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Research Article

SOME STUDIES OF POSTERIOR PITUITARY AND ADRENAL CORTICAL INTERRELATIONSHIPS IN PATIENTS WITH AND WITHOUT CIRRHOSIS OF THE LIVER [1, 2]

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It is well recognized that both the adrenal cortical and posterior pituitary hormones play an important part in the regulation of salt and water metabolism (1). Antagonistic relations between these two hormones have been postulated (2). It has also been shown that in the human a reciprocal relationship exists between the antidiuretic activity of serum and the corticosteroid of urine (3). During diuresis, the antidiuretic activity in serum is low and the corticosteroid excretion in urine is high, whereas, during water retention, the converse situation is found.

Increased amounts of antidiuretic material were recovered from patients with active cirrhosis of the liver by Ralli, Robson, Clarke, and Hoagland (4). In the experimental animal, the liver has been found to be the most effective site of inactivation of the posterior pituitary hormone (5, 6, 7). It was decided, therefore, to study the effects in patients with liver disease of artificially elevating the levels of circulating antidiuretic material by the administration of posterior pituitary extract.

This report is concerned with: a) the changes in metabolism of water and sodium resulting from repeated administration of pitressin tannate in oil, and b) the relationship between plasma sodium and urinary excretion of corticosteroid. The response to exogenous adrenal cortical steroids given concomitantly with posterior pituitary extract was also studied.

METHODS

The studies of the response to pitressin tannate injected daily have been carried out on five patients with Laennec's cirrhosis and on five "control" patients recovering from various diseases, but without evidence of Laennec's cirrhosis. In addition, one patient (Case 11), a confirmed alcoholic with history of phosphorus poisoning as a child, but with no laboratory evidence of cirrhosis, was studied. He was under treatment for erythromelalgia following frost-bite. Further study, reported under Case 11 in the Appendix, provided evidence of some degree of adrenal insufficiency. For these reasons the patient could be considered neither as a control patient nor a patient with liver disease.

All of the cirrhotics had had ascites, but at the time of the studies only one patient was in positive water balance. The subjects were maintained on a controlled diet of known sodium content and five Gm. of salt in solution was given in addition each day. Fluid intake was maintained at a constant level for each patient, usually 2,500 cc. each day. Measurements of weight, urine volume, and urine sodium and potassium were made daily. Frequent determinations of plasma sodium and potassium were obtained by means of the flame photometer. Urinary corticosteroid was measured by a method which has been previously described (8). The normal values range from .200 to .750 mg. of corticosteroid per 24 hours. Pitressin tannate was administered intramuscularly in oil in a dose of 5 units once daily for approximately the first week of the experiment. In several cases, when no effect upon water or electrolyte excretion was observed, the dose was increased to ten or more units daily in two divided doses. When the administration of pitressin tannate had caused significant water retention and depletion of plasma sodium levels, adrenal cortical extract, *i.e.*, lipo-adrenal cortex (Upjohn) intramuscularly, aqueous cortical extract (Upjohn) intravenously, was given while the pitressin tannate injections were continued. The course in each patient is reported separately in the Appendix.

RESULTS

The Effect of Continued Administration of Pitressin Tannate upon Water and Sodium Balance

Injection of pitressin tannate resulted in weight gain from water retention in all patients, but of varying degree.

[1] This paper was read in part before the American Society for Clinical Investigation in May, 1951.

[2] This work was in part supported by grants from the Ciba Company and the Upjohn Company. The pitressin tannate used was supplied through the courtesy of Dr. D. A. McGinty of Parke, Davis & Company. The adrenal cortical extract and lipo-adrenal cortex was supplied by Dr. H. F. Hailman of the Upjohn Company.

For the purpose of comparison, Cases 1–5 (see Appendix) are reported together as control patients and Cases 6–10 are reported as cirrhotic patients. Case 11 is reported separately.

Figure 1 records the weight changes of the cirrhotic and control patients up through the seventh day of the study (fourth day of pitressin administration). Both groups received 5 units of pitression tannate in oil intramuscularly daily. After the seventh day of the study, the sensitivity responses were not entirely comparable since pitressin dosage was increased in several cases. Some subjects were given adrenal cortical hormone after this date and were, therefore, not included in the graph after such administration.

By the fourth day of the administration of five units of pitressin tannate daily intramuscularly, the cirrhotic group had an average weight gain of 6.4 lbs., a maximum of 13 lbs. Control subjects gained an average of 2.9 lbs. The maximum was 7 lbs. of fluid retained. There is considerable spread in the weight gains recorded for individual subjects. The one cirrhotic who did not gain weight failed to do so because of severe vomiting.

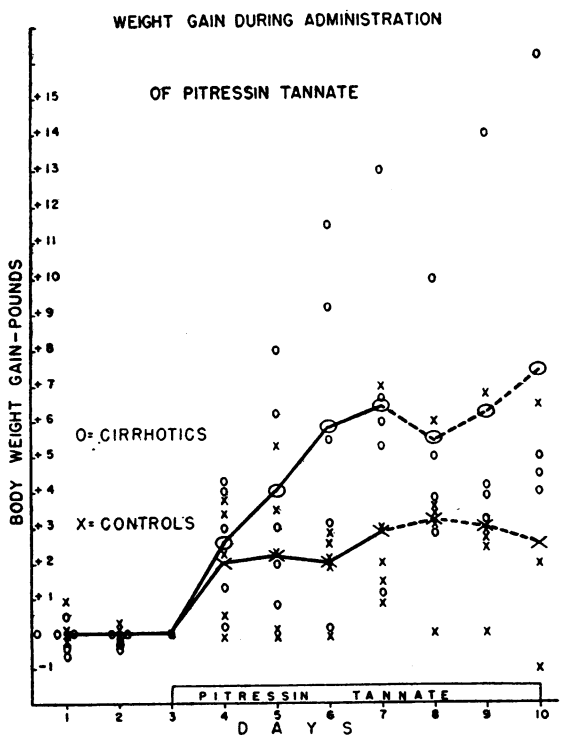

FIG. 1.

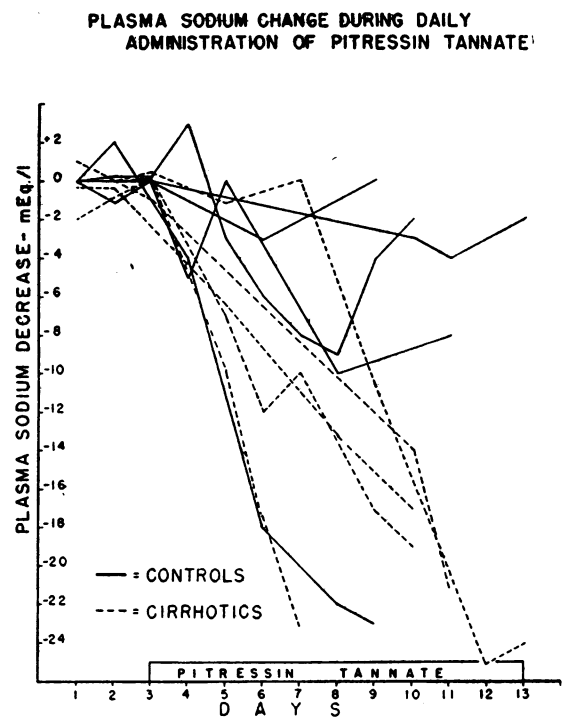

FIG. 2.

The remaining cirrhotics all gained more than five pounds and the amount of fluid lost as vomitus by the fifth cirrhotic was considerably more than five pounds. One of the control subjects had a weight gain comparable to the average of the cirrhotics. None of the remaining control patients gained more than three pounds of weight. For these reasons, it is felt that although the groups are too small to permit positive proof of statistical significance of the differences in the groups, the data suggest a definite trend for the cirrhotic group to gain more weight than the control group.

Continued administration of pitressin tannate also produced a decrease in plasma sodium in both groups. Figure 2 compares the degree of response in the two groups during this part of the study. The cirrhotic patients responded with a dramatic drop in plasma sodium levels ranging between 17 and 25 mEq. per liter. Only one control patient (Case 5) evidenced a comparable plasma sodium decrease. The remaining four control subjects responded with only a moderate hyponatremia of 2 to 10 mEq. per liter. The plasma sodium levels could not be well correlated with water retention and weight gain in all in-

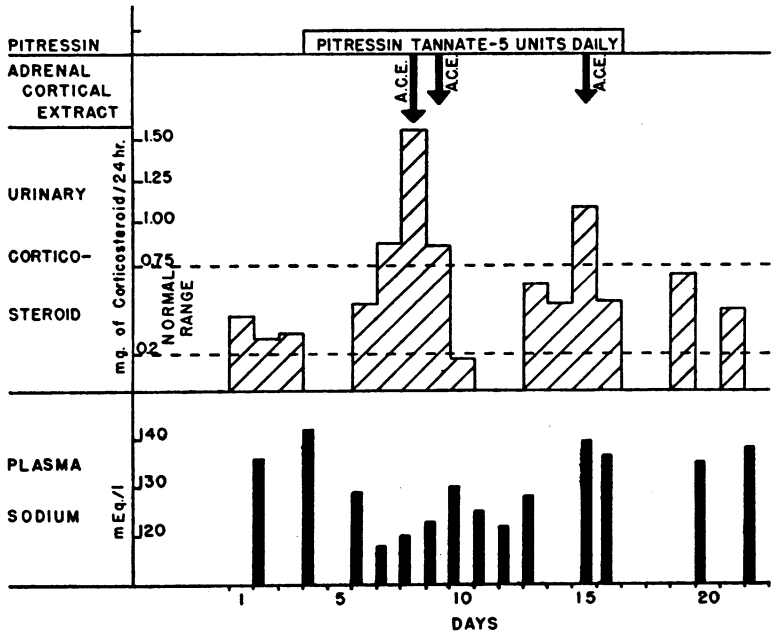

FIG. 3 (CASE 11). ALTERATIONS IN PLASMA SODIUM AND URINARY CORTICOSTEROID LEVELS OCCURRING DURING ADMINISTRATION OF PITRESSIN TANNATE AND ADRENAL CORTICAL EXTRACT

dividuals. In the control group, Case 5, who responded after six days of 5 units of pitressin daily with a precipitous drop in the plasma sodium level from 142 to 117 mEq. per liter, retained only 2.8 lbs. of fluid. Meanwhile, the patient who gained the most weight in the control group (Case 2), showed only a moderate hyponatremia. Similarly, in the cirrhotic group, Case 10, whose plasma sodium level fell from 133 to 108 mEq. per liter, retained only 2 lbs. of fluid. This patient, however, lost considerable fluid through vomiting. In most of the patients with cirrhosis an antidiuresis with increasing edema and ascites was associated with a progressive drop in plasma sodium levels.

Case 11 is reported separately for reasons described under Methods. Figures 3 and 4 record the response of this patient following pitressin tannate administration. Within four days, the plasma sodium level fell from 139 to 120 mEq. per liter and body weight increased from 109 to 116 lbs.

The Effect of Continued Administration of Pitressin Tannate on Urinary Corticosteroid

The excretion of corticosteroid has been studied during daily pitressin tannate administration in seven subjects; three with diagnoses of Laennec's cirrhosis, one with chronic alcoholism, and three with no evidence of liver disease. All determinations of corticosteroid excretion in the urine were within the normal range during the control period except in two individuals with cirrhosis whose corticosteroid excretions were .95 mg. per 24 hrs. and .81 mg. per 24 hrs., respectively.

No appreciable increase in urinary corticosteroid was observed in any subject until a significant decrease in plasma sodium had occurred. During the time that the plasma sodium was maintained at a low level with the continued administration of pitressin tannate, the urinary corticosteroid usually remained above the control levels. Figure 5 illustrates that during the continued administration of pitressin tannate to a normal subject who had little change in plasma sodium, there was no increase in urinary corticosteroids. Figure 6 illustrates that when pitressin tannate produced a striking depression of serum sodium in the cirrhotic, there was a concomitant increase in corticosteroid.

Chromatographic fractionation of corticosteroids excreted by one of these patients, Case 10, has

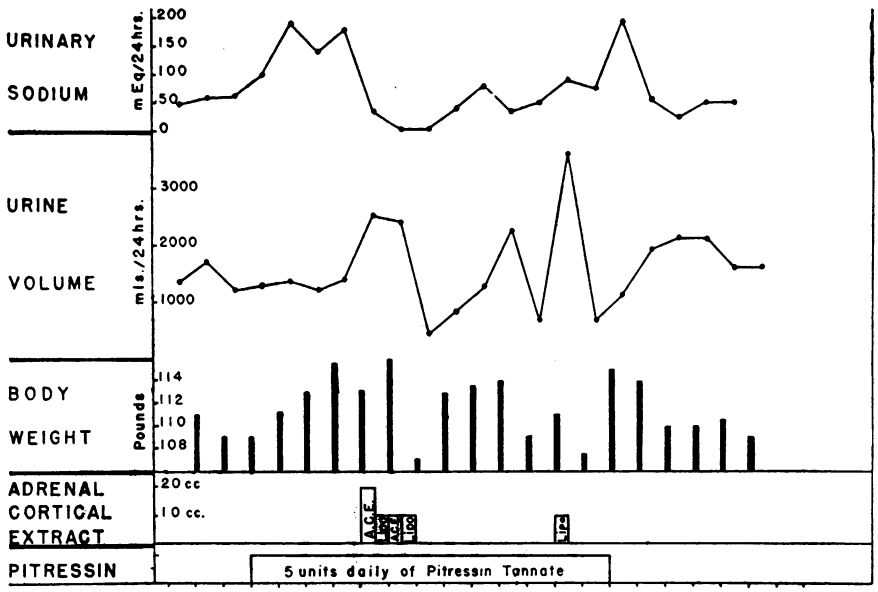

FIG. 4 (CASE 11). ALTERATIONS IN URINARY SODIUM EXCRETION, URINE VOLUME, AND BODY WEIGHT OCCURRING DURING ADMINISTRATION OF PITRESSIN TANNATE AND ADRENAL CORTICAL EXTRACT

demonstrated an alpha-ketol which moves more rapidly than desoxycorticosterone, and which forms formaldehyde upon oxidation with periodic acid. Based on the rate of flow, it seems probable that this material contains three oxygens. No further identification has as yet been possible.

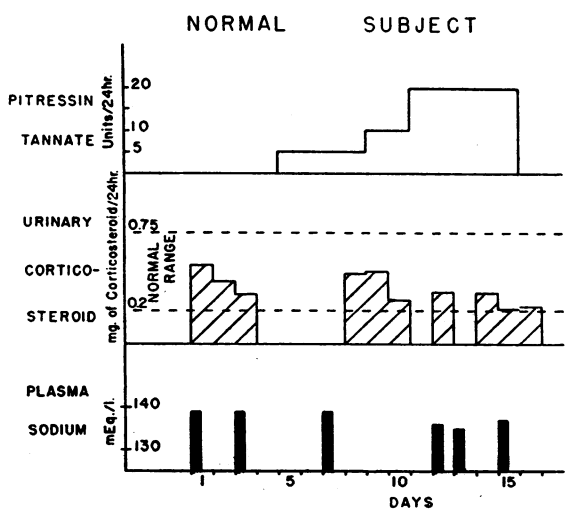

FIG. 5. EFFECT OF CONTINUED ADMINISTRATION OF PITRESSIN TANNATE ON PLASMA SODIUM AND URINARY CORTICOSTEROID—NORMAL SUBJECT

The Effects of Exogenous Adrenal Steroids on Water and Electrolyte Disturbances Caused by the Continued Administration of Posterior Pituitary Extract

Two patients from the control group, five patients with cirrhosis and Case 11 received adrenal cortical extract during the course of pitressin tannate administration. Adrenal cortical extract appeared to promote salt retention in two controls (Cases 2 and 3) when the pitressin dosage was maintained at 5 units per day, but no effect was apparent in Case 3 after pitressin dosage had been increased to 15 units per day.

Adrenal cortical extract was administered for a total of 17 experimental days in the cirrhotic group. It is worth noting that the urine volume and sodium excretion varied considerably from day to day, making it difficult to assess the effects of adrenal cortical extract. Furthermore, when antidiuresis was very pronounced, the urine sodium content was markedly reduced secondary to oliguria (see Case 9). On only two of the 17 experimental days (Day 20, Case 6; Day 17, Case 10) did a sodium retention result which might be ascribed to the effects of adrenal cortical extract. Adrenal cortical extract failed to promote

an obvious diuresis in either the control or the cirrhotic patients. In Case 7, however, the degree of water retention and weight gain was less after adrenal cortical extract, and in Case 10 a definite weight loss occurred concomitantly.

The hyponatremia resulting from pitressin tannate administration was improved in only one patient (Case 10).

In Case 11, pitressin tannate administration promoted an antidiuresis and natriuresis, both of which were reversed with adrenal cortical extract. Antidiuresis returned as pitressin was continued and was again reversed with adrenal cortical extract, although there was little immediate effect upon sodium excretion. The hyponatremia resulting from pitressin tannate tended to be corrected also.

DISCUSSION

These experiments have raised the following points for discussion: The tolerance of patients with liver disease to pitressin; the causes of the resulting hyponatremia; the effects of pitressin administration upon adrenal cortical function; and the reversal of the effects of pitressin by adrenal cortical extract.

White, Rubin, and Leiter (9), and Nelson and Welt (10) have found that when relatively small doses of pitressin are given in an acute experiment, no difference in effect is found, and they concluded that the patient with cirrhosis can inactivate physiological doses of pitressin as well as the normal. Our preliminary experiments with small amounts of aqueous pitressin yielded the same result.

It seems probable that extrahepatic sites of pitressin inactivation are capable of removing the antidiuretic activity present in small amounts of pitressin given either intravenously or subcutaneously. Fairly large doses of pitressin are required to demonstrate a defect in hepatic inactivation. Eversole, Birnie, and Gaunt (6) found it necessary to give a dose of 40 milliunits of pitressin to 200 Gm. rats in order to demonstrate differences in effectiveness of the intrasplenic or subcutaneous routes. This dose is approximately fifteen times the amount of pitressin required to produce a state of antidiuresis. Heller (11) has found that rabbit blood is capable of inactivating several milliunits of pitressin per cc. of blood and believes that this inactivation actually represents a loose combination with protein. Birnie, Jenkins,

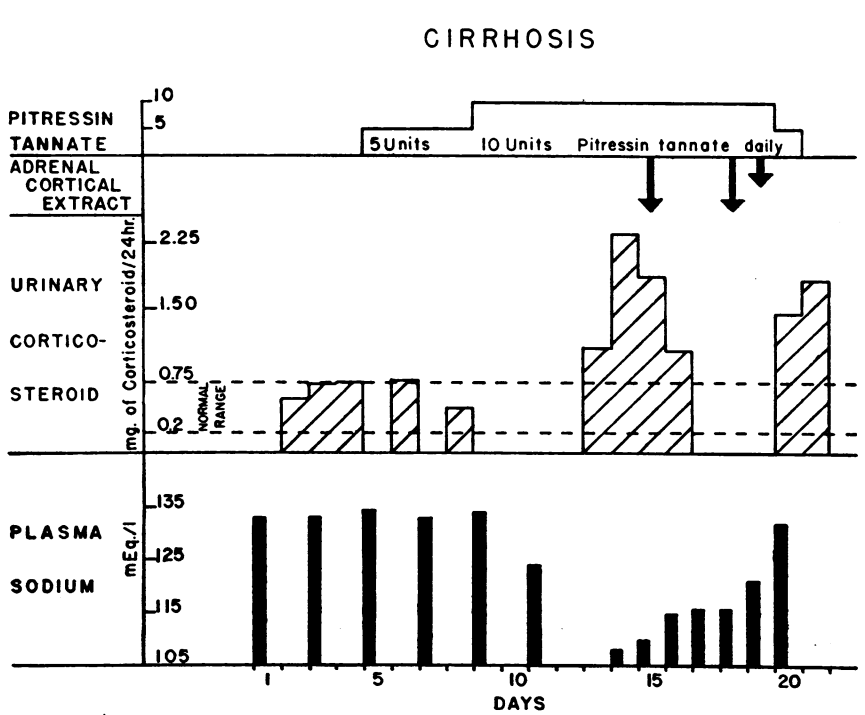

FIG. 6. EFFECT OF CONTINUED ADMINISTRATION OF PITRESSIN TANNATE ON PLASMA SODIUM AND URINARY CORTICOSTEROID—PATIENT WITH CIRRHOSIS

Eversole, and Gaunt (12) have found that rat serum is capable of destroying the antidiuretic activity in pitressin and a few preliminary studies in our laboratory indicate that human blood has the same property.

The data of these experiments suggest that by taking advantage of a possible accumulative effect, differences in rate of inactivation of pitressin by patients with and without liver disease can be shown. Although the liver is the most active single tissue in pitressin inactivation, it is only one of many mechanisms which remove antidiuretic activity from blood. Therefore, even if the hepatic inactivating mechanisms are strikingly less efficient than normal, the total overall ability of the body to inactivate pitressin may not be very greatly decreased and the defect is made apparent only when large amounts of pitressin are administered over a period of several days.

Animal experiments by Loewy and Lloyd (13) have compared the effectiveness of pitressin tannate given to normal rats and to rats with fatty livers produced by diet low in protein and high in fat. The fatty livers were capable of inactivating *in vitro* only one-third of the antidiuretic activity of an amount of pitressin which normal liver could completely destroy. These findings agree with those of Birnie, Blackmore, and Heller (14), who reported that a low protein diet greatly decreases the pitressin inactivating ability of the mouse liver *in vitro*.

The relatively minor differences in the response between the cirrhotic and the normal group in this study and the complete absence of differences between cirrhotics and normals when pitressin is given intravenously suggest that hepatic inactivation of posterior pituitary hormone probably plays relatively little part in removal of antidiuretic activity from blood under normal physiological conditions and that failure of this process may very well have only minor importance in the production of ascites.

Bartter (15), in discussing an experiment carried out in collaboration with Leaf, has pointed out that the normal individual may be quite sensitive to pitressin tannate with rather striking water retention. Our experiences are certainly in agreement. There is no question that certain normal subjects have considerable antidiuresis as a result of pitressin tannate administration, but the degree of antidiuresis is usually not as marked as in the cirrhotic and frequently, relatively little effect is apparent.

The natriuretic and antidiuretic effects of exogenous pitressin could be minimized presumably by various hormonal and physiologic mechanisms within the body. If this were so, abrupt withdrawal of exogenous pitressin would be expected to lead to sudden and profound diuresis with rapid return of the plasma sodium level to initial levels. This occurred in eight of the ten patients followed. The effects of withdrawal of pitressin were far more obvious than the slow accumulative effects of pitressin administration. The pattern of changes resulting from pitressin administration suggested by these studies are supported, therefore, by the dramatic reversal of effects on discontinuing pitressin tannate.

The effect of prolonged administration of pitressin tannate on the plasma sodium could be mediated in three possible ways. A natriuresis frequently occurred following administration of pitressin tannate in oil. Other investigators, who have studied the excretion of sodium following the administration of aqueous extract of pitressin have been unable to demonstrate a natriuresis in the acute experiment. By the methods used in this study, however, an increased loss of sodium in the urine occurred in four patients, (Cases 5, 6, 7, 10). Equally significant was the acute retention of sodium when pitressin tannate was abruptly withdrawn.

The second way in which the plasma sodium might be depressed is by dilution with retained water. In some patients, this could account for most or all of the decrease in plasma sodium, since as much as ten liters of fluid were retained. It is difficult to account for the decrease in plasma sodium in other patients, however, by either an increased sodium excretion or by simple dilution with retained water. A third mechanism must be considered, that is, a redistribution of sodium from an extracellular to an intracellular position. The suggestion that this may occur has also been made by White, Rubin, and Leiter (9). Pitressin causes a shift of sodium into tissue from plasma in guinea pigs (16). Keutmann (17) has been able to demonstrate an increased intracellular sodium concentration in several patients with edema occurring as a result of heart failure. Whether such

an intracellular shift of sodium in the series here presented might have occurred in response to pitressin administration, or whether it might have been mediated through an increased amount of circulating adrenal steroids containing three oxygens, is as yet undetermined. The latter possibility must be considered since suggestive evidence has been presented that an increased amount of a three oxygen containing steroid was present in the urine of one patient, and it has been shown that desoxycorticosterone is capable of causing a shift of extracellular sodium into the cell (18). If the alpha-ketol demonstrated in the urine of one patient in this series had physiological activity similar to desoxycorticosterone, it might have been responsible for such a shift. However, the only time that the three oxygen containing steroid was found in these patients was when the plasma sodium level was already at a low level, so that it now seems more likely that the hyponatremia might very well be the stimulus which caused the appearance of the three oxygen containing steroids. A shift of sodium to the intracellular position would seem to be a direct pitressin action since this shift has been reported to occur (9) during the acute administration of small amounts of pitressin.

The lack of direct effect of pitressin tannate administration on adrenal cortical steroid excretion is apparent. Only when the plasma sodium is depressed to a level which is associated with signs of the low salt syndrome could an increased amount of steroid be discovered in the urine. The failure to find an increased amount of steroid does not mean, of course, that the gland itself is not producing more, since it is easily possible that the increased output of the gland might be balanced by increased utilization with the result that no additional hormone was available for wasting in the urine. However, the studies of Nagareda and Gaunt (19) have shown that pitressin in physiological amounts does not cause a change in adrenal ascorbic acid. Studies on the urinary corticosteroid and serum antidiuretic levels during water diuresis have shown that a reciprocity exists and that the antidiuretic activity decreases and the corticosteroid level increases during water diuresis. Since this reciprocity is not a direct one, the hypothesis has been made that a response to a common stimulus (hypotonicity) decreases secretion of posterior lobe hormone and increases secretion of adrenal cortical steroids.

The increased level of adrenal cortical steroids in diuresis, and the known opposing effects of adrenal steroids and pitressin, constituted the rationale for administration of adrenal cortical extract concomitantly with pitressin tannate. Only in Case 11 in whom there was some clinical evidence of adrenal insufficiency, did adrenal cortical extract produce an obvious diuresis with retention of sodium. In several of the remaining cases, an apparent retention of sodium occurred on some occasions, but without obvious diuresis. The failure to produce this effect more frequently may be the result of an inadequate dosage. No attempts to reproduce these experiments using cortisone or 17-hydroxycortisone have been made.

SUMMARY

1. Pitressin tannate in oil was given by intramuscular injection daily to five patients with cirrhosis of the liver and to five "control" patients. One patient, a chronic alcoholic with evidence of poor adrenal function, was also studied.

2. Administration of pitressin tannate in oil can produce hyponatremia and antidiuresis in both the control and the cirrhotic patients. These effects are greater in the cirrhotic, and frequently lead to a stage of progressive hyponatremia and edema.

3. The opposite effect, profound diuresis and return of plasma sodium towards normal, occurs promptly when exogenous pitressin is withdrawn.

4. Pitressin administration lowers plasma sodium levels by at least two mechanisms: Antidiuresis with dilution of extracellular sodium by retained water; and a direct natriuresis. A third mechanism must be considered: A shift of sodium from the extracellular to the intracellular space.

5. Urinary excretion of corticosteroid increases when plasma sodium concentration falls to low levels, but does not increase as a result of pitressin administration *per se*.

6. Adrenal cortical extract produced an obvious diuresis and retention of sodium in only one patient who had developed water retention and hyponatremia as a result of pitressin tannate administration. In several other patients an apparent retention of sodium occurred on occasion without obvious diuresis.

APPENDIX

37 year-old white male. Diagnosis - myeloradiculopathy, achlorhydria. No history of liver disease or alcoholism.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			139	1680	168	67	0.54	139	4.3	116	Showed no evidence of edema at any time.
2			139	1260	86	53	0.42				
3			139	1750	70	66	0.32	139	4.2		
4	5u		139	1060	94	60		139	4.1		
5	5u		139.5	1255	113	72					
6	5u		139	1525	130	126					
7	5u		139	1285	100	48	0.47				
8	10u		140.5	2050	142	84	0.50				
9	10u		139	1520	103	60	0.30				
10	20u		139	1495	81	69					
11	20u		138	1000	139	75	0.36	136	4.7		
12	20u		138	2070	164	76		135			
13	20u		138	1000	108	81	0.35				
14	20u		140	885	130	61	0.21	137	3.8		
15			144	1215	144	65	0.25				
16			143	5200	81	114					
17			136.5								

CASE I—M. C.

35 year-old white male. Diagnosis - migrating thrombophlebitis. Denies alcoholism or history of liver disease. Liver not palpable. Liver function tests normal.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			153.8	2200	132	43	0.54	143	5.1		Actual salt intake unknown.
2			155	1195	95	42	0.36				
3			154.3	2295	124	40		142	4.3		
4	5u		154	780	102	57		143	3.7	90	No apparent edema at any time.
5	5u		157.8	2720	98	59		138	3.7		
6	5u		157.5	790	42	45		143	4.4		
7	5u		156.5	960	136	56	0.73				
8	5u		161	2270	119	56	0.59				
9	5u		160	1560	123	53	0.70	133	5.2		
10	5u		160.8	1920	101	50					
11	5u		160.5	1605	149	72					
12	5u	10L* - 10A	162.8	2100	85	32		135	4.7		
13	5u		161.3	2580	193	56		130	4.5		
14			161	3790	13	52					
15			155.5					142	4.2		

*L = Lipo-adrenal cortex

A = Aqueous adrenal cortex

CASE II—J. W.

22 year-old white male. Recovered from mild hepatitis with jaundice. Denies alcoholism. Liver not enlarged. Cephalin flocculation - trace. Bromsulphathalein retention (5 mg./kg.) 0% at 60 mins. Albumin 5.1 gm.%, globulin 2.5 gm.%. Eosinophil response to adrenalin: basal 122/mm^3, 4 hrs 57/mm^3. Urinary 17-ketosteroid excretion 15 mg./24 hrs. Diet high in potassium due to protinal and fresh fruit supplement.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			164.5	2500	119	118				106	No edema or ascites
2			165	1920	119	93					
3			164	1300	33	100					
4			164	1540	22	121					
5	5u		164	1200	44	113					
6	5u		166.3	2060	180	113		140	4.4		
7	5u		166.3	2320	122	102					
8	5u		167	960	60	73		137	4.5		
9	5u		167	1920	65	120					
10	5u		167	2680	60	144					
11	5u	10L - 10A*	167	1320	27	103		140	4.7		
12	5u	18L - 23A	168	1880	59	105		136	4.4		
13	5u		166	2080	92	112		135	4.0		
14	10u		169.5	1380	152	135		135	4.0		
15	10u		171.5	2320	58	157					
16	10u		170	1380	66	130		133	3.8		
17	15u		170	1160	64	159					
18	15u		174.3	1460	166	108		129	4.1		
19	15u	10L - 20A	177	1100	111	119		127	4.2		
20	15u	15L - 20A	181	1140	90	84		125	4.1		
21			178	2190	159	117					
22			175.5	6840	68	68		128	4.3		
23			166	1880	6	85					
24			167.8					138	3.9		
25								145	3.4		

*L= Lipo-adrenal cortex
A= Aqueous adrenal cortex

CASE III—S. S.

33 year-old Negro male. Recovered from lobar pneumonia. Denies alcoholism. No evidence of liver disease. House diet. Fluids ad lib. Urine not collected.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			150					142	5.2	Approx. 190	No edema at any time during study.
2	5u		150					142	5.1		
3	5u		150					145	5.0		
4	5u		150					139	4.5		
5	5u		152					136	5.3		
6	5u		152					134	4.5		
7	5u		153.5					133	4.4		
8	5u		152.5					138			
9			152					140	3.8		
10			151.5						4.3		
11			152					141			

CASE IV—J. S.

56 year-old white woman. Diagnosis - neurasthenia. EEG suggestive of epilepsy. History of repeated trauma to head. Denies alcoholism or liver disease. Bromsulphathalein retention (5 mg./Kg.) 0% at 45 mins. Cephalin flocculation 2+ repeat trace. Albumin 4.3 gm.%, globulin 2.1 gm.%. Eosinophil response to adrenalin: basal 480/mm^3, 4 hrs. 133/mm^3. Urinary 17-ketosteroid excretion 3.8 mg./24 hrs.

Day	Pitressin Tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			129	1732	125	61	0.42	140	4.6	116	No edema, ascites
2			129.8	2130	167	74	0.52				
3			129.8	2558	123	82		142	4.3		Abd. circ. 34½".
4	5 u		130	1440	147	94					
5	5 u		133.5	1700	282	75		136	4.9		
6	5 u		135.3	1535	242	74					Vomited 1200 cc.
7	5 u		132	1070	48	48	0.78	122	4.0		Abd. circ. 37", ankle
8	5 u		131	1355	94	56	0.58	120	4.5		edema 1+.
9	5 u		133.5	2350	265	66		118	5.7		
10			132.8	2122	75	43		117	5.4		Abd. circ. 38", ankle edema cleared
11			127	3810	5.6	32		120	5.4		
12			123.8	1805	7.6	55		133	5.4		Abd. circ. 34"
13			126					135	3.9		

CASE V—G. H.

45 year-old white male. Diagnosis - Laennec's cirrhosis. History of prolonged alcoholism. Liver and spleen enlarged. Bromsulphathalein retention (5 mg./kg.), 19% at 45 mins. Cephalin flocculation 4+. Albumin 3.3 gm.%, globulin 4.3 gm.%. Eosinophil response to adrenalin: basal 230/mm^3, 4 hrs. 124/mm^3.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			158	2720	126	61		136	3.8	109	No evidence of edema or ascites
2			158	2000	93	65					
3	5u		158	1620	138	71		138	3.6		
4	5u		159.3	1360	109	57					
5	5u		160	1420	135	50		131	4.3		
6	5u		161	1675	171	55		126	3.8		
7	5u		163.3	2100	192	60		128	4.3		
8	5u		161	1780	107	63					
9	10u		162	1720	96	52		121	4.3		
10	10u	20L-20A*	162.5	1920	61	68		119	3.9		2+ ankle edema.
11	10u		163.8	2480	67	62		119			
12	10u		163.5	2600	77	50		123	3.8		Ankle edema clearing.
13			162	4240	12	56		126			
14			158.3	2900	37	80		135	3.8		
15			158.5	2560	56	60					
16			158.5	2400	78	62		136	4.1		
17	5u		158.5	1910	137	63		136	3.9		
18	5u		159.5	1755	156	63					
19	5u		160.3	2160	216	63		127	3.5		
20	5u	15L-20A	160.5	1465	39	75		125	4.1		
21	5u	10L-20A	161	2140	93	74		128	3.8		
22	5u		161	1700	94	46		126	3.6		
23	5u		160	2218	144	57		128	3.4		
24			162.5					124	3.6		Transferred from hospital.

*L=Lipo-adrenal cortex
A=Aqueous adrenal cortex

CASE VI—C. C.

42 year-old white female. Diagnosis - Laennec's cirrhosis. History of alcoholism. Liver and spleen enlarged. Bromsulphathalein retention (5 mg./kg.) 28% in 45 mins., cephalin flocculation 1+. Albumin 3.6 gm.%, globulin 2.0 gm.%. Liver biopsy showed marked fatty metamorphosis. Eosinophil response to ACTH: basal 294/mm³, 4 hrs. 118/mm³.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			176	2440	51	47	0.81			116	No ankle edema or ascites. Abd. circ. 43½".
2			176	1545	72	26					
3			175.3	1860	65	23					
4			175.5	2140	65	37	0.80				
5	5u		176.5	465	92	43		139	4.2		
6	5u		180	547	93	30	0.38				
7	5u		184	600	113	40	0.55	129	3.8		Abd. Circ. 43½"
8	5u		187.5	465	95	25		121	4.1		
9	5u	20L-20A*	189	1170	175	77	1.02	116	4.3		Abd. circ. 46" 2+ edema
10	5u	20L-20A	188.5	1040	92	55		113	4.1		
11	5u		190.8	1615	167	40		113			Abd. circ. 44"
12	5u		191.5	1805	160	45	0.97	113	4.2		3+ ankle edema
13	5u		191.3	1075	95	39	0.68	112	4.7		Abd. circ. 48".
14			193.5	5425	83	54	1.30	110	5.2		Face puffy
15			182.3	4690	76	52		129	4.4		Edema cleared
16			177.8								Abd. circ. 42"

*L = Lipo-adrenal cortex
A = Aqueous adrenal cortex

CASE VII—N. K.

39 year old white female. Diagnosis - Laennec's cirrhosis. History of chronic alcoholism. Liver enlarged, tender. Two previous paracenteses. Bromsulphathalein retention (5 mg./kg) 14% at 45 mins. Cephalin flocculation 2+. Albumin 3.0 gm.%, globulin 3.6 gm.%. Eosinophil response to adrenalin: basal 744/mm³, 4 hrs. 600/mm³. Urinary 17-ketosteroid excretion 1.3 mg./24 hrs.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24hrs.	Remarks
1			111	1830	29	36	0.58	139	4.0	109	Ascites minimal
2			110.3	1420	21	26	0.62	139	3.2		No ankle, sacral edema
3			110.5	690	20	15					
4	5 u		110.8	355	10	10			4.5		
5	5 u		113.8	275	7	20					
6	5 u		117	430	7	22		132	3.5		
7	5 u		120	1940	8	27					
8	5 u		117.5	880	20	33	1.21				Increasing ascites
9	5 u		120.8	410	5	23		126	4.8		Ankle edema 2+
10	5 u		124.8	345	3	15					Ankle and sacral edema
11	5 u	10L*	127	410	1.3	14		122	4.4		Marked ascites
12	5 u	10L - 20A*	129	315	2.3	24		121	3.6		(Hemorrhage from bowel. Transfusions 500 cc. blood)
13	5 u	10L - 37A	130	590	4.4	21		120	3.7		
14	5 u		133.3** 125	410	0.7	18		120	4.0		Abd. paracentesis.
15			126.8	3470	3	27					
16			119.5	3280	0.8	25		128	3.7		
17			116	1860	0.8	15		129	3.7		
18			114.8	900	0.3	7					
19			114.5	2310	43	59					
20			115	1120	3	16		131	2.5		

*L=Lipo-adrenal cortex
A=Aqueous adrenal cortex

**Wts. before and after abdominal paracentesis

CASE VIII—M. P.

76 year old white woman. Diagnosis-Laennec's cirrhosis. Denies history of alcoholism or hepatitis. History of recent hematemesis from esophageal varices. Liver and spleen enlarged. Bromsulphathalein retention (5 mg./kg.) 20% at 45 mins. Cephalin flocculation 3+. Albumin 3.3 gm.%, globulin 3.3 gm.%. Fluid intake ad lib.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Cortico-Steroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24hrs.	Remarks
1			124.8	1420	23	37				61	No evidence of edema
2				1235	27	51					
3				2240	35	31		133	4.4		
4			123.5	2285	53	63					
5				1918	61	41		132	4.3		
6	5 u		123	300	14	17					
7	5 u		127	1430	132	64					
8	5 u		126	390	6	20					
9	5 u		128.5	370	49	70					
10	5 u		129	2000	91	56					
11	5 u		128	2835	35	43					
12	10 u		126	1420	37	59					Apathetic
13	10 u		128	815	76	39		118	4.3	208	No edema
14	10 u	15L-20A*	131.5	1415	156	65		111	4.1	168	
15	10 u	17L-20A	132.8	495	18	21		112	4.0	199	Basilar rales
16			134.5	4520	121	52		117	3.9	156	Ankle and sacral edema
17			126.3	1520	80	21		132	3.6	156	Edema cleared
18			126.5	2825	215	35		133	4.4	190	
19			127	2860	170	37				156	
20			125.5	2440	162	55					
21	10 u		124.8	2255	159	53		134	4.0		
22	10 u		124.8	1860	110	51					
23	10 u		124	780	81	44		130	4.0		
24	10 u		126.3	2545	171	53		119	4.2		
25			125.8	4536	16	38					
26			121.5	2165	38	46		136	4.5		
27			122	1790	82	52					
28			123	1680	78	28					
29			123	2710	184	60					
30			122	2570	132	58					
31			123.5	1940	95	50					
32			123	2305	118	60					
33			123	2590	159	60					
34			123	2000	109	45		138	4.4		
35	10 u		123	2410	152	70					
36	10 u		123	1650	109	56					
37	10 u		125.3	950	112	40					
38	10 u	20L*	128.5	1340	190	45		114			Vomiting clear fluid
39	10 u	20L	130.3	1050	73	41		118	4.0		Severe precordial pain
40	10 u	20L-30A*	128	480	22	19		119	4.1		EKG negative
41	10 u	20L-30A	128.5	1310	124	38		113	3.4		
42	10 u		128.3	3060	67	18		118	3.2		
43	10 u		123.5	1180	49	23		129	3.9	Unknown	Gross hematemesis, shock received 200 cc. whole blood.
44	10 u			1215	11	21					
45				1455	117	12		140	3.5		

*L= Lipo-adrenal cortex

A= Aqueous adrenal cortex

CASE IX—E. M.

46 year old Negress. Diagnosis-Laennec's cirrhosis. Prolonged alcoholism. Liver much enlarged and tender. Bromsulphathalein retention (5 mg/kg.) 40% at 45 mins. Cephalin flocculation 1+. Albumin 3.6 gm.%, globulin 3.6 gm.%. Given 500 ml. 10% dextrose in water, 500 ml. 10% dextrose in saline, and 1000 ml. ammosol in 5% dextrose intravenously daily, plus oral feeding of special formula containing 30 mEq. Na+. Patient unable to take regular diet or fruit juice mixture. Periods of vomiting during the study.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Corticosteroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			118	2135	95	41	0.58	133	3.9	108	No ankle edema
2				1988	82	46	0.73	133	4.0		or ascites
3			116	1812	34	41	0.95				Abd. circ. 37 in.
4	5 u			2615	93	51		134	3.4		
5	5 u		116	1695	95	38	0.71				
6	5 u		116.8	1430	59	27		133	3.8		
7	5 u		116	1460	85	39	0.47				Abd. circ. 38 3/4 in.
8	10 u		117	1350	120	40		134	3.9		
9	10 u		119.8	2465	165	41					
10	10 u		120	1940	158	47		124	3.6		
11	10 u		120	924	41	49					
12	10 u		120	1820	95	52	1.13				
13	10 u		118	1336	81	47	2.34	108	3.0		Abd. circ. 39 in.
14	10 u	20L*	118	2460	77	49	1.88	110	3.4		
15	10 u		115.5	2090	72	52	1.09	115	3.2		Diffuse joint tenderness
16	10 u		116	2430	83	32		116	2.8		Ankle edema, fingers puffy
17	10 u	20L-20A*	114	1410	15	27		116	3.0		Dull, apathetic
18	10 u		112	1335	22	23		121	2.7		
19	5 u	10L-20A	110	1730	51	23	1.50	132	2.9		Generalized convulsions
20				1230	54	18	1.86				Convulsions
21				1720	42	11					Abd. circ. 34 in.
22			111	908	14	6					Abd. circ. 35 3/4 in.

*L = Lipo-adrenal cortex
A = Aqueous adrenal cortex

Case X—C. M.

59 year old white male. Diagnosis-erythromelalgia, phosphorus poisoning as a child. Chronic alcoholic. Liver not enlarged. Bromsulphathalein retention (5 mg./kg.) 0% at 45 mins. Albumin 4.9 gm.%, globulin 2.0 gm.%. Cephalin flocculation 1+. Urinary 17-ketosteroid exgretion 4 mg./24 hrs. Glucose tolerance curve flat. Eosinophil response to adrenalin: basal 88/mm^3, 4 hrs. 105/mm^3.

Day	Pitressin tannate units/day	Adrenal Cortical Extract cc./24 hrs.	Weight lbs.	Urine Vol. cc./24 hrs.	Urine Na mEq./24 hrs.	Urine K mEq./24 hrs.	Urinary Corticosteroid mg./24 hrs.	Plasma Na mEq./l.	Plasma K mEq./l.	Sodium Intake mEq./24 hrs.	Remarks
1			109	1355	49	25	0.43			90	1+ ankle edema with erythromelalgia
2			109	1690	62	20	0.32	139	3.9		
3			109	1210	66	25	0.33				
4	5 u		109	590	99	36		139	4.0		
5	5 u		111.8	1385	189	38					
6	5 u		113	1200	139	43	0.52	129	3.9		
7	5 u		115.5	1395	181	64	0.82	118	4.3		3+ leg edema
8	5 u	10L-20A*	116	2510	35	70	1.56	120	4.2		Face puffy
9	5 u	10L-20A	116	2300	5	21	0.86	123	4.5		
10	5 u		107	460	5	18	0.18	130	4.3		Edema cleared
11	5 u		113	850	39	26		125	4.3		
12	5 u		113.5	1250	81	33		122	5.9		Edema recurring
13	5 u		114.3	2250	37	25	0.62	128	4.6		
14	5 u		109	620	51	17	0.52				
15	5 u	10L	111	3575	91	33	1.09				
16	5 u		107.5	670	75	32	0.53	136	4.5		Edema cleared
17	5 u		115	1085	196	36					
18			114	1890	54	18					Edema recurring
19			110	2125	22	20	0.69				Edema cleared
20			110	2120	49	42		135	4.5		
21			110	1620	49	22	0.49				
22								138	4.4		

*L=Lipo-adrenal cortex
A=Aqueous adrenal cortex

Case XI—J. M.

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