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KIDNEY FUNCTION IN ADRENAL INSUFFICIENCY¹

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An association between adrenal insufficiency and disturbed kidney function has been demonstrated repeatedly. The first report on renal failure in Addison's disease was that of Smith (1) in 1897. In 1942 Talbott *et al.* (2) reviewed the literature and reported studies on patients who had adrenal insufficiency but were not in crises. They found formation of glomerular filtrate to be reduced. After institution of treatment with desoxycorticosterone acetate, there was an increase in glomerular filtration of 32 per cent in five patients. However, the values obtained were still below normal. With diminished absorption from implanted pellets of desoxycorticosterone acetate the rate of formation of glomerular filtrate decreased again. Moderate reduction of renal plasma flow was observed also as well as slight reduction of the maximum capacity of the tubules for excreting diodrast.

In recent years renotropic effects have been demonstrated after the administration of various steroid hormones to mammals, especially androgens (3, 4). Testosterone propionate was found to increase the maximal capacity of the kidney tubules to excrete diodrast in castrated female dogs (5). No increase of renal function could be demonstrated when the same hormone was given to normal men, a eunuroid male, and patients with kidney disease (6, 7), even when the dose was as large as 300 mg. per diem. Nevertheless, since the renotropic action is believed to affect mainly the tubular cells and since in some cases of Addison's disease atrophy of these cells has been described (8 to 10) it was thought advisable to observe the influence of hormone therapy on the kidney by means of the more refined tests of renal function which are now available.

¹ The testosterone propionate and desoxycorticosterone acetate used in these studies were furnished by the Ciba Company.

CLINICAL MATERIAL AND METHODS

Thirteen patients were studied. None had evidence of any primary renal disorder. None had proteinuria or abnormal urinary sediments when not in crisis. Most of the clinical data pertinent to the investigations of this report are summarized in Table I.

In the group with Addison's disease, there were four men and five women. All gave typical histories, namely, weakness, languor, anorexia, loss of weight, nausea, and vomiting. All had been in crisis on one or more occasions. Physical examination of each showed the characteristic pigmentation of the skin and mucous membranes. All developed hypotension and nausea when not treated. In each case the shape of the sugar tolerance curve after 50 grams of glucose by mouth was flat, with hypoglycemia developing two to three hours after administration of the glucose. In several of the earlier cases chloride excretion tests (11) had been attempted but could not be completed because of impending crisis. The neutral 17-ketosteroid excretion in the urine, done by the method of Talbot *et al.* (12), was decreased in all patients (Table I). Patient A. F. was found to have pulmonary tuberculosis which was considered quiescent after serial x-ray studies. In none of the other patients was there evidence of tuberculosis.

Four patients, two men and two women, had pituitary insufficiency. That of the men (W. K. and A. B.) was the result of chromophobe adenomata. The women, R. F. and A. M., had no evidence of tumors; in both the beginning of the disease followed pregnancy. They had the typical appearance of "pituitary myxedema" as described by Means *et al.* (13). In each of these four patients the excretion of neutral 17-ketosteroids in the urine was reduced to very low levels. Chloride excretion tests, done according to the regime outlined by Cutler, Power, and Wilder (11), gave results characteristic of adrenal insufficiency. Oral sugar tolerance curves were flat and there was failure of the blood sugar to rise when hypoglycemia was produced with the insulin tolerance test of Fraser, Albright and Smith (14). This test was not done in the case of A. M. because when she fasted for comparatively short periods her blood sugar frequently decreased to less than 50 mg. without tendency to rise unless carbohydrate was given.

A. B. revealed evidence by x-ray of a gradually expanding mass in the pituitary fossa since 1933. Definite symptoms of pituitary insufficiency had been present since 1935. Since 1940 he has gradually developed hyperten-

TABLE I
Data concerning patients with Addison's disease and pituitary insufficiency

Patient	Sex	Age	Onset of symptoms	Treatment				Blood pressure	Blood			Urine neutral 17 K.S.	B.M.R.	Remarks	
				Salt	D.C.A.*	Testosterone propionate	Adrenal cortex extract		Hgb.	Hemat.	Serum proteins				
				grams per diem	mg. per diem	mg. per week	mi. per diem	mm. Hg	grams per 100 ml.	per cent	grams per 100 ml.	mg. per diem			per cent
Addison's disease															
D. B.	F	36	1945-46	20 20 4-12 3-20	5 5	87.5 25.0 25.0 25.0	3-6† 5 50 5	60-80/40-55 75-92/50-62 85-100/50-65 80-110/60-70 84-102/64-64 88-95/68-76 88-110/60-80 85-120/64-80	13.0 10.5 11.5	31 34	4.8 4.4 5.8	<0.5	-25	Had thyroidectomy in 1936 followed by hypothyroidism; taking thyroid 'til '46 Heart failure	
M. M.	F	39	1945	12 3	2.5 4 pellets	25.0		100-110/60-70 95/60 90-106/50-70	13.0 14.9	40 44	6.2 5.1	0	-41	Heart failure	
E. L.	F	41	1941	3 3 6 6 6	4 2.5 2.5 2.5	30.0 25.0	50	100-118/60-80 85-100/60-70 90-100/58-62 95-110/60-80 90-105/60-70	10.4-12.8 13.8 13.0	41 38 35	6.1 5.5	<0.5	-18 -18	Joint pains after D.C.A.	
E. W.	F	60	1943	3 3-6	5 8 pellets 4 pellets	25.0		100-115/65-80 112/74 100-130/65-82 95-100/70-75	12.2 11.4 12.0 12.6		5.7 6.2	<0.5	-2	Arthritis before onset Raynaud's phenomenon beginning Jan.'45	

* D.C.A. = desoxycorticosterone acetate.

† Pork adrenal cortex extract in oil.

TABLE I—Continued

Patient	Sex	Age	Onset of symptoms	Treatment				Blood pressure	Blood			Urine neutral 17 K.S.	B.M.R.	Remarks
				Salt	D.C.A.*	Testosterone propionate	Adrenal cortex extract		Hgb.	Hemat.	Serum proteins			
				grams per diem	mg. per diem	mg. per diem	ml. per diem	mm. Hg	grams per 100 ml.	per cent	grams per 100 ml.	mg. per diem		
Addison's disease—Continued														
S. E.	F	48	1943	3 3 3 3	1.25 1.25 1.25 1.0	17.5 87.5 25.0		98-130/62-90 84-118/64-68 116/66 115-125/75-82	11.0-13.0 11.1 11.1	34 39	5.5	<0.5	+14	Hypertension before onset Rheumatoid arthritis before onset Increased joint pains after D.C.A.
J. M.	M	45	1944	3-6	5 pellets			112-126/60-75	12.0 10.5-12.0	35 31-35	5.4 4.8-5.5	6.4	-7	
H. W.	M	30	1943	3-6	5 pellets		occasional	112-126/60-70 98-110/62-76	14.7 14.0	42	6.0 5.8	4.3	-17	Raynaud's phenomenon before onset
A. F.	M	44	1943		9 pellets 4 pellets			92-120/56-84 110-122/70-80	14.0 13.0		5.5 5.7	3.3	-16 -20	
T. D.	M	52	1943	3	7 pellets 4-5			122-128/78-80 150-170/94-100 100-115/65-80 132-170/90-100	13.8 12.8 13.3	33 36 38	5.4 5.0	4.4 3.8	-7	Hypertension beginning Feb. '45 Raynaud's phenomenon
Pituitary insufficiency														
R. F.	F	47	1939	6 6 4 4	1.25	25.0		100-115/75-80 100/68 94-106/64-75 88-115/58-70 100-110/60	9.4 12.7 10.0-11.0 10.0 13.0	30-32 38	5.5	0.8	-33 -39 -14	Thyroid 0.065 gram/day No medication Thyroid 0.100 gram/day Thyroid 0.100 gram/day
A. M.	F	47	1931	3				80-88/60-68	9.3	28	4.8	0	-44	Frequent hypoglycemia
W. K.	M	31	1944	3-6		occasional		90-115/60-75	10.5-13.0	31-37		3.1	-26	No testosterone propionate 6 months before test
A. B.	M	65	1935-1939 1940-1946	3-6 6				85-110/58-70 140-210/100-110	11.8-12.0 11.6		5.4 5.3	0.5	-30	Hypertension beginning 1940

TABLE II
Renal clearance studies in Addison's disease and in pituitary insufficiency

Patient	Sex	Date	Glomerular filtration rate ml./1.73 sq.m./min.	Effective renal plasma flow ml./1.73 sq.m./min.	Effective renal blood flow ml./1.73 sq.m./min.	Maximum tubular excretion mg. PAH/ 1.73 sq.m./min.	Filtration fraction (GFR/RPF) per cent	RPF/Tm	RBF/Tm	Blood pressure mm. Hg	Urine flow ml./min.	Remarks
Addison's disease												
D. B.	F	10-11-'46	76	485	700	53	15.8	9.1	13.2	80/40	4.00	Salt therapy *
		10-28-'46	71	481	560	53	14.7	9.1	11.9	85/50	1.70	Salt, D.C.A. 17 days, pork adrenal extract 8 days
		2-11-'47	85	424		47	20.0	9.0		109/75	2.00	Aqueous adrenal cortex extract 50 ml. daily—4 days
M. M.	F	2-15-'46	63	390	650	52	16.2	7.5	12.5	98/70	6.94	Salt
		9-30-'46	64	300	536		21.2	5.8	10.3	104/60	1.75	Salt and D.C.A.
E. L.	F	6-12-'46	51	274	465	53	18.7	5.2	8.8	92/60	1.48	Salt and D.C.A.
		12-16-'46	56	212	342	48	26.5	4.4	7.2	100/80	1.53	Salt and D.C.A. and testosterone propionate
		2-22-'47	66	259	400	52	25.5	5.0	7.7	96/70	1.80	Salt and D.C.A. plus 50 ml. aqueous adrenal cortex extract—4 days
E. W.	F	4-15-'46	56	225	358	52	24.8	4.3	6.9	100/70	2.89	Salt, D.C.A., and testosterone propionate
S. E.	F	1-22-'46	61	241	365	40	24.6	6.0	9.1	130/78	2.72	Salt and D.C.A.
		6-24-'46	68	267	400	49	25.5	5.5	8.3	130/86	2.00	Salt, D.C.A., and testosterone propionate
		12-9-'46	60	244	400	48	24.6	5.0		130/88	1.70	Salt, D.C.A., and testosterone propionate
J. M.	M	2-11-'46	91	616	893	91	13.1	5.6	9.8	110/60	2.48	4 months after implantation of D.C.A. pellets
		12-4-'46	97	620	960	78	15.6	8.0	12.3	120/80	1.95	14 months after implantation of D.C.A. pellets, extra salt
H. W.	M	5-23-'46	69	390	700	88	17.9	4.4	8.0	105/60	1.74	12 months after implantation of D.C.A. pellets, extra salt
A. F.	M	3-25-'46	80	370	463	67	21.7	5.5	7.0	110/84	3.79	12 months after implantation of D.C.A. pellets
		4-29-'47	67	319	463	66	21.0	4.8		90/70	2.00	25 months after implantation of D.C.A. pellets, extra salt
T. D.	M	5-8-'46	67	320	516	48	20.9	6.7	10.7	170/100	3.89	D.C.A.
Pituitary insufficiency												
R. F.	F	12-5-'45	77	273	400	51	28.2	5.2	7.9	110/70	6.15	Salt therapy
		1-2-'46	73	322	457	51	24.6	6.3	8.9	100/60	4.33	Thyroid plus salt
		1-27-'46	84	340	482	48	24.6	7.1	10.0	105/72	4.39	D.C.A. plus salt
		4-22-'46	78	276	392	51	28.2	5.5	7.7	110/60	5.61	Testosterone propionate plus salt
		9-6-'46	84	261	405	56	32.3	4.7	9.2	150/96	8.99	Testosterone propionate plus salt
		1-23-'47	69	251	405	44	27.2	5.7		126/88	7.85	Testosterone propionate plus salt
A. M.	F	6-25-'47	76	255	354	36	29.8	7.0	10.0	88/60	3.60	Salt therapy
W. K.	M	1-15-'46	76	474	718	82	16.0	7.2	10.7	100/75	1.95	Salt therapy
		2-5-'46	72	589	890		12.2			120/80	9.65	Salt therapy
A. B.	M	10-16-'46	54	250	378	34	21.7	7.2	11.0	170/100	3.97	Salt therapy
Average values—female—normal			117	594	982	77	20.2	7.1	12.8			
Average values—male—normal (16, 19, 20)			131	697	1209	77	19.0	8.2	15.7			

* For duration and amount, see Table I.

sion, yet tests enumerated above have continued to be abnormal and he develops symptoms of sodium chloride deficiency when not treated with salt or testosterone propionate.

All the patients were studied when in good clinical condition, it being our purpose to avoid the complicating factors present in crisis or shock. Observations were made while the patients were under basal conditions, *i.e.*, about 14 hours after the previous meal. Several patients, who had a tendency to develop spontaneous hypoglycemia, were given 200 ml. of orange juice one hour before the test since it was found that this did not change the results.

Two patients with Addison's disease (D. B. and M. M.) and all those with hypopituitarism were studied first on salt alone. The other seven patients with Addison's disease had been treated with desoxycorticosterone acetate (D.C.A.) before studies were begun. After satisfactory observations had been made under either of the above conditions, treatment with other hormone preparations was superimposed when possible. We were thus able to study the influence of desoxycorticosterone acetate (D.C.A.), testosterone propionate, aqueous adrenal cortex extract, extract of pork adrenal cortex in oil, and desiccated thyroid, U.S.P.

Renal function studies were made by the multiple period technique advocated by Goldring *et al.* (15). Rates of glomerular filtration were determined as mannitol clearances (16). Effective renal plasma flow and maximum tubular excretory capacity were determined from para-amino-hippuric acid (P.A.H.) clearances at the proper plasma levels as outlined by Chasis *et al.* (17). Analyses were made upon plasma filtrates prepared according to Fujita and Iwatake (18) and on diluted aliquots of urine. Mannitol was determined according to the method of Smith, Finkelstein, and Smith (16). Para-amino-hippuric acid (P.A.H.) was determined according to the method of Bratton and Marshall as modified by Smith *et al.* (19). All results were corrected in proportion to surface area, the final figure being in terms of a surface area of 1.73 sq. meters. Values for these clearances obtained in our laboratory on normal persons are approximately the same as those published by Smith, Goldring, Chasis *et al.* (17, 20, 21).

RESULTS

The results of all observations are recorded in Table II, and a typical test for each patient when either on sodium chloride alone or when receiving D.C.A. is illustrated in Figure 1.

Rates of glomerular filtration were below normal in all patients at all times. This is in agreement with the data published by Talbott *et al.* (2). Treatment with hormones resulted in little if any improvement above that found when salt was used in sufficient amounts to cause adequate improvement in the clinical condition and restoration of

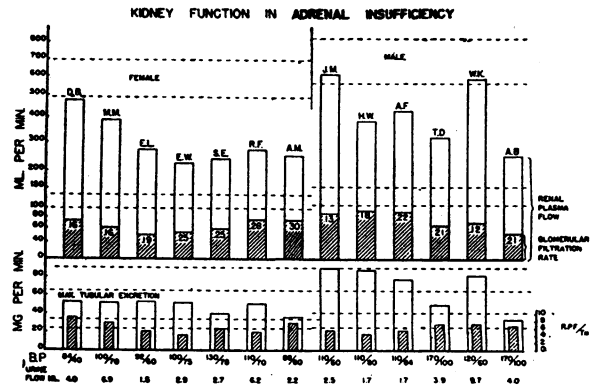


FIG. 1. RENAL CLEARANCE STUDIES IN ADDISON'S DISEASE AND IN PITUITARY INSUFFICIENCY

Patients, D. B., M. M., R. F., A. M., W. K., and A. B., were receiving sodium chloride in sufficient amounts to control symptoms, serum electrolytes, etc. All other patients were receiving desoxycorticosterone acetate. Normal values for the various functions fall between the broken lines. The maximum tubular excretion is for P.A.H. The numbers appearing in the upper, cross-hatched columns are the filtration fractions.

extracellular electrolytes, water and blood pressure (see D. B., M. M., and R. F., Table II). In A. F. there was a slight decrease between the observations made 12 months and 25 months after implantation of nine pellets of D.C.A.² Decreased electrolyte retention between the two periods of observation was to be expected and can explain the decrease in glomerular filtration.

When extract of adrenal cortex was given in large amounts (50 ml. daily) there was perhaps slight increase of filtration but the values were still far below normal.

The filtration fraction

$$\left(\frac{\text{Glomerular Filtration Rate}}{\text{Renal Plasma Flow}} \right)$$

varied considerably at different times in the same subject and also from individual to individual. In general it was normal or high but in three instances it was exceptionally low. The variations cannot be explained without more control observations prior to the institution of hormonal therapy. In the two female patients with Addison's disease (D. B. and M. M.) who had previously been controlled with salt, the filtration

² Two months after the last observation reported here the remnants of two of the nine pellets implanted 27 months previously were recovered.

fraction increased after administration of adrenal cortical hormones which suggests that specific medication may have been a contributing factor.

The maximum excretory capacity of the tubular cells for para-amino hippuric acid (P.A.H.) showed the most interesting deviations from normal. It was low in all female patients and normal in all male patients with the exception of the two men, T. D. and A. B., who had hypertension. As both had had elevated blood pressures for more than a year, the decreased excretion of P.A.H. may have been a hypertensive phenomenon (19). In Patient T. D., hyperpiesa followed excessive treatment with desoxycorticosterone. In A. B. the etiology was not clear and it was present in spite of evidence of insufficiency of the anterior lobe of the pituitary and the adrenal cortex.

Testosterone propionate was given intramuscularly to several of the female patients (see Table I). S. E. received 25 mg. every other day for 20 weeks. At the end of this time a second series of observations showed no significant change from the controls. Treatment was then continued with 25 mg. per week for 24 weeks and again there was no improvement. Patient D. B. was given 25 mg. every other day for four weeks and then 25 mg. once a week without influencing the function studies. To test the possibility of causing improvement by giving small doses over a long period of time, Patient R. F. was given 25 mg. weekly for over a year and E. L. the same dose for six and a half months but no change was observed in either case.

Admittedly the doses given the last two patients were rather small but it was enough to cause marked improvement in their clinical condition. The amount of hormone given S. E. on the other hand should have been ample to bring out any potential effects.

Aqueous adrenal cortex extract was given to patients, D. B. and E. L., in doses of 50 ml. daily for three days, followed by administration of the extract during the tests, and no change was observed in the Tm for P.A.H. D. B. had received 5 ml. of extract daily for three months before the large amounts were given.

Thyroid substance likewise produced no change when given to one female patient, R. F., who had pituitary myxedema.

Effective renal blood flow was always reduced below normal. This was also true of the *effective renal plasma flow* except in two male patients who had moderate anemia (J. M. and W. K.). In the latter the effective renal plasma flow was within low normal values but the whole blood flow was well below normal. Similar findings have been reported in various anemias by Bradley and Bradley (22). Whether the patients were controlled on salt alone or receiving specific therapy seems to have made little if any difference in this function.

DISCUSSION

The distinctive features of the derangement of renal function found in these studies were (a) permanent decrease of renal blood flow and glomerular filtration rate in all patients and (b) reduction of the maximum capacity of the tubules to excrete P.A.H. in all female patients. The consistent finding of decrease of renal blood flow and glomerular filtration rate regardless of the presence or absence of impairment on the part of the tubular cells to excrete P.A.H. is a point of considerable interest. The height of the blood pressure did not seem to be a factor as long as the patients were in good clinical condition. Indeed, comparatively high functional values were obtained at times even in the presence of low blood pressure (see D. B.). Hydration of the patients was always good so that decreased volume of the circulating blood was probably not responsible. While this has been found below normal in untreated adrenal insufficiency it is restored to normal by treatment with desoxycorticosterone or adrenal cortex extract (23, 24). As may be noted in Table II, low renal blood flow and glomerular filtration rates were obtained in our patients while receiving adequate treatment with these preparations. The several tests employed may indicate the status of various parts of the renal vasculature. Consideration of all the data compels us to postulate a reduction in the effective vascular bed in the kidneys with resulting decrease of renal plasma flow and concomitant reduction in the rate of glomerular filtration.

In those patients with Addison's disease whom we were able to study while on salt therapy alone, the ratios, R. B. F./Tm, were low normal and this fact may be interpreted as evidence against rela-

tive ischemia of the functioning excretory tubular tissue of the kidneys (21). The Addisonian patients who had been under the influence of desoxycorticosterone acetate for long periods of time as well as all those with pituitary insufficiency were found to have a relatively greater reduction of renal blood flow than of their maximum ability to excrete P.A.H. (low ratio of R.B.F./Tm) or relative ischemia of the tubular tissues (21). It is uncertain whether this latter finding was the result of disease or was due to treatment.

Information on whether specific therapy affects the filtration apparatus should be afforded by examination of the filtration fraction. Talbott (2) found low filtration fractions in two cases of Addison's disease treated with sodium chloride alone, and this agrees with our observations in two cases studied under similar conditions. All but one of our nine Addisonian patients had normal or slightly elevated filtration fractions after treatment with D.C.A. or aqueous adrenal extract. Of four pan-hypopituitary patients in our series all but one had high filtration fractions. This was true also in two cases studied by Talbott. From the evidence at hand it appears that the patient with Addison's disease prior to specific treatment will show a low filtration fraction in contradistinction to pan-hypopituitarism where the untreated subject may be expected to have a high filtration fraction.

Unusual sensitivity of the blood vessels in patients with Addison's disease to vasoconstrictor as well as vasodilator influences has been reported (25, 26). Roth, Robinson and Wilder (25) found that the unusual hyperreactivity of the Addisonian patient to the constrictor influence of cold was increased by treatment with desoxycorticosterone acetate. From the data available it seems more than probable that treatment with this steroid exerted a vasoconstrictor influence on the vascular bed of the kidneys in our patients. The unexplainable variations in general obtained in some of our patients, especially those with pan-hypopituitarism, are probably due to opposing influences and trophic factors which are not understood.

The failure of any of the functions to improve with the medication given may have been due to several causes. The dose of adrenal cortex hormone may have been insufficient or not given for a

long enough time, in spite of the prompt and adequate restoration which such doses cause in other functions (27, 28). Irreversible structural or functional changes may have taken place. Whether or not histological changes accompany functional changes in kidneys in adrenal insufficiency has been the subject of considerable controversy (8 to 10, 29, 30). It is possible that this may be clarified to some extent if the sex of the patients or animals studied is taken into consideration. Gaunt (31) was unable to correct the defect in water diuresis in adrenalectomized rats, even when adequate hormonal therapy was instituted in less than a week after adrenalectomy.

Finally, the factors responsible for maintenance of the functions mentioned may not have been present in any of the preparations given. The failure of testosterone propionate to restore the Tm/P.A.H. in the female patients is of special interest. The hormonal factors which help maintain this function in the males are undoubtedly made by the testis, but cannot be replaced by testosterone propionate.

SUMMARY

1. Studies on glomerular filtration rate, renal plasma flow and maximum excretory capacity are reported on 13 patients with adrenal insufficiency.
2. Maximum excretory capacity was reduced in female patients and was not affected by hormone therapy.
3. Filtration rates were reduced and it is postulated that absolute reduction at least in the long standing, well controlled Addisonian, is secondary to reduction in renal plasma flow.
4. Changes in the renal blood flow are discussed with regard to the disease per se and to hormonal therapy.

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