	96	− 50	538	105	+262	12.50	0.34	+0.63	177.2	− 97.5	64.15	3.20	+ 5.4
56	20–21	1.1	75.5	125	96	− 8	687	105	+113	10.62	0.34	+2.51	101.1	− 21.4	79.03	3.20	− 9.5
57	21–22	1.6	75.4	125	96	− 8	925	105	−125	11.84	0.34	+1.29	103.6	− 23.9	96.75	3.20	−27.2
58	22–23	1.5	75.2	137	96	− 20	853	105	− 53	11.07	0.34	+2.07	115.2	− 35.5	92.17	3.20	−22.6
59	23–24	1.1	74.9	120	96	− 3	713	105	+ 87	9.97	0.34	+3.17	78.7	+ 1.0	77.77	3.20	− 8.2
60	24–25	1.4	75.0	138	96	− 21	690	105	+110	10.98	0.34	+2.16	67.8	+ 11.9	83.49	3.20	−13.9
61	25–26	1.4	75.0	155	96	− 38	619	105	+181	11.28	0.34	+1.85	67.3	+ 12.4	70.33	3.20	− 0.8
62	26–27	1.1	75.0	106	374	−267	597	385	− 77	10.03	1.45	+1.99	23.9	+ 55.8	87.94	11.79	−27.0
63	27–28	1.0	75.3	122	374	−283	526	385	− 6	9.59	1.45	+2.44	16.4	+ 63.3	81.16	11.79	−20.2
64	28–29	1.0	75.3	121	374	−282	510	385	+ 10	9.34	1.45	+2.69	20.6	+ 59.1	70.70	11.79	− 9.7
65	29–30	1.0	75.9	137	374	−298	564	385	− 44	9.90	1.45	+2.12	29.9	+ 49.8	81.21	11.79	−20.2
66	30–31	1.0	76.3	147	374	−308	609	385	− 89	9.45	1.45	+2.57	46.5	+ 33.2	80.16	11.79	−19.2
	Jan.																
67	31–1	.9	76.3	139	374	−300	559	385	− 39	9.44	1.45	+2.59	62.5	+ 17.2	77.01	11.79	−16.0
68	1–2	1.2	76.5	147	374	−308	594	385	− 74	9.61	1.45	+2.42	69.1	+ 10.6	72.79	11.79	−11.8
69	2–3	1.2	76.4	133	217	−137	554	233	+118	8.72	1.26	+3.50	119.6	− 39.9	58.81	8.41	+ 5.6
70	3–4	1.2	76.2	132	217	−136	505	233	+167	9.32	1.26	+2.90	95.9	− 16.1	71.58	8.41	− 7.2
71	4–5	1.1	76.0	131	217	−135	581	233	+111	9.36	1.26	+2.85	86.5	− 6.8	71.72	8.41	− 7.4
72	5–6	.9	76.0	122	217	−126	584	233	+ 88	9.76	1.26	+2.45	60.8	+ 18.9	71.14	8.41	− 6.8
73	6–7	.9	76.1	113	217	−117	568	233	+104	9.66	1.26	+2.56	51.3	+ 28.4	77.32	8.41	−13.0
74	7–8	.9	76.2	132	217	−136	568	233	+104	9.71	1.26	+2.51	73.8	+ 5.9	69.73	8.41	− 5.4
75	8–9	1.1	76.2	120	217	−124	631	233	+ 41	10.16	1.26	+2.06	61.2	+ 18.2	74.02	8.41	− 9.7

* Intakes per 24 hr. were as follows: Ca 213 mg.; P 905 mg.; N 13.48 gm.; Na 81.3 m.eq.; K 72.77 m.eq.
† Fecal Na assumed to be 2 per cent of intake. ‡ Expressed as equivalent of Armour Standard LA 1A.

TABLE VIII—*Continued*

Day	Urinary Excretion					Serum Values						Treatment‡
	Chloride	17-Keto-steroids	11-Oxy-steroids	Creatinine	Creatine	Ca	P	Cl	K	Na	Glucose	
	m.eq./24 hr.	*mg./24 hr.*	*mg./24 hr.*	*gm./24 hr.*	*gm./24 hr.*	*mg.%*	*mg.%*	*m.eq./L*	*m.eq./L*	*m.eq./L*	*mg.%*	
1	45.92			1.18	0.13							
2	41.35			1.22	0.16							
3	44.67	0.8	0.07	1.34	0.20	9.7	4.6	104	5.5	139.5		
4	64.75			1.32	0.25							
5	77.41			1.32	0.19							
6	84.03			1.32	0.25							
7	54.94			1.19	0.25	9.8	4.1	98	5.1	138.2	100	
8	54.00			1.27	0.21							
9	74.37	1.7	0.09	1.22	0.26							
10	—			—	—							
11	65.89			1.29	0.27							
12	60.50			1.10	0.31	9.6	4.3					
13	58.85			1.15	0.29			100	5.4	136.8		
14	74.01			1.29	0.28							
15	72.04	2.3	0.10	1.26	0.30							
16	58.20			1.34	0.33							
17	64.82			1.43	0.57							
18	71.56			1.33	0.35							
19	91.33			1.32	0.50		4.1	101	5.1	140.8		
20	73.73			1.33	0.21		3.9	100		139.5		
21	54.33	7.7	1.39	1.33	0.0							ACTH 100 *mg./24 hr.*
22	35.67			1.20	0.08							
23	54.85			1.37	0.0		4.0	100	5.2	139.0		
24	52.80			1.30	0.0							
25	22.33			1.30	0.0							
26	103.91			1.36	0.0							
27	170.29	4.0	0.14	1.24	0.0							
28	101.75			1.16	0.0							
29	66.26			1.33	0.0							
30	79.58			1.32	0.15							
31	93.26			1.30	0.20		3.9	104	4.7	139.6		
32	56.04			1.34	0.22			101		137.4		
33	46.19			1.38	0.04							
34	44.89	8.0	2.41	1.37	0.10							ACTH 100 *mg./24 hr.*
35	32.94			1.33	0.24							
36	51.34			1.32	0.15							
37	37.76			1.30	0.11							
38	36.01			1.28	0.09		3.1	103	5.0	142.4		
39	194.22			1.33	0.11							
40	193.39	4.4	0.25	1.28	0.10							
41	103.62			1.32	0.16							
42	57.92			1.28	0.20							
43	48.43			1.37	0.21							
44	45.41			1.31	0.34							
45	49.09	1.3	0.05	1.33	0.30							
46	71.02			1.28	0.32							
47	74.48			1.34	0.34							
48	78.62			1.42	0.19						94	
49	69.16	3.7	0.08	1.34	0.31		3.5	105				
50	64.33			1.26	0.21		3.1	106				ACTH LI *60 mg./24 hr.*
51	65.59			1.32	0.22							
52	54.17	4.6	0.83	1.29	0.28							
53	69.93			1.27	0.27							
54	38.32			1.29	0.14	9.0	3.9	102	5.5	142.9		
55	148.91	2.9	0.03	1.32	0.13							
56	86.62			1.26	0.10							
57	72.60			1.27	0.27							
58	88.43			1.31	0.34							
59	73.16	1.6	0.19	1.13	0.43							
60	70.88			1.22	0.49							
61	67.51			1.34	0.46							
62	41.36			1.35	0.37	9.2	3.7	100	5.1	142.1		
63	28.61	1.7	0.31	1.22	0.35							
64	32.59			1.33	0.35							
65	42.91			1.33	0.27							DOCG *16 mg. /24 hrs.*
66	52.50	1.3	0.04	1.27	0.40							
67	67.41			1.32	0.39							
68	70.10			1.26	0.40							
69	89.25			1.25	0.33	9.5	3.7	102				
70	104.22	1.5	0.08	1.36	0.35							
71	86.18			1.35	0.38							
72	67.35			1.32	0.33							
73	60.71	0.6	0.05	1.30	0.40							
74	71.72			1.28	0.38							
75	68.04			1.32	0.46							

steroids. These first appear in the urine at about the time that there is evidence of secretion of L.H., which controls ovulation in the female and the development of Leydig cells in the male.

i) Comparison of the effect of electrophoretically pure sheep ACTH (Li and Evans) with that of less purified hog ACTH (Armour); effect of prolactin

In experiment 5, the electrophoretically pure ACTH of Li and Evans was given for a six day period, in order to determine to what extent the effects produced by the Armour preparations might be due to the small amounts of contaminants which they contain (Table II).

The results (see Table VIII and Figures 7–9) indicate that there are no qualitative differences between the action of the preparation of Armour, poor in pitressin, and that of Li and Evans. Milligram for milligram, Li and Evans' ACTH may have produced a more marked rise in urinary Ca. In all other respects, the effects of the two products were quite similar.

Prolactin, which is present in Armour ACTH

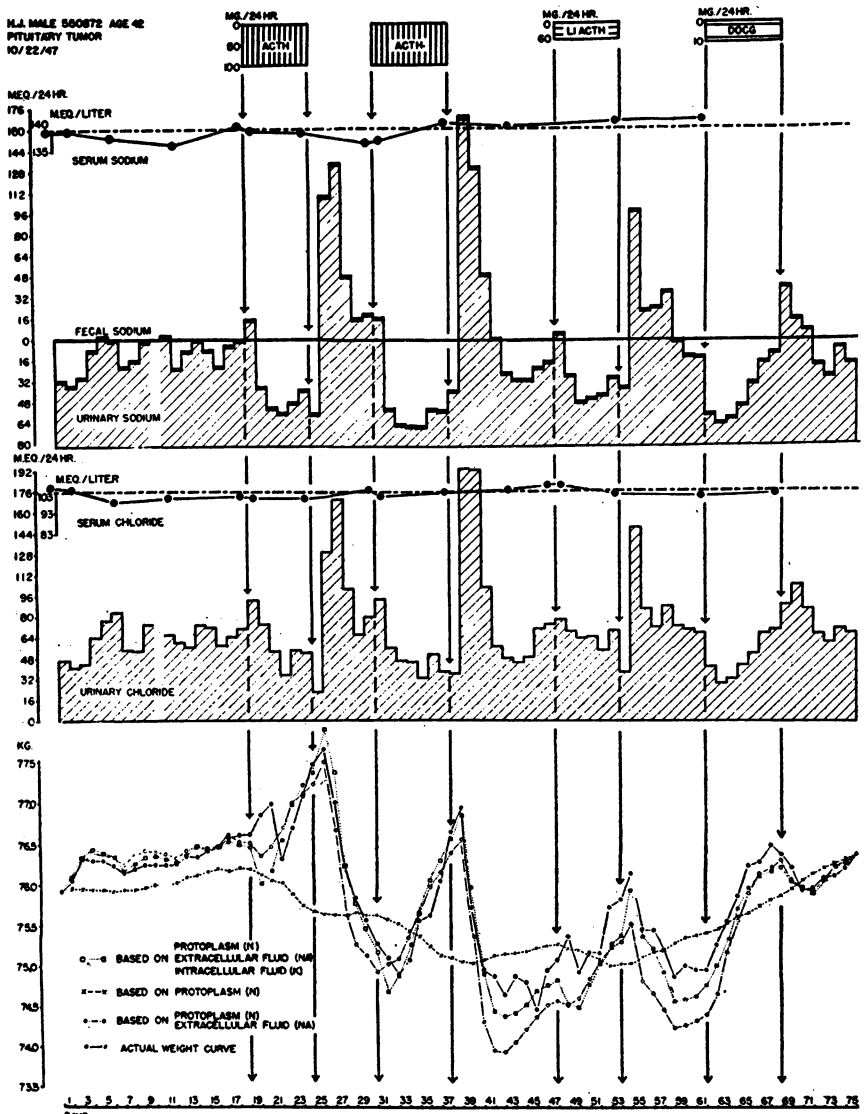

FIG. 8. EXPERIMENT 5, CONTINUED. EFFECT OF ACTH AND DOCG ON NA BALANCE, URINARY CL, ON THE ACTUAL AND "THEORETICAL" WEIGHT CURVES, AND ON SERUM NA AND CL

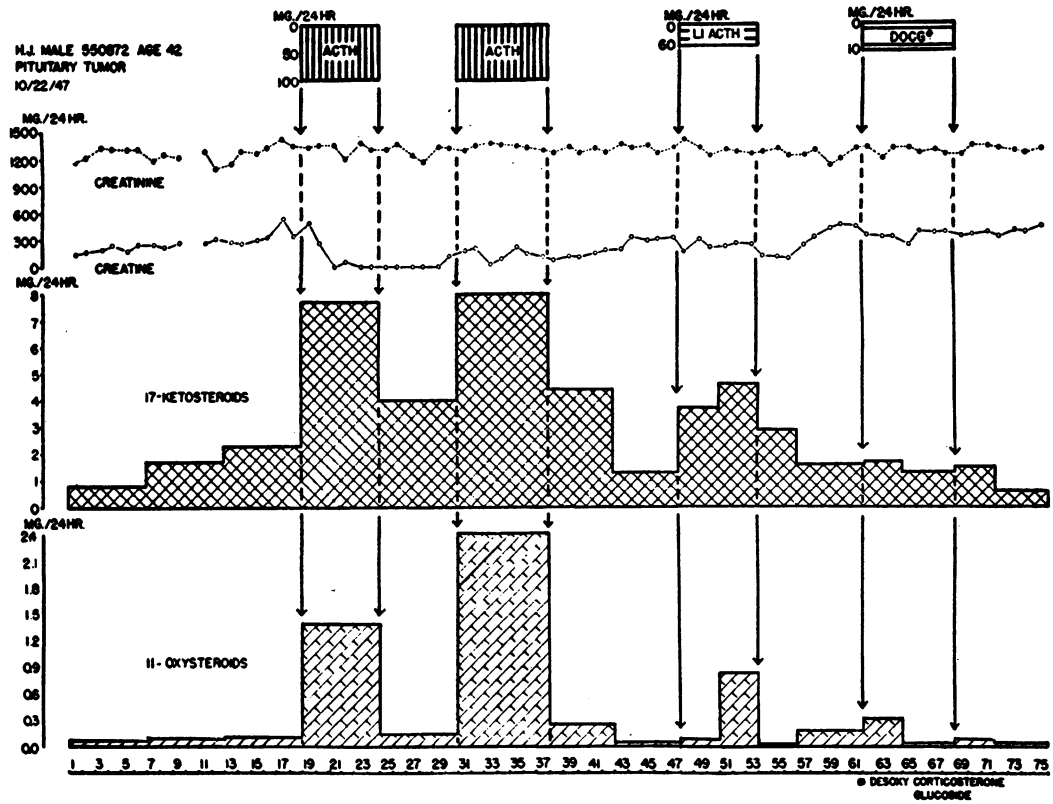

FIG. 9. EXPERIMENT 5, CONTINUED. EFFECT OF ACTH AND DOCG ON URINARY CREATININE, CREATINE, 17-KETOSTEROIDS, AND "11-OXYSTEROIDS"

(Table II), had no measurable effects when given alone (Table VI and Figures 3 and 4, days 43 through 48).

DISCUSSION

The first and most consistent response to ACTH is the loss of K, almost surely from cells, on the first day. This is accompanied by a relatively smaller loss of P, and is countered by a retention of Na. The reserve occurs when ACTH is stopped. The significance of this phenomenon is not clear.

A second group of sequelae is more comprehensible. ACTH is apparently an essential link in the "alarm reaction" of Selye (22). It leads to the following sequence of events:

1) Adrenal cortical "sugar" hormone is liberated (cf. rise in corticoids by chemical and biological tests).

2) The "sugar" hormone causes anti-anabolism of protoplasm, so that amino acids become available.

3) The amino acids thus freed are deaminized; the N is excreted; the carbohydrate and fatty acid fragments are added to the "metabolic pool."

4) Glycogen is formed from the "metabolic pool."

5) The P and K of intracelluluar fluid, made available by the excess of protoplasmic catabolism over anabolism, are retained with the glycogen.

Teleologically, such a sequence is readily understandable, since the net result of forming glycogen at the expense of protoplasm is to create an easily mobilizable source of energy.

SUMMARY

1. The effects of ACTH (Armour) in doses ranging from 10 to 100 mg. daily were observed in three patients with panhypopituitarism. Metabolic balances of N, Ca, P, Na, K and the urinary excretion of Cl, corticoids and 17-ketosteroids are shown.

2. ACTH produced:

a) loss of N without commensurate loss of P and K. (This discrepancy can be explained if there is a concomitant deposition of glycogen).

b) loss of Ca.

c) retention of Na and Cl in extracellular fluid.

d) transient loss of K, which was apparently partly replaced by Na in intracellular fluid.

e) rise in urinary corticoid excretion.

f) rise in 17-ketosteroid excretion in one patient who still produced luteinizing hormone but not in the other two patients.

3. The effects of Armour ACTH were compared with those of pitressin and prolactin (which are present as contaminants in Armour ACTH) and with those of Li and Evans' ACTH (which is electrophoretically pure). Pitressin produced a loss of Ca, and a transient loss of Na and Cl; prolactin had no effect; ACTH (Li and Evans) produced all the effects of ACTH (Armour).

4. The effects of ACTH were compared with those of desoxycorticosterone glucoside (DOCG). DOCG had an effect on K, Na and Cl similar to that of ACTH, but the effect on K was less.

5. These effects of ACTH could all be due to release of "sugar" hormone, but whether the rise in 17-ketosteroids is to be so interpreted remains doubtful.

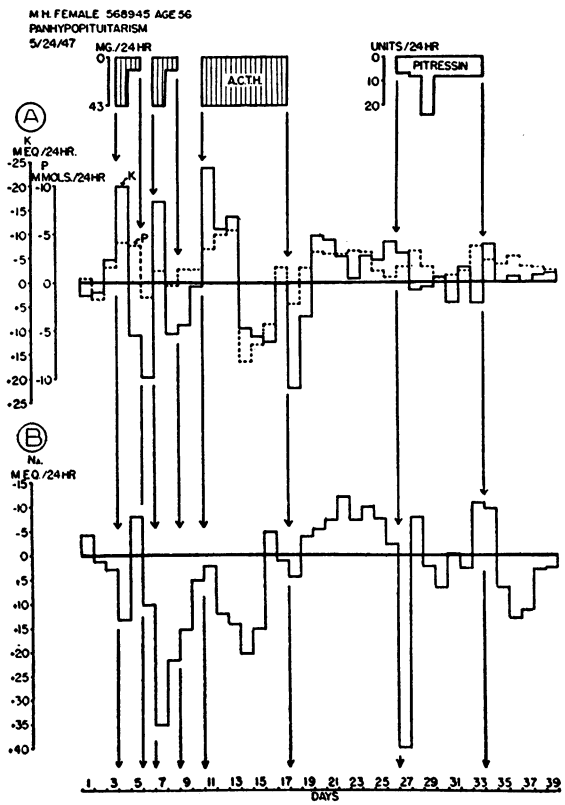

FIG. 10. URINARY DATA FROM EXPERIMENT 3 RECALCULATED, AND EXPRESSED AS DEVIATIONS FROM THE AVERAGES OF CONTROL VALUES

A. "Corrected" K (solid line) and P (dotted line). P is plotted with a "valence" of 2.

B. "Corrected" Na.

Factors used in calculating the data are as follows (see [13]):

K/N in "protoplasm" = 2.7; K/Cl in ECF = 0.05. The K in the diagram = K excreted − 2.7 N − 0.05 Cl.

P/N in "protoplasm" = 0.068; P/Cl in ECF = 0.38. Ca/Cl in ECF = 0.5; P/Ca in bone = 0.448.

The P in the diagram:

= P excreted − 0.068N − 0.38 Cl − 0.448 (Ca − 0.5 Cl).

= P excreted − 0.068N − 0.16 Cl −0.448 Ca.

$$\text{Na/Cl in ECF} = \frac{.97 \text{ Na serum}}{1.04 \text{ Cl serum}}.$$

Na in ECF = 1.145 Cl in ECF (for this patient). The Na in the diagram = Na excreted − 1.145 Cl. For discussion see text.

APPENDIX

Analysis of K and P data

The relation between the K and P data obtained after "correcting" for protoplasm, bone and extracellular fluid changes has been determined from the linear regression of K on P for the data of experiments 2–5. The general form of the linear regression equation is:

$$y = a + b(x - \bar{x}).$$

In this case y is K and x is P. Here we are concerned with the value of b, the regression coefficient giving the slope of the line relating K to P. With K in milliequivalents and P in 100 mg. the values of b given by the corrected data are:

Experiment No.	ACTH Administration	No. of data	Value of b	Variance	Combined value of b	Variance
5	on	19	10.6	2.7	7.44	.39
	off	24	8.1	0.3		
3	on	7	6.9	3.1	7.01	2.24
	off	9	13.9	18.6		
2	on	18	9.0	3.6	8.99	2.62
	off	12	17.6	5.8		
4	on	13	8.0	13.3	9.52	6.71
	off	7	13.1	4.3		

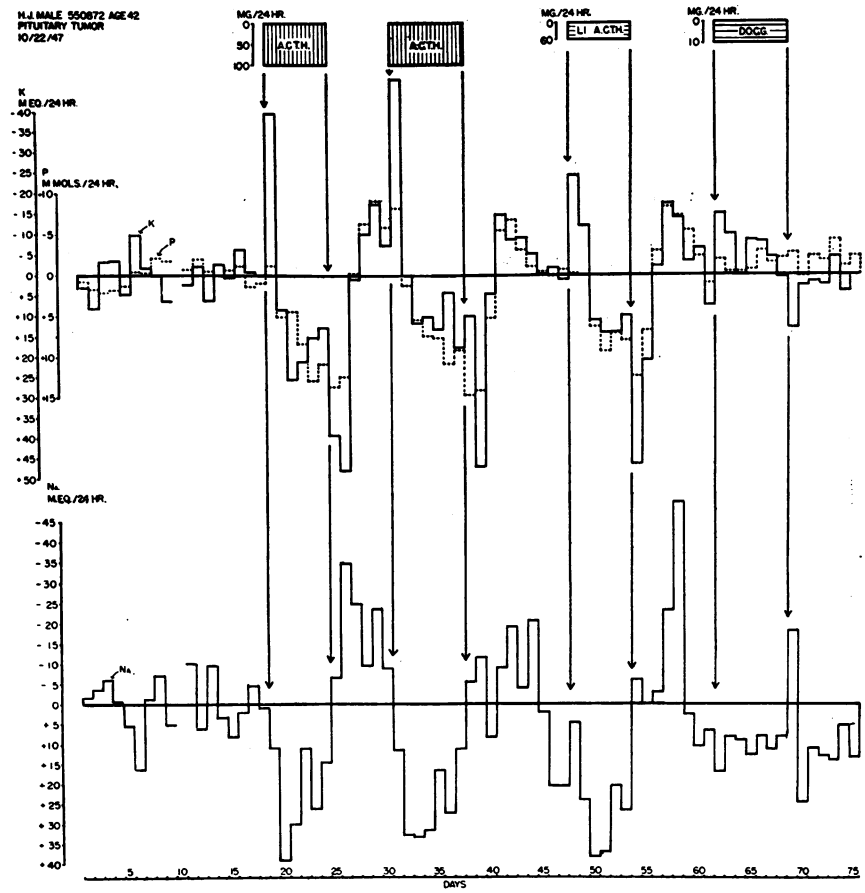

FIG. 11. URINARY DATA FROM EXPERIMENT 5 RECALCULATED AND EXPRESSED AS DEVIATIONS FROM THE AVERAGE OF CONTROL VALUES

A. "Corrected" K (solid line) and P (dotted line).
B. "Corrected" Na.
For factors used see legend to Figure 10.
Na in this patient = Na excreted − 1.268 Cl.
For discussion, see text.

The regression coefficients differ significantly from 0, implying that the K and P values are not independent.

Similar results were obtained with data from two experiments on patients with other diseases:

Disease	Treatment	No. of data	Value of b	Variance	Combined value of b	Variance
Carcinomatosis	on	13	4.8	3.5	7.11	1.53
	off	8	9.3	8.1		
Acromegaly		10			7.94	6.87

The weighted mean of the regression coefficients for all the data on and off ACTH taken together is 7.63 ± 0.5. This represents the number of milliequivalents change in K for every 100 mg. change in P. Since 100 mg. P = 3.2 mM P, for each millimol change in P there is 2.36 ± 0.16 m.eq. change in K. Thus the changes in K are greater than would be expected if they were due merely to intracellular fluid shifts, since in intracellular fluid the ratio of K (m.eq.) to P (mM) is only 1.5.

The scatter diagram in Figure 12 gives the graphic interpretation of the regressions calculated for experiment 5. The data for the days when therapy was started and stopped increase the slope of the regression line. If these data be arbitrarily omitted from the calculation of the regression, we obtain a value of 1.65 ± 0.17 for the milliequivalents change in K for each millimol change in P. This value indicates that except when ACTH administration is started and stopped, K and P are associated in a ratio such that the changes in these ions could be due to intracellular fluid changes.

An attempt was made to relate statistically the K changes to the calculated changes in intracellular sodium,

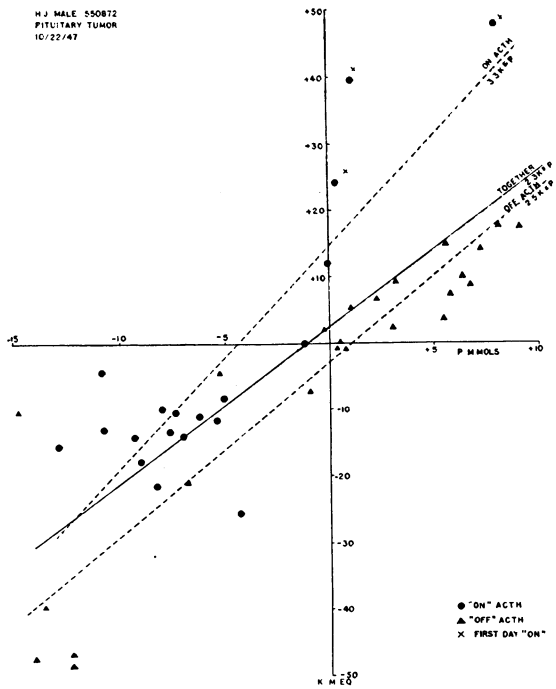

FIG. 12. "CORRECTED" URINARY DATA FROM EXPERIMENT 5. SCATTER DIAGRAM SHOWING THE REGRESSION OF K ON P FOR THE DATA SHOWN IN FIGURE 10, EXCLUDING CONTROL DATA AND THOSE FOR DOCG

The dotted lines show the regressions calculated separately for the data during and after ACTH. The joint regression is discussed in appendix.

derived from the sodium and chloride data. (See Figures 10-B and 11-B.) It can be shown that the K changes are not correlated with intracellular Na changes except when the association of K with P is taken into account. When this is done we find a significant negative correlation between K and intracellular Na:

$$K\ (\text{m.eq.}) = a + 2.33 \pm 0.06\ P\ (\text{mM}) - 0.17 \pm 0.02\ Na\ (\text{m.eq.})$$

("a" is a constant which depends on the mean values of K, P and Na).

This means that the changes in K beyond those that are associated with P are negatively correlated with Na. This in turn is interpreted to mean that K may change because of intracellular fluid shifts (association with P) or because it is lost from, or restored to intracellular fluid (exchange with Na). While the significant negative correlation with intracellular Na is of some interest, the actual value of the coefficient means very little, since it does not take into account the time lag between K and Na change in the body.

The calculated relations have been determined from data derived on the basis of many assumptions. In particular, the corrected data are based on the assumption that changes in nitrogen excretion should be associated with certain changes in K and P excretion. To see whether we have introduced an artificial relation between K and P by correcting for presumed protoplasm changes, we have calculated the multiple linear regression of K on P independent of N for the urine data of experiment 5 omitting the data for on and after DOCG. This experiment was chosen because it has the most data. The regression equation is:

$$K\ (\text{m.eq.}) = a' - 0.8 \pm 0.7\ N\ (\text{gm.}) + 3.1 \pm 0.3\ P\ (\text{mM})$$

(a' is a constant which depends on the mean values of K, N, and P). K excretion is correlated with P excretion independently of any correlation of these two variables with N excretion. The regression coefficient for P is high compared with the mean coefficient for the corrected values, partly because Ca changes are allowed for in the corrected values. The correlation found for the corrected values is not likely to be simply an artefact due to correcting for assumed protoplasm changes.

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