DIABETES INSIPIDUS. A METABOLIC STUDY OF THE EFFECT OF PITUITARY ADMINISTRATION

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Introduction: The following paper contains:

1. A brief resume of the literature in which most of the recent writers regard the disease as due to hypofunction of the hypophysis.
2. A clinical description of a case in a woman, age 58 years, in which the chief symptoms were thirst; polyuria; pain in head, back, and limbs; impaired eyesight; loss of weight.
3. Physical examination; leucodermic patches on arms and chest, dry skin, body otherwise normal. Patient nervous and irritable.
4. Previous illness negative; family history of cancer, diabetes, and insanity.
5. X-ray examination; sella turcica slightly enlarged, anterior clinoidal processes thin; posterior clinoidal processes thin and of mushroom type.
6. Eyes; concentric contraction of visual and color fields, and other changes suggesting a functional disturbance due to physiological factors.
7. Average amount of urine passed daily when no pituitrin was given (78 days), 6277 cc. Average amount passed daily when pituitrin was given (142 days), 3767 cc.
8. Diets low in carbohydrates, proteins, fats, and salt had little effect on diuresis.
9. Administration of anterior lobe pituitary body by mouth was ineffective in controlling diuresis.
10. Administration of posterior lobe by mouth was also without effect.

11. Removal of spinal fluid to lessen intracerebral pressure diminished diuresis for one day only.

12. The effect of pituitary administration is purely transitory. Its continued use over a period of 8 months has afforded no evidence of permanent improvement.

13. The blood sugar level on a diet rich in carbohydrates was inappreciably influenced by the administration of pituitrin.

14. There was a considerable increase in the cholesterolin and fat content of the blood which was uninfluenced by the treatment.

15. The study of the urine excretion by means of the Mosenthal two hour renal test showed that when pituitrin is not given the kidneys eliminate large and variable amounts of urine during the day and an even greater amount during the night period. The percentage of solids or specific gravity is fixed on a low plane and fluctuates very little. When pituitrin is administered, much less urine is excreted during the day periods but the night amount is quite as large as in the previous test. The percentage of concentration of solids in the urine is much greater and more variable. Without pituitrin, nitrogen elimination was quite variable during the day with a pronounced response to the noon meal although the percentage of concentration was fixed during all but two of the periods. The administration of pituitrin seemed to stimulate nitrogen excretion during the latter part of the day and during the night, more than half of it being eliminated during the night hours. Salt elimination is also on a higher plane after the administration of pituitrin.

When pituitrin is not given, salt elimination is on a low plane, there being quite a well-marked fixation of concentration. When pituitrin is administered, both the amount and the percentage of concentration vary considerably, showing that the kidneys have a greater amplitude of function. As in the case of water and nitrogen, more than half of the salt is eliminated during the night hours.

16. The blood creatinin was normal. The urea content of the blood was normal but the rate of excretion was apparently improved by the administration of pituitrin, as evidenced by the lower Ambard coefficient.

Resume of recent literature. Many writers have reviewed the literature relating to the hypophysis. In this paper no attempt will be made to do more than call attention to the views of recent students of the subject with reference to the relationship of the pituitary body to diabetes insipidus, in so far as therapeutics is concerned. In the first and second issues of this journal will be found abstracts of practically all the literature of value that has been published recently. From these reviews have been epitomized the following notes which have a bearing on the case studied in this paper.

Boyd reports a case of glioma constricting the infundibulum of the pituitary body which he believes supports the theory that the secretion of the posterior lobe of the pituitary body passes by the way of the infundibular stalk into the third ventricle. Hoppe-Seyler reports a case in which he brings out the following salient points: "Polyuria from excessive ingestion of fluid is differentiated by the specific grav-

ity remaining low, independent of the amount of food or drink taken. The polyuria is controlled by the vasomotor nervous system and not by the disturbed kidney cells. The prompt reaction of the body to small doses of pituitrin results in the normal excretion of urine, saliva, and sweat. In the case of the urine there is a rapid rise in the specific gravity and

FIG. 1

Chart showing visual fields in the case reported (see page 321).

salts. Insufficiency of the pituitary gland is the cause. All signs rule against the opinion that the disease is due to irritation of the gland or hyperfunction." Hoppe-Seyler refers to work of Magnus and Schafer who conclude that there is a hyperfunction of the hypophysis. Romer showed by animal experimentation and clinical study that there is a hypofunction.

v. Konschegg, E. Schuster, and Graul, from clinical studies, conclude that there is hypofuntcion. Rosenfeld found oral administration of pituitrin as effective as injection.

Motzfeldt (Journal of Experimental Medicine, 1917, 25, 153) has shown that pituitrin does not influence the polyuria caused by the excessive ingestion of salt. He also shows that extracts of the pars intermedia and posterior lobe of the hypophysis, when given by mouth, subcutaneously, or intravenously, have an anti-diuretic effect on experimental animals. Extracts of the anterior lobe have a similar effect but to a lesser degree. The anti-diuretic action exerted by pituitary extracts on experimental animals is caused by stimulation of the sympathetic nervous system and the renal vasomotor system in this respect is of chief importance.

HISTORY OF AUTHOR'S CASE:

Patient is a widow, age 58 years, American born. Complains of excessive urination, thirst, pain in left side of head, tired feeling, pain in limbs, lower back, and distress in epigastrium; dryness of throat.

The illness began in the summer of 1911 with thirst and excessive urination and gradual loss of weight. Lips were dry and cracked, and healed with difficulty. Eyes ached much of the time. When the polyuria first began, the patient had peculiar spells as though she were sinking through the floor. These phenomena she ascribes to severe constipation from which she suffered at the time.

Urinary history. During the day, she urinates from 8 to 10 times, voiding from 4000 cc. to 6000 cc.; during the night, she urinates from 4 to 5 times, passing from 2000 cc. to 4000 cc.

Edema. Formerly, patient thinks eyes were puffy; there is no evidence of edema now. There is no cough or pallor.

Patient suffers daily from headache on left side and back of head; is dizzy nearly every day. Vision is gradually failing. No specks or light flashes before eyes. Complains of stiffness and lameness in limbs, but joints do not swell or become inflamed. Bowels are constipated; takes mild ca-

tharsis daily. Sleeps well except when disturbed by diuresis.

Weight. In 1896, 168 pounds; 1911, 150 pounds; 1916, 131 pounds; October 23, 1916, net weight, 118 pounds; April 9, 1917, net weight, 129 pounds.

Married 34 years. Pregnant twice; no abortions.

Previous illness. Measles, whooping cough, mumps, and scarlet fever as child; good recoveries. Pneumonia at 29 years, again at 32 years, with good recoveries. Had much trouble with teeth and all were removed except lower incisors which are in fair condition. Has been moderately nervous since illness began; is not hysterical and does not suffer from motor excitement. Is troubled somewhat with hemorrhoids.

Family history. Father died at 72 years of liver disease; had cancer on his nose. Mother died at 75 years of heart disease. One sister died of cancer; one paternal cousin died of diabetes mellitus, and two paternal uncles died of insanity. Patient has two living, healthy, adult children.

Physical examination. Patient is a middle aged woman, medium height, thin, pale, worried expression. Face, arms and chest blotched with large leucodermic patches. Skin is dry and elastic. Subcutaneous fat thin, muscles moderately developed. Hair, eyes, ears, nose, normal. Tonsils small, cryptic, no evident degeneration. Tongue slightly swollen and edematous. Thyroid normal; no evident thymus, lymph glands all normal, arteries, soft; no abnormal sclerosis. Blood pressure, systolic 115 mm., diastolic 70 mm. Veins normal. Lungs, normal resonance and breath sounds; no rales. Heart normal in size, rhythm regular, no bruit. Abdomen slightly pendulous, muscle wall flaccid. Aside from a slight tenderness on deep pressure in the region of the gall bladder, nothing abnormal is to be noted in the abdomen. Reflexes, pupillary and patellar both active. Romberg's sign negative. Coordination and tremor normal. Limbs, spine, and pelvis, normal. No evidence of edema.

Teeth, upper plate; lower molars removed; lower incisors normal except one which shows slight pyorrhea. Weight, 118¼ pounds.

Laboratory Examinations:

Blood. October 26, 1916: Red cells, 4,500,000; white cells, 7,600; Hb. 85 per cent.; Hb. index, 94.

Wassermann Test. October 31, 1916, negative.

Non-protein nitrogen in blood, 23 mg. per 100 cc.

A large number of urine examinations were made. The specific gravity was usually low, ranging from 1004 to 1013. Neither sugar nor albumen was found. Several microscopic examinations of the urine were negative.

Functional tests of the kidney were made October 30, 1916. Phthalein, 2 hours, 42 per cent.; November 5, 1916, Phthalein, 50 per cent.

Study of urinary excretion under various conditions. From October 23 to October 30 inclusive, patient voided from 5,500 cc. to 7,100 cc. daily, averaging approximately 6,500 cc. daily. On October 29th, 20 cc. spinal fluid were removed, after the suggestion of Dr. Dean Lewis. The fluid was normal in appearance and cell content. On October 30th the urine dropped to 3,600 cc. but on the two following days, it rose to over 5,000 cc. The effect of pituitrin hypodermatically was then tried. The results of this are shown in the following summary.

TABLE I
EFFECT OF PITUITRIN ADMINISTERED HYPODERMATICALLY
ON OUTPUT OF URINE

Date	Vol. Urine cc.	Sp. Gr.	Pituitrin hypo.	Carb.	Diet Prot.	Fat	Calories	Remarks
			cc.	g.	g.	g.		
Nov. 2	2375	1007	1	50	40	48	790	No thirst
3	5850	1006	0	59	44	64	950	Severe thirst
4	1100	1011	2	53	44	72	1025	No thirst
5	1075	1013	1	73	62	68	1150	No thirst
6	3900	1005	1	74	63	78	1255	No thirst
7	1700	1010	1	74	63	78	1255	No thirst
8	2725	1009	1	74	63	78	1255	No thirst
9	2025	1010	1	61	50	107	1338	No thirst
13	3800	1008	1	125	67	106	1705	No thirst
14	2600	1008	2	109	51	91	1438	No thirst
15	1375	1011	1	116	70	116	1660	No thirst
22	3120		2	Diet approximately the same				No thirst
23	3100		2	Diet approximately the same				No thirst
24	4340		2	Diet approximately the same				No thirst
25	3840		2	Diet approximately the same				No thirst
26	3840		2	Diet approximately the same				No thirst
27	3360		1	Diet approximately the same				No thirst
28	4800		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
29	6960		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
30	6960		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
Dec. 1	5520		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
2	6960		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
3	6960		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
4	7000		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
5	7720		6	grains pituitary body (Armour)				
				by mouth				Severe-thirst
6	7300		1-10	grain pituitary body post. lobe				
				by mouth				Severe thirst

TABLE I (continued)

	7	7000	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	8	7000	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	9	6800	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	10	7000	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	14	6400	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	19	5800	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	23	5900	1-10 grain pituitary body post. lobe by mouth	Severe thirst
	24	2800	1 cc. pituitrin per hypo.	No thirst
	25	3000	1 cc. pituitrin per hypo.	No thirst
	26	2900	1 cc. pituitrin per hypo.	No thirst
	30	2800	1 cc. pituitrin per hypo.	No thirst
Jan.	1	1700	1 cc. pituitrin per hypo.	No thirst
	2	2850	1 cc. pituitrin per hypo.	No thirst
	3	4850	1 cc. pituitrin per hypo.	Patient has "cold"
	5	5450	1 cc. pituitrin per hypo.	Patient has "cold"
	5	5100	1 cc. pituitrin per hypo.	Patient has "cold"
	14	5700	1 cc. pituitrin per hypo.	Patient has "cold"
	29	3900	1 cc. pituitrin per hypo.	No thirst
	30	3800	1 cc. pituitrin per hypo.	No thirst
	31	6800	0	Severe thirst
Feb.	1	6300	0	Severe thirst
	2	6400	0	Severe thirst
	3	7800	0	Severe thirst
	6	5500	0	Severe thirst
	7	3300	1 cc. pituitrin per hypo.	No thirst
	8	3400	1 cc. pituitrin per hypo.	No thirst
	9	3100	1	No thirst
	10	2600	1	No thirst
	17	3100	1	No thirst
	18	5100	1	Ate candy freely
	19	4200	1	No thirst
	21	3500	1	No thirst
	27	6900	0	Severe thirst
	28	7100	0	Severe thirst
Mar.	1	7800	0	Severe thirst
	4	5450	0	Severe thirst
	5	7800	0	Severe thirst
	6	4000	1	No thirst
	8	3800	1	No thirst
	12	3200	1	No thirst
Apr.	10	3700	1	No thirst
	12	6000	0	Severe thirst
	14	7100	0	Severe thirst
	15	5200	1	No thirst
	16	2800	1	No thirst

Comment. It will be noticed that pituitrin administered hypodermatically appreciably lessened the urine output. One cubic centimeter was quite as effective clinically as were two

doses. Pituitrin by mouth had no antidiuretic action in this case.

TABLE II
TWO-HOUR RENAL TEST, APRIL 5, 1917

Diet: Carbohydrate 293 grams. Protein 85 grams. Fat 125 grams. Calories 2641. Salt approximately 5 grams. No pituitrin administered.

Hours	Fluid Intake	Urine cc.	Specific Gravity	Nitrogen		Salt	
				Grams	Per Cent.	Grams	Per Cent.
7-9 a.m.	300	250	1006	0.53	0.21	0.30	0.12
9-11 a.m.	540	100	1008	0.24	0.24	0.08	0.08
11-1 p.m.	720	300	1007	0.66	0.22	0.18	0.06
1-3 p.m.	810	550	1007	2.15	0.39	0.33	0.06
3-5 p.m.	0	500	1007	1.55	0.31	0.10	0.02
5-7 p.m.	900	350	1008	0.91	0.26	0.21	0.06
7-9 p.m.	60	200	1009	0.55	0.22	0.15	0.06
9 p.m.-7 a.m.	2040	3150	1007	4.73	0.15	1.88	0.06
Totals	5370	5400		11.32		3.23	

Summary. The excretion of urine is variable during the day, but there is considerable storage and elimination during the night. There is no evidence of fixation of elimination of water. The specific gravity is so constant as to suggest fixation of concentration of solids. The amounts of nitrogen eliminated during the daylight hours vary widely, suggesting an absence of fixation; there is considerable storage, however, for nearly half of the nitrogen is eliminated during the night. The percentage of concentration of nitrogen shows more tendency to fixation. The elimination of salt is on a low plane and, as in the case of the water and nitrogen, there is evidence of delay and elimination during the night. There is noticeable evidence of fixation of percentage of concentration and probably also of some salt retention. The response to the noon meal is fairly prompt in water, salt, and nitrogen.

TABLE III
TWO-HOUR RENAL TEST, APRIL 9, 1917

Diet: Carbohydrates, 300 grams. Protein, 85 grams. Fat, 119 grams. Calories, 2615. Salt, approximately 5 grams. 1 cc. pituitrin administered hypodermatically.

Hours	Fluid Intake	Urine cc.	Specific Gravity	Nitrogen		Salt	
				Grams	Per Cent.	Grams	Per Cent.
7-9 a.m.	0	450	1006	0.59	.13	.63	.14
9-11 a.m.	360	44	1025	0.43	.98	.38	.86
11-1 p.m.	90	64	1025	0.72	1.12	.60	.94
1-3 p.m.	510	42	1025	0.55	1.26	.24	.58
3-5 p.m.	90	100	1020	1.03	1.03	.54	.54
5-7 p.m.	0	175	1014	1.43	.82	.28	.16
7-9 p.m.	1230	300	1011	1.50	.50	.42	.14
9 p.m.-7 a.m.	0	3110	1007	6.61	.21	3.11	.10
Totals	2280	4325		12.86		6.24

FIG. 2

Chart showing examination of visual and color fields, made February 9, 1917. The outer line is the boundary of the visual field. The next lines enclose the blue, red, and green color fields in the order named. Note the concentric contraction of both the visual and color fields.

FIG. 3

Chart showing examination of visual and color fields, made July 17, 1917. Note the concentric contraction of both the visual and color fields which has occurred since the previous examination.

Summary. The elimination of water during the day is quite variable. It is on a much lower plane during the day than during the night when there is a noteworthy polyuria. There is little response to the noon meal. The specific gravity likewise fluctuates widely and is much higher than in the previous test. The elimination of nitrogen is normal as to quantity when compared with the protein intake; during the daylight hours, however, it is on quite a low plane, showing a moderate degree of fixation of amount and percentage, although there is considerable fluctuation in the daylight hours. As in the case of the water, more than half of the nitrogen is eliminated during the night. The response to the noon meal is much delayed. The elimination of salt is also on a low plane during the daylight hours, half of it being excreted during the night. There is little response to the noon meal. The percentage of concentration fluctuates considerably. It is noteworthy that the thirst of the patient varies in intensity during the day, the desire for fluid occurring chiefly at breakfast, dinner, and after supper, with none during the night.

Comment on the two-hour renal tests. It seems likely that the administration of the pituitrin assuages the thirst because during the first test when no pituitrin was given, the patient drank large quantities of water throughout the entire 24 hours, whereas during the second test, the effect of the pituitrin evidenced itself chiefly at meal hours and not at all during the night. Excretion of water, nitrogen, and salt apparently takes place continuously throughout the twenty-four hours, but apparently there is delay in excretion or storage of these materials so that night elimination is quite equal to that of the day. This is wholly unlike that of the normal kidney which eliminates quite promptly and efficiently the materials ingested during the day, so that the entire night urine may contain but little more water, nitrogen, and salt than any of the day two-hour periods. It is quite possible that the excessive thirst and the consequent ingestion of large quantities of fluid exhibited in this disease tend to exhaust the kidney rather than to produce a specific lesion. The absence of nitrogen retention in the blood, the normal nitrogen elimination in urine and nitrogen equilibrium in this severe case indicate that the disturbance is not one of faulty nitrogen metabolism or elimination. The same may be said of the salt although it would seem that salt and nitrogen excretion are stimulated by the pituitrin. The normal blood sugar and absence of glycosuria in diets containing large amounts of carbohydrate food, much of it in the form

of sugar, prove conclusively that there is no disturbance of carbohydrate metabolism and that the kidneys have the normal degree of resistance to the passage of sugar. The absence of albumen and renal elements is further evidence that the kidneys are not structurally diseased. It is possible that the improvement in renal output after the administration of pituitrin is partly explained by the rise in blood pressure which follows, although this is denied by some investigators.

TABLE IV
CHEMICAL STUDIES OF BLOOD AND URINE

With and without the administration of pituitrin hypodermatically.

Date	Vol. urine cc.	Blood					Diet				
		Cholesterol mg.	Fat mg.	Non-prot. nitro. mg.	Pressure Syst.-diast.	Sugar	Carb.	Prot.	Fat	Fluid Intake	Pituitrin cc.
Apr. 3	7100						297	85	122	4500	0
4	6250	312	835	36	110-80	0.10	292	75	112	3180	0
6	3000						300	85	125	2940	1
7	2900						295	84	125	2160	1
8	4075	312	906	36	140-75	0.08	300	85	119	2130	1

TABLE V

			Pit. cc.
June 27	Urea in blood	25.2 mg. per 100 cc.	0
June 28	Urea in blood	40.6 mg. per 100 cc. Ambard Coeff.	0.16 0
June 29	Urea in blood	25.4 mg. per 100 cc. Ambard Coeff.	0.11 1
June 29	Creatinin in blood	2.3 mg. per 100 cc.	

Comment. The samples of blood were taken before breakfast after the night's fast. Cholesterol and blood fat were determined by Bloor's method; the non-protein nitrogen by Folin's micro-kjeldahl method; the blood-sugar by the Lewis-Benedict method. Normal blood rarely contains more than 250 mg. cholesterol per 100 cc. This patient exhibits a well marked cholesterinemia, both before and after the administration of pituitrin. Normal blood of a fasting patient rarely contains more than 600 mg. fat per 100 cc. The blood fat in this case is increased. The non-protein nitrogen in the blood in this case is normal, both before and after the administration of pituitrin. There is no evidence of nitrogen retention. The blood pressure, both diastolic and systolic, are increased by the administration of the pituitrin. On the days when the patient had no pituitrin, twice as much water was drunk as when it was given. The fluid intake is a measure of the patient's thirst. The carbon-dioxide content of the

alveolar air was 41 mm. (barometric tension) before and 39 mm. after the administration of pituitrin. These figures are normal and show that acidosis is not a factor in the disease.

Examination of eyes by Dr. Elmer J. Bissell, February 12, 1917. "Patient has a moderate amount of hyperopia and astigmatism, and slight incipient cataracts which are not of the type found in diabetes mellitus. Retinal arteries slightly tortuous. Visual and color fields somewhat contracted. Surrounding the outer area of the blind spot in the left eye, there is a relative scotoma. These tests would indicate that there are some changes in the optic nerve fibres which are not yet discernible with the ophthalmoscope." Patient was re-examined June 17, 1917, and the following changes noted:

FIG. 4

Sella turcica. Drawing made from tracing of X-ray plate. Note the indistinct anterior clinoidal process and the thin dorsum sella and mushroom type of posterior clinoidal process. The measurements would indicate that the sella turcica is slightly larger than normal.

"No increase in the incipient cataracts. The retinal arteries are slightly attenuated and the temporal side at each optic disc is paler than normal. Visual fields for form and color are very much contracted concentrically. The relative scotoma which was present in the region of the blind spot of the left eye in February has disappeared. This is quite significant and may indicate that some physiologic condition is influencing the function of the retina without producing structural changes. The same condition may be the cause of the contracted visual and color fields."

Report of radiologist, Dr. M. W. Palmer. "The X-ray findings of the sellar region in this case, except in one or two important particulars, do not differ essentially from many other cases in which there is no history of diabetes insipidus. There are, however, certain markings which should not be

overlooked in future examinations of the sella turcica in this disease."

Stereoscopic plates were employed. Dimensions, long diameter of the opening, 11 mm., vertical diameter, 10 mm.

The anterior clinoidal processes are indistinct or absent. The posterior clinoidal processes are also thin. The dorsum sella is about 2 mm. thick; at the top it branches anteriorly and posteriorly into frayed edges to form the posterior clinoidal processes. This peculiar mushroom type is rarely seen except where the posterior lobe of the hypophysis is involved, therefore the absorption of the dorsum sella and posterior clinoidal processes should be considered in the interpretation of plates in this disease.