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STUDIES ON THE MAINTENANCE OF THE ADRENALECTOMIZED PATIENTS WITH ADVANCED CANCER OF THE BREAST

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From the clinical observation, single glucocorticoid such as prednisolone, 6-methylprednisolone, triamcinolone, and dexamethasone in the daily dose equivalent to 20 mg of hydrocortisone in glucocorticoid activity was not capable of maintaining the adrenalectomized patients and could not prevent the adrenal insufficiency (weakness, nausea, vomiting and hypotension).

In the adrenalectomized patients maintained on hydrocortisone or cortisone, their urinary excretions of sodium and potassium were within the normal limits and the serum sodium and potassium concentrations were also within the normal limits. On the other hand, urinary excretion of sodium in the patients maintained on prednisolone, 6-methylprednisolone, triamcinolone, and dexamethasone was increased.

Evaluation of blood sugar, pyruvic acid, lactic acid following the ingestion of glucose in the adrenalectomized patients: In the patients maintained on hydrocotisone, cortisone or prednisolone, the blood sugar curve was almost normal. Blood pyruvic acid level reached the maximum in 30 to 60 minutes after the ingestion of glucose and fell down to the fasting level within three hours. Blood lactic acid level showed a parallel curve to that of pyruvic acid. Blood sugar, pyruvic acid, lactic acid curves of the patients maintained on 6-methylprednisolone, triamcinolone or dexamethasone were slightly diabetic in some cases. There was a significant rise in the level of pyruvic acid and it remained elevated even three hours after the ingestion of glucose.

The level of serum albumin was reduced and the level of globulin remained elevated in many of the adrenalectomized patients maintained on cortisone.

It was concluded that the hydrocortisone was the best medicine for the replacement therapy of the adrenalectomized patients.

In all the patients, the symptomes of adrenal insufficiency appeared on the third to fourth day of withdrawal of steroid for replacement.

INTRODUCTION

Since Huggins[1] had got the start of performing bilateral adrenalectomy

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for the patients with some metastatic carcinoma of the breast on palliative effects in 1952, there have been a number of papers by other groups of investigators[2)3)4)5)] reporting similar observation.

In our clinic of adrenal surgery, *43* patients with advanced cancer of the breast had been submitted to this procedures during the past seven years and have had clinical improvement in about half of the cases thus treated. Since adrenalectomy induces serious metabolic disturbances after the removal of the gland, careful management of replacement therapy is imperative for the survival of patients following adrenalectomy.

With the advent of cortisone, total adrenalectomy became a practical proposition and cortisone has been supplied as the only drug for replacement therapy after the ablative procedures.

A long term replacement therapy was considered to be adequate when the following conditions were satisfied; 1) Maintenance of normal metabolism, and normal liver function, maintenance of daily blood pressure normal, 2) avoidance of side effects such as edema, obesity, 3) Since it is generally accepted that the glucocorticoid may be converted to estrogenic substance, the dose of glucocorticoid should be the irrectucible minimum of the requirement.

If we could select more adequate activities of glucocorticoid for replacement therapy than that of cortisone, it would be desirable for adrenalectomized patients to make them feel a sensation of well being without unwanted side effects for a long time after adrenalectomy.

From this point of view, all the adrenalectomized patients on whom we employed various kinds of glucocorticoids as replacement therapy were observed through 1) clinical signs and symptoms 2) various side effects 3) maintenance of daily blood pressure normal 4) urinary excretion of sodium and potassium 5) liver function 6) carbohydrate metabolism.

MATERIAL AND METHOD

Forty-three patients with advanced breast cancer had been submitted to bilateral adrenalectomy (Table 1). Six kinds of glucocorticoids, hydrocortisone, cortisone, prednisolono, 6-methylprednisolone, triamcinolone, and dexamethasone were administered to them in the doses equivalent to 20 mg of hydrocortisone as replacement therapy. These drugs were given by mouth in divided doses or once in the early morning. All the adrenalectomized patients on whom we employed various kind of glucocorticoids were observed clinicaly checking up daily blood pressure. Sodium and potassium in urine and in serum were determined by flame photometry. Liver functions were followed up once in a month for a long period of time after adrenalectomy. Blood sugar, pyruvic acid, and lactic acid were determined under basal condition, and immediately after that, 30-50 g of glucose solved in water was given by mouth. Blood

TABLE 1. Results of Adrenalectomy and Oophorectomy

Patient No.	yr.	Maintenance	Location of metastasis	Time since mastectomy	Survival since adrenalectomy	Time of palliation	Objective response	Subjective response
13	44	Cortisone 25 mg	Lymphnode	0	3 yr. 1 mo.	2 yr. 9 mo.	Diminution in size of tumor	+
14	34	Cortisone 25 mg	Lymphnode	2 yr. 2 mo.	3 yr. 1 mo.	2 yr. 9 mo.	Diminution in size of tumor, Healing of ulcer	+
15	47	Cortisone 25 mg	Lymphnode Skin. Lung Pleura	8 yr.	Died	—	None	None
17	35	Cortisone 25 mg	Lymphnode Lung, Liver	1 mo.	6 mo.	—	None	None
22	43	Cortisone 25 mg	Lymphnode Lung, Bone Liver	8 mo.	Died	—	None	None
23	56	Cortisone 25 mg	Lymphnode	1 mo.	5 yr. under our observation			
25	49	Cortisone 25 mg	Lymphnode Skin, Liver	—	4 yr.	1 yr. 7 mo.	Healing of ulcer Diminution in size of tumor	+
26	38	Cortisone 25 mg	Lymphnode	5 mo.	1 yr. 5 mo.	11 mo.	Diminution in size of tumor	+
29	54	Cortisone 25 mg	Lymphnode	7 yr.	2 yr. 11 mo.	9 mo.	Diminution in size of tumor	getting appetite
30	35	Cortisone 25 mg	Lymphnode	10 mo.	5 mo.	—	None	None
31	52	Cortisone 25 mg	Lymphnode Bone, Liver Brain Pleura	4 yr. 2 mo.	1 mo.	—	None	Cessation of pain
32	40	Cortisone 25 mg	Lymphnode Bone	3 yr.	2 yr. 3 mo.	1 yr. 1 mo.	Recalcification of osteolytic lesion	Cessation of pain
33	42	Cortisone 25 mg	Lymphnode Bone, Skin Lung, Pleura	—	1 mo.	—	None	None
36	61	Cortisone 25 mg	Lymphnode	—	1 mo.		Diminution in size of tumor, Healing of ulcer	Cessation of pain
37	42	Cortisone 25 mg	Lymphnode	3 yr.	Died	—	None	None
38	40	Hydrocortisone 20 mg	Lymphnode	3 mo.	2 yr. 4 mo.	1 yr. 2 mo.	Diminution in size of tumor	+
40	40	Hydrocortisone 30 mg	Lymphnode	6 mo.	4 mo.	—	None	None
41	57	Hydrocortisone 30 mg	Lymphnode	16 d.	3 yr. 7 mo. under our observation			
42	42	Hydrocortisone 30 mg	Skin, Liver Peritoneum	5 mo.	2 yr. 6 mo.	2 yr. 4 mo.	Diminution in size of tumor	Cessation of pain
44	38	Hydrocortisone 30 mg	Lymphnode	—	8 mo.		Diminution in size of tumor	+
45	65	Hydrocortisone 30 mg	Lymphnode, Chest wall ulceration	—	1 yr. 3 mo.	1 yr. 4 mo.	Diminution in size of tumor, Healing of ulcer	+

46	56	Hydrocortisone 20 mg	Lymphnode Pleura	—	1 yr. 6 mo.	7 mo.	Disappearance of shortness of breath	+
47	38	Hydrocortisone 30 mg		—	1 yr. 5 mo.	1 yr.		
48	40	Hydrocortisone 30 mg	Lymphnode Brain	1 yr.	4 mo.	—	None	None
49	34	Hydrocortisone 30 mg	Lymphnode Lung	2 yr. 2 mo.	4 mo.	—	None	None
50	56	Hydrocortisone 30 mg	Osseous, Liver	2 yr. 6 mo.	3 mo.	2 mo.	+	Cessation of pain
51	37	Hydrocortisone 20 mg	None	3 mo.	2 yr. 8 mo.	under our observation		
52	43	Hydrocortisone 30 mg	Lymphnode Lung	2 yr. 10 mo.	1 yr. 2 mo.	8 mo.	Diminution in size of tumor	+
53	52	Hydrocortisone 30 mg	Lymphnode	—	6 mo.	—	None	None
54	38	Hydrocortisone 30 mg	Skin, Brain	6 mo.	2 mo.	—	None	Nonə
55	54	Hydrocortisone 20 mg	Pleura	4 yr.	1 yr. 1 mo.	7 mo.	Cessation of pleural effusion	
56	45	Hydrocortisone 20 mg	Lymphnode, Skin Osseous	8 yr.	1 yr.	8 mo.	Diminution in size of tumor, Recalcification of osteolytic lesion	Cessation of pain
57	62	Hydrocortisone 20 mg	Lung, Pleura	7 yr.	Died	—	None	None
58	45	Hydrocortisone 20 mg	Lymphnode, Skin	4 yr.	2 mo.	—	None	None
59	43	Hydrocortisone 30 mg	Lymphnode, Liver Lung	4 yr.	1 mo.	—	None	None
60	54	Hydrocortisone 20 mg	Lymphnode, Bone Brain	—	10 mo.	4 mo.	Diminution in size of tumor, Epithelization of ulce	Cessation of pain
62	55	Hydrocortisone 20 mg	Liver, Pleura Lung	2 yr. 9 mo.	2 mo.	—	None	None
63	36	Hydrocortisone 30 mg	Lymphnode	1 yr. 10 mo.	2 mo.	—	None	None
64	32	Hydrocortisone 20 mg	Lymphnode	1 yr.	1 yr. 1 mo. under ouro bserv.		Diminution in size of tumor	
65	38	Hydrocortisone 30 mg	Local develonement		5 mo.	—	None	None
66	56	Hydrocortisone 20 mg	Local developement	1 mo. 15 d.	3 mo.	—	None	None
67	50	Hydrocortisone 20 mg	Liver, Bone		3 mo.		None	Cessation of pain
68	61	Hydrocortisone 20 mg	Lymphnode	5 yr. 5 mo.	10 mo. under out observation			

specimens were taken at 30 or 60 minutes intervals over a period of three hours, the subject remaining at rest in bed. Blood sugar was determined by the method of Hagedorn-Jensen. Pyruvic acid in blood was determined by Shimizu's method, blood lactic acid by Barker-Summarson's.

RESULTS

1. Clinical signs and symptoms, blood pressure

1) Maintenance on prednisolone 5 mg daily:

Case No. 25, the patient, a 49 year old woman, had had bilateral adrenalectomy on August 18, 1959 because of advanced cancer of the breast. Two months later, prednisolone in stead of cortisone, in a dose of 5 mg daily was given orally. She began to have signs of adrenal insufficiency—general fatigue, headache, dizziness, anorexia, and hypotension—which was easily relieved by the administration of cortisone, as shown in Fig. 1.

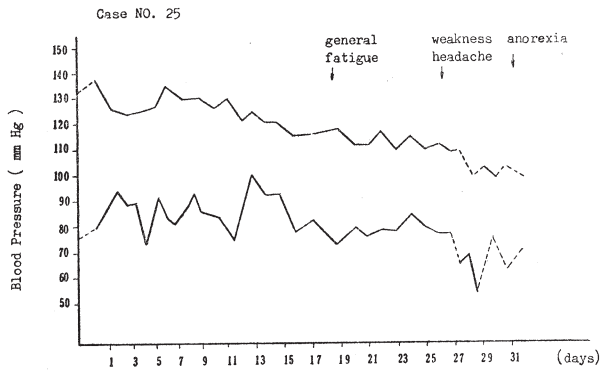

FIG. 1. Clinical course of a 49-yera-old woman after adrenalectomy, in response to the maintenance of prednisolone 5 mg a day.

2) Maintenance on prednisolone 10 mg daily:

Four adrenalectomized patients were maintained on prednisolone 10 mg without any unwanted side effects This maintenance dose when compared with 20 mg of hydrocortisone, seems to be rather excessive. Gradually, obesity and moon face developed in these patients.

3) Maintenance on 6-methylprednisolone 12 mg daily:

In case No. 25, 12 mg of 6-methylprednisolone was given daily. On the third day of the administration, the patient began to complain the ringing of the ears and severe head-ache. As it was thought that this might be due to its least effect of sodium retaining, the dose of 6-methylprednisolone was reduced to 8 mg daily and DOC was administered in a dose twice 5 mg a week.

Despite this treatment, the disturbance of water-electrolyte metabolism seemed to develop gradually.

4) Maintenance on triamcinolone 4 mg daily:

Case No. 26 The patient, a 38 year old woman, had had an ablative procedure performed on September 9, 1959. As shown in Fig. 2, triamcinolone was used as the replacement of hydrocortisone from two months after adrenalectomy. On the 11th day of triamcinolone, signs of adrenal insufficiency had developed and systolic blood pressure fell down below 100 mg Hg. It was impossible to maintain the patients normal on this glucocorticoid. The patient, case No. 53, was also given triamcinolone 4 mg daily without success because of unwanted side effects. The patient, Case No. 46, had maintained on triamcinolone 8 mg daily, but she was attacked by hypertension on the 20th day of this drug.

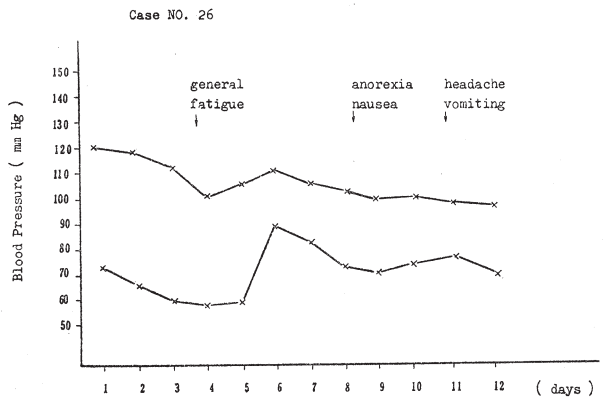

FIG. 2. Clinical course of a 38-year-old woman after adrenalectomy, in response to the maintenance of triamcinolone 4 mg a day.

5) Maintenance on dexamethasone 1 mg daily:

The maintenance on daily dose of 1 mg of dexamethasone was tried in three patients (Case No. 26, 46 and 52). Signs of adrenal insufficiency developed in all cases. If the dose were increased to 5 mg daily, the patient could well be maintained without side effects such as headache, nausea, vomiting. But it would be innevitable to have symptome of hypercortisolism since 5 mg of dexamethasone corresponds to to fairly large amount of hydrocortisone.

6) Maintenance on cortisone 25 mg daily:

Twelve adrenalectomized patients were maintained on cortisone 25 mg daily without any side effects.

7) Maintenace on hydrocortisone 20 mg daily:

Twenty eight adrenalectomized patients were maintained on hydrocortisone

20 mg daily.

2. Urinary excretion of sodium and potassium after adrenalectomy in response to various changes in replacement program

In seven patients on whom we employed prednisolone 10 mg, 6 methylprednisolome 12 mg, triamcinolone 4 mg, and dexamethasone 1 mg as replacement therapy, urinary sodium excretion was increased ranging from 166 mEq. to 313 mEq. per day. Since these steroids were found to have a sodium diuretic effect, it is quite natural that urinary excretion of sodium was increased.

Serum sodium and potassium of the patients who had received hydrocortisone were within normal range: Serum sodium: 132 mEq./L to 146 mEq./L, serum potassium: 3.3 mEq./L to 5.2 mEq./L.

3. Liver function

Fig. 3 shows laboratory findings of liver function in the patients maintained on hydrocortisone and cortisone. In the group of patients maintained on cortisone, the level of serum protein was 5.8 g/dl to 8.7 g/dl and the level of serum albumin ranged from 2.8 g/dl to 4.3 g/dl, serum globulin: 3.6 g/dl to 4.8 g/dl. Abnormal BSP retention was found in a few cases. On the other hand, in the group of hydrocortisone, the level of serum protein was from 6.3 g/dl to 7.8 g/dl and no abnormality was found in other liver function. But as shown in Table 2 these patients had been maintained on cortisone for a long period of over two years without presenting any evidence of alteration in liver function.

4. Serial changes in blood sugar, pyruvic acid, lactic acid following the ingestion of glucose

As shown in Fig. 4 the maximum rises of blood glucose and pyruvic acid

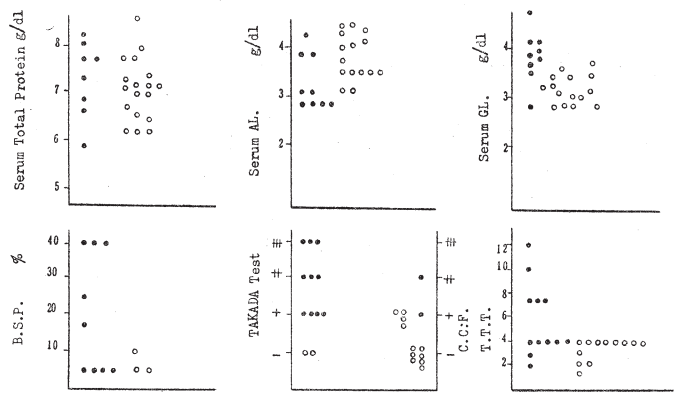

FIG. 3. Laboratory findings of serum protein and other liver function.
○ adrenalectomized patients maintained on hydrocortisone
● adrenalectomized patients maintained on cortisone.

TABLE 2. Long Term Observations on Liver Function after Adrenalectomy

	Case No. 41 Maintenance: Hydrocortisone							Case No. 23 Maintenance: Cortisone		
Serum Protein g/dl	6.4	7.8	6.1	7.0	7.1	7.9	8.5	7.1	7.0	8.7
Albumin	3.4	4.4	4.0	4.3	3.5	4.7	5.3	5.8	4.8	5.6
Globulin	3.0	3.4	2.9	2.7	3.6	3.2	3.2	1.3	2.2	3.1
AG	1.1	1.3	1.7	1.6	0.9	1.5	1.7	4.4	2.2	1.8
T.T.T.		4	2	3	1	2		1	2	
C.C.F.							−			+
Cholesterol	148	222	218	230				173	236	
Alkali phosphatase	6.5	1.9	4.0	3.6		7.8		5.7	4.4	
G.T.O.				46	50	43	14		4	15
G.P.T.				42	36	34	29		6	7
days after Bilateral Adrenalectomy	2 mo.	3 mo.	5 mo.	2 yr. 3 mo.	2 yr. 7 mo.	3 yr.	3 yr. 2 mo.	2 yr. 60 mo.	2 yr. 10 mo.	4 yr. 3 mo.

occurred at the end of 1 hour after the ingestion of glucose and then, the blood sugar and pyruvic acid level fell down to the fasting range before the third hour in a control subject. In adrenalectomized patients, the blood sugar curves were slightly diabetic in all the cases of hydrocortisone 40 mg and triamcinolone 4 mg as shown in Table 3.

Fig. 5 shows serial changes of blood sugar, pyruvic acid, and lactic acid following the glucose ingestion in the patients maintained on hydrocortisone, cortisone, and prednisolone. The levels of fasting blood pyruvic acid were all below the titer of 1.0 mg/dl in these instances, and the maximum rises occurred 30 to 60 minutes, later, and then level of pyruvic acid fell down reaching the fasting range at or before the third hour in all instances. On the other hand, in the groups maintained

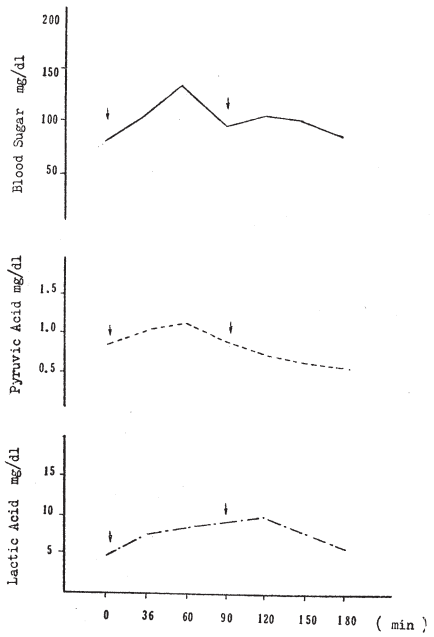

FIG. 4. Serial changes in blood sugar-pyruvate-lactate response to p.o. glucose in control subject.
(↓ 30 mg of glucose)

TABLE 3. Results of Glucose Tolerance Tests Performed on Adrenalectomized Patients

Patient No.	Patient yr.	Maintenance	Time (min)	Fasting	30	60	90	120	150	180
51	37	Hydrocortisone 20 mg	Blood sugar mg dl	85	120	145	110	125	—	100
40	40	Hydrocortisone 30 mg		90	120	127	94	129	—	115
41	57	Hydrocortisone 40 mg		95	115	167	153	190	—	150
23	56	Corticone 25 mg		95	130	105	121	126	155	128
25	49	Cortisone 25 mg		76 99	112 140	152 141	130 168	129 167	141 108	128 72
26	38	Cortisone 25 mg Prednisolone 10 mg		91 84	95 121	100 82	102 115	96 139	102 80	84 68
23	56	Prednisolone 10 mg		82	124	100	80	120	115	82
52	43	6-Methyl Prednisolone 6 mg		77	170	125	136	159	142	111
53	52	Triamcinolone 4 mg		72	146	150	—	—	—	190
52	43	Dexamethasone 1 mg		83	144	133	106	155	150	106

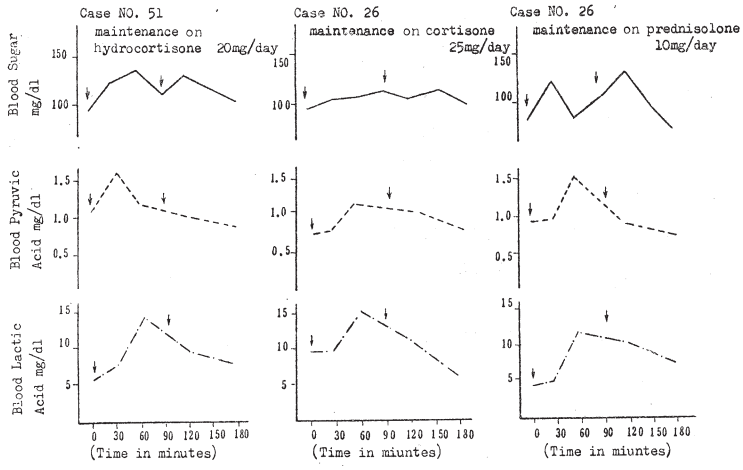

FIG. 5. Serial changes in blood sugar-pyruvate-lactate response to p.o. glucose in an adrenalectomized patients. (↓ 30 g of glucose).

on 6-methyl-prednisolone, triamcinolone, and dexamethasone, pyruvic acid levels were significantly elevated and reached the maximum 30 to 60 minutes after the ingestion of glucose and the high levels abnormally prolonged (Fig. 6).

5. Cortisone withdrawal est

Maintenance therapy has been withdrawn from all the adrenalectomized

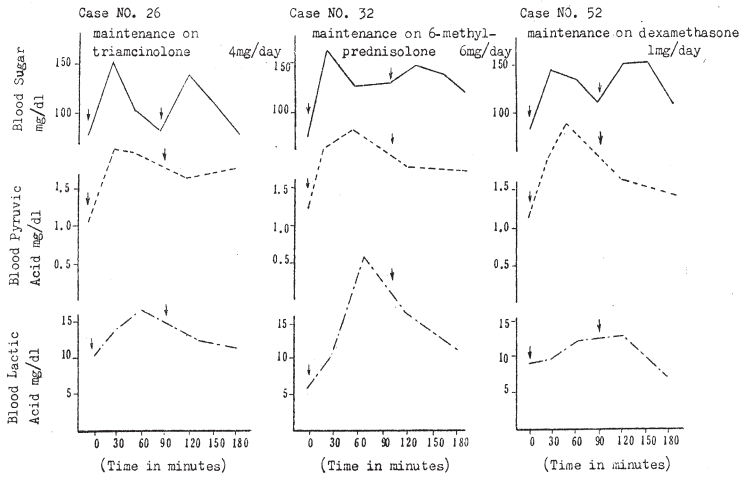

FIG. 6. Serial changes in blood sugar-pyruvate-pyruvate·lactate response to p.o. glucose on an adrenalectomized patients. (↓ 30 g of glucose)

patients under carefully controlled conditions. In no cases did adrenal insufficiency fail to appear after 3 to 4 days of withdrawal. In the course of this study, observations were made on the sequence of events in the development of adrenal insufficiency. Fig. 7 shows the fall and rise of the fasting blood sugar following the withdrawal of cortisone. Hypoglycemia ranging from 54 mg/dl to 68 mg/dl developed in three cases out of fiveexamined. Urinary excretion of sodium increased and potassium decreased in the course of withdrawal.

6. Management of bilateral adrenalectomized patients with the surgical measures

Huggins devised a plan of replacement therapy after bilateral adrenalectomy based on intramuscular administration of cortisone. In the present investigation hydrocortisone was administered intravenously as described below.

the day before operation	: nothing was administered	
during the operation	: hydrocortisone	100 mg iv
	(mixed in 5% glucose solution 500 cc, sums up 100 mg-200 mg of hydrocortisone)	
post operative day	: hydrocortisone	200 mg iv
the second operative day	: hydrocortisone	150 mg iv
the third operative day	: hydrocortisone	100 mg iv
the fourth operative day	: hydrocortisone	60 mg po
subsequent days	: hydrocortisone	20 mg po

The intravenous administration of the glucocorticoid is custumarily replaced by the oral intake as soon as possible. Postoperative treatment was performed

TABLE 4. Operations Performed on Totally Adrenalectomized Patients

Case No.	Operation	Days after adrenalectomy	before Operation	Operations day	1	2	3	4	5	6	7
25 T.N.	γ-Mastectomy	2 yr. 8 mo.		H.C. 300 mg	80	40	40	40	40	30	20 mg
30 T.O.	γ-Mastectomy	2 mo.	DOC 5 mg	H.C. 200 mg	100 (Cortisone)	75	50	50	50	50	25 mg
32 T.Y.	Incision of abscess	1 mo.	DOC 5 mg	H.C. 100 mg	10 (Prednisolone)	10	10	10	10	10	10 mg
45 T.	local Removal of tumor	3 mo.		H.C. 100 mg	20	20	20	20	20	20	20 mg
48 M.T.	frontal Craniotomy	2 mo.	DOC 5 mg	H.C. 300 mg	150	150	80	80	80	40	40 mg
53 S.K.	Tumor extirpation	1 mo.		H.C. 300 mg	200	120	120	80	80	60	40 mg
64 Y.I.	Tumor extirpation	1 mo.		H.C. 100 mg	20	20	20	20	20	20	20 mg

with extreme safety in all cases. It is well known that surgical measures and similar trauma provoke increased activities of adrenal cortex[6)7)]. When an adrenalectomized patient is submitted to a surgical stress, his requirement for the intake of glucocorticoid usually increased. Seven adrenalectomized patients were later subjected to operative measures as shown in Table 4.

On these seven patients various operations were performed without showing any signs of adrenal insufficiency. In the major cases we found it advisable to follow the plan of the maintenance therapy after the ablative procedures.

DISCUSSION

Experimentally, the first performance of adrenalectomy in dogs were carried out by Pfiffer[8)] and Rogoff[9)] in 1929. They maintained the dogs on adrenal extract with success in prolongation of life and they called this adrenal extract "Interrenalin". Coincidentally, Hartman[10)] had obtained a substance from the adrenal cortex (ox) which has an effect of prolongation of the life of adrenalectomized cats.

In 1945 Huggins[11)] performed adrenalectomy on patients with prostatic cancer but since cortisone was not available at that time, it was impossible to perform this procedure with success.

Since Huggins[1)] had got the start of performing bilateral adrenalectomy for patients with some metastic carcinoma of the breast on palliative effects in 1952, there have been a number of papers reporting similar observations by other groups of investigators.

According to Buttler[12)], Cade[13)] and Pearson[14)], the maintenance dose of cortisone by oral intake was 25–50 mg daily. However, Coller[15)] preferred to use 35 mg of hydrocortisone together with 0.05–0.1 mg of 9 α-hydrocortisone for the replacement therapy. Glante[5)] suggested that since it is necessary to supplement the somewhat insufficient sodium-retaining action and blood pres-

sure stabilizing action of this maintenance dose of cortisone acetate, the patient was given 25-50 mg of trimethyl acetate of desoxycorticosterone every 21 or 30 days, regulated so as to maintain adequate hydration and weight on a normal diet. Simkin[16] preferred to use cortisone in daily dose of 37.5 to 50 mg daily and 2 mg of DOCA sublingually. Huggins[1] suggested that the adrenalectomized patient can well be maintained on cortisone in a dose of 37.5 mg to 50 mg with 2-4 g of supplementary salt daily. In our series of 43 adrenalectomized patients, 14 cases were sufficiently maintained on cortisone by mouth in a daily dose of 25 mg. The doses they reported to be necessary for the maintenance of such patients are larger than those estimated by the present authors. This may well be attributed to the difference of constitutions between European and Japanese. Frankson suggested that the daily dose of 10 mg of prednisolone will be able to maintain sufficiently the patients. We have had the same experience with this regimen, but in a few cases, ultimately it caused edema and rounding of face.

In 1953, attempts were made by Bondy[17] to estimate the rate of secretion of adrenal cortical hormone in the blood directly obtained from renal vein. In this experiment, the hormones were secreted at rates equivalent to 15 to 25 mg of hydrocortisone per day. In recent years, secretion rate of hydrocortisone has been determined by many investigators applying the isotope dilution method and they reported similar result; Flood[18]: 12.2-20.5 mg, Romanof[19]: 15.9-31.3 mg, Cope[20]: 4.9-27.9 mg. In our clinic, 20 mg of hydrocortisone was employed as the standard dose of daily oral intake.

Urinary sodium excretion was increased when the patients were maintained on triamcinolone, 6-methylprednisolone or dexamethasone. Since these steroids were found to have little or no effect of sodium retaining, it is quite natural that urinary excretion of sodium increased in these patients.

It is of interest that Henken[21] reported that the salt threshold is lowered after the adrenalectomy in animal and in human, and also the administration of pure glucocorticoids to patients with induced adrenal insufficiency returned the threshold to normal. Mechanism of lowering of the salt teste threshold has not yet been understood, it is of interest to consider the loss of sodium in adrenal insufficiency in connection with salt taste of these patients. It is well known that a small proportion of Addison's disease manifests a definite salt craving. Thorn[22][23] and his co-investigators found this symptom to be present in 16% of 68 patients. From this findings, it should be borne in mind that the involved adrenal glands of Addison's disease has been in the state of hypofunction or dysfunction and it should be definitely differentiated this condition of Addison's disease from the post operative situation of adrenalectomized patient for whom the maintenance therapy has well been conducted adequately without side effects. No adrenalectomized patients manifested a definite salt craving. Buttler reported that ordinary daily diet the adrenalectomized patient

is taking contains 6 g of salt. However, the patients in our series were taking/ diets containing each 18 g of salt. The difference of the mode of eating between foreign people and Japanese may be one of the reasons not requiring supplementary salt intake in our patients.

It is well recognized that the steroid hormones are partly metabolized in the liver and possibly in other tissues. Therefore, it is easily considered that the long term administration of steroid hormone to adrenalectomized patients has an important effect upon the liver which offers a key for the analysis of metabolism of this hormone. Heany[24] and Kory[25] reported that abnormal BSP retention was found in patients who had received steroid hormone for a long period. Friedgood[26] and Berman[27] suggested that the administration of A.C.E. restored the degenerative power of liver to form new tissue protein in adrenalectomized animal. Furthermore, Begg[28] suggested that catalase activity in the rat's liver was lowered after the adrenalectomy. In our series, the level of serum globulin remained elevated. But there are some cases which were maintained on cortisone without presenting any alteration of liver function for a long period after the procedures. In other word, maintenance of cortisone arises not always impairement of liver function in adrenalectomized patients. In the group of patients which were maintained on hydrocortisone, liver functions were almost normal. From this point of view, the maintenance with 20 mg of hydrocortisone is thought to be the most ideal.

Adrenal cortex is essential to life and plays an important role in carbohydrate metabolism: this fact was shown by Long[29], and many other groups of investigators. It is evident that alteration in carbohydrate metabolism occurs in adrenalectomized patients unless they are well maintained on hydrocortisone. From this point of view, carbohydrate metabolism was observed after the ingestion of glucose. From the observation on the adrenalectomized patients to whom we employed hydrocortisone 20 mg, cortisone 25 mg, and prednisolone 10 mg as the replacement thrapy, the blood sugar curves were never abnormally elevated nor prolonged and showed the same serial changes as the normal control subjects. In each instance, there was a rise in blood pyruvic acid in 30-60 minutes following the ingestion of glucose. Blood lactic acid curve was parallel to pyruvic acid curve. On the other hand, blood sugar curves in the groups of 6-methyl-prednisolone, triamcinolone, and dexamethasone were slightly diabetic in some cases and there were significant rises in pyruvic acid and it remained elevated even three hours after the ingestion of glucose. This fact suggests an alteration of carbohydrate metabolism in these instances.

Replacement therapy has been withdrawn from all the adrenalectomized patients under carefully controlled condition. This examination was done for the two purposes: first, it is essential to let the patients know the signs and the symptoms of adrenal insufficiency in order that they can prevent the

development of such troubles, second, it is a question, however, as to the presence of the adrenal accessory bodies in relation to cancer relapse after the ablative procedures, and when the accessory bodies, which would sufficiently be functional to maintain the patient's life, present, the replacement therapy would not be required after the operation. So we could realize indirectly whether the accessory adrenal tissue might be located anywhere in the body. An attempt has been made aiming at those two purposes under carefully controlled condition.

After withdrawal, three of five cases examined developed hypoglycemia in the fasting. That is, hypoglycemia not always developed in all the cases after the withdrawal of cortisone. It is quite natural that we could not observe the development of hypoglycemia in all cases since we had to discontinue the withdrawal test before the development of complete signs of adrenal insufficiency. As it is observed by Mendelssohn[30] and Lipset[31], initial signs and symptoms of adrenal insufficiency developed in all cases thus tested after 3-4 days of withdrawal. Graham[32] found some accessory adrenal tissue in 32 instances out of 100 human autopsies. Soffer[33] stated that complete accessory bodies are more common in animal and have been reported with an incidence as high as 16% in human subjects. In our series, the presence of adrenal accessory tissue which would sufficiently be functional to maintain the patient's life was denied.

CONCLUSION

No adrenalectomized patients were capable of maintaining their lives without the administration of the glucocorticoid. In all the commercial glucocorticoids tested, hydrocortisone 20 mg daily provided the most adequate replacement therapy in the long term treatment of the adrenalectomized patients. The administration of DOC and supplementary salt were not necessary.

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