MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL
October 16, 1969

ADDISON'S DISEASE

Case 1. [redacted]

This 44 year old [redacted] woman was first seen at [redacted] at the age of 12 when she was diagnosed as having pulmonary tuberculosis with disease limited to the right upper lobe. She was hospitalized at Woodlawn for 2 years with treatment consisting of bedrest and a pneumothorax on the right. She left the hospital against medical advice and was not seen again for 17 years.

In [redacted], 1957 she came to the [redacted] emergency room with a short history of cough, fever, and thick sputum production. In addition a history was obtained of weakness and malaise for about a year and of increasing pigmentation for six months. She had sustained a five pound weight loss during this time. Vomiting had been noted during the acute illness. Because of the history of proven tuberculosis and an x-ray which continued to show apical disease of undetermined activity, she was admitted to [redacted] [redacted]. On physical examination the B.P. was 85/60, pulse 76, T - 101° and respirations 18. She was noted to be very brown and pigmentation was particularly noticeable in scars, over skin pressure points, in the nipples and areolar areas, and in the mouth. She had dullness to percussion in the right lower lung field, and a few rales in the apices. The remainder of the examination, except for a sparseness of pubic hair, was described as being normal. Laboratory workup showed a hemoglobin of 11.8 grams% and a white blood cell count of 3850 with 7% eosinophils, 59% lymphocytes, and 31% neutrophils. The serum sodium was 135 meq/liter while the serum potassium was 3.5 meq/liter. CO_2 was 24.8 meq/liter and the BUN was 7 mg%. Fasting blood sugars ranged from 73 to 105 mg%. Smears for acid fast bacilli were negative and a bacterial pneumonia was thought to be present. She was transferred to Parkland three days after admission. A 24 hour urine collection was obtained and showed a 17 keto steroid output of 3.6 mg. 17-OH steroids were not obtained. The patient was started on treatment with hydrocortisone 30 mg daily in divided doses and 9-α-fluoro-hydrocortisone 0.1 mg daily. Within 5 days she was stated to be markedly improved and skin pigmentation was thought to have decreased.

Subsequent to her discharge the patient did well and was followed in the clinic. In [redacted] 1957 she developed severe abdominal pain which was thought to represent acute appendicitis or pelvic inflammatory disease. She was admitted to the hospital and underwent exploratory laparotomy. She was found to have extensive disease of the pelvic contents and a bilateral salpingo-oophorectomy and hysterectomy were carried out. She tolerated the procedure well, having received intravenous hydrocortisone during surgery. Pathologic examination and cultures showed active tuberculosis of the surgical specimens. She was transferred to [redacted] and given intensive chemotherapy for 8 months. She was discharged in good condition on PAS and INH. In the clinic, subsequent to discharge, she was noted to be edematous and fluorohydrocortisone was decreased to 50 micrograms a day. In the next two years the patient was admitted twice more, once for a draining otitis media and once for acute cholecystitis which was treated by cholecystectomy.

Following discharge the patient did not return to clinic for three years. In 1965 she presented with a history of increasing pigmentation for 6 months, a three pound weight loss, shortness of breath on exertion, and cough with sputum production. She had decreased her cortisol intake to 20 mg daily, 5 days of each week. B.P. was 120/85 and the pulse was 80. Apart from the increased pigmentation physical examination was unchanged from the time she was last seen. Initial laboratory work included a serum sodium of 132 meq/liter, a potassium of 4.7 meq/liter, a CO_2 of 28 meq/liter and a blood sugar of 96 mg%. She was admitted to the hospital and hydrocortisone was stopped with the patient under careful

observation on [redacted]/65. On [redacted]/65 40 units of ACTH was given by IV drip and 40 units injected intramuscularly at twelve hour intervals for an additional day. The following 24 hour steroid excretion patterns were obtained:

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17-OH steroids	13.7	3.7	0.9	0.9	1.7
17-ketosteroids	12.1	5.9	7.0	4.1	

During the steroid withdrawal serum sodium decreased to 122 meq/liter. Hydrocortisone and fluoro-hydrocortisone were restarted. No evidence of active tuberculosis was obtained and the patient rapidly improved.

Two weeks after discharge the patient was seen in the clinic and found to be edematous with a serum sodium of 143 meq/liter, serum potassium of 2.9 meq/liter, and CO_2 of 32 meq/liter. Florinef was decreased to 50 micrograms per day and potassium supplementation was started. She rapidly improved on this therapy. She has had two subsequent admissions, one for pneumococcal pneumonia and the other for a radical mastoidectomy, both of which were tolerated well. She is currently asymptomatic on 30 mg of hydrocortisone in divided doses and does not require fluoro-hydrocortisone replacement.

Case 2. [redacted]

This 37 year old woman first became ill approximately 3 years prior to admission when she noticed a gradual increase in fatigue with the inability to do normal household chores. In addition she noted a craving for sleep and loss of libido. She subsequently developed posterior leg weakness which further decreased her exercise tolerance. Two years prior to admission she developed an upper respiratory infection for which she consulted a physician. On examination an enlarged thyroid gland was noted and therapy was started with exogenous thyroid, 0.2 mg daily. There was no history to suggest thyroiditis. The patient complained of extreme nervousness on therapy and thyroid was discontinued after one month. The gland was stated to have decreased slightly in size. Six months prior to admission she began to complain of palpitations and shortness of breath. She also noted nausea, morning vomiting, and, on 2 occasions, post-prandial diarrhea. Her weight decreased from 116 to 109 pounds. She consulted another physician who noted a blood pressure of 90/50. He performed a 5 hour glucose tolerance test with the following values obtained: Control - 78 mg%, 1 hour - 126 mg%, 2 hours - 86 mg%, 3 hours - 88 mg%, 4 hours - 63 mg%, and 5 hours - 60 mg%. On the basis of this test a diagnosis of functional hypoglycemia was made. Therapy included a high protein, low carbohydrate diet and weekly injections of ACTH and estrogens. She did not improve to any extent and began to complain of a generalized "heaviness" over the body after meals together with weakness in the jaws which made mastication difficult. She consulted another physician who told her that the diagnosis of hypoglycemia was incorrect. He suspected that the patient's problems were largely emotional, but referred her to Dr. Kaplan for evaluation.

Further history obtained at the time of admission included the fact that she had noticed a darkening of the skin following her last pregnancy 6 years previously which had persisted to the present time. She had also noted a progressive disappearance of pubic and axillary hair. The latter required shaving only at 6 month intervals. Menstrual periods had become irregular 3 years previously. She had had no surgery. There was no history of exposure to tuberculosis, though her son had a positive skin test with a negative chest x-ray. Family history was unremarkable except for a question of diabetes in the mother.

On physical examination the patient was alert and cooperative. She appeared to be in no distress. B.P. was 90/60, pulse was 72, temperature was 98° and respirations were 18. The skin was noted to be generally tanned and very dry. There was virtually no body hair. Examination of the eyes, ears, nose, and throat were normal. Moderate buccal pigmentation was noted. The thyroid was diffusely enlarged without nodules or bruits. Heart and lungs were normal as was abdominal examination. Neurological testing showed delayed return of the stretch reflexes.

Initial laboratory workup showed a hemoglobin of 12.3 grams% with a hematocrit of 36.5%. The white blood cell count was 4700 with 61% lymphocytes, 36% neutrophils, and 3% eosinophils. Urinalysis was normal except for a few white blood cells. BUN was 16 mg%, while the fasting blood sugar was 51 and 55 mg% on successive days. Serum sodium was 137 meq/liter the day of admission and 126 and 128 meq/liter on two other days. Serum potassium ranged from 4.0 to 5.0 meq/liter. Cholesterol was 300 mg%.

Endocrine workup revealed a PBI of 3.9 µG% with thyroxine iodine of 1.1 µG%. RAI uptake was 12% and after three days of TSH was 15%. Antibodies to thyroglobulin were negative. Twenty-four hour urine 17-hydroxysteroids were undetectable and 0.5 mg on two occasions while simultaneously determined 17-ketosteroids were 1.4 and 2.1 mg respectively. The patient then underwent an ACTH stimulation test while protected with dexamethasone. Forty units of ACTH were given IM daily for three days. The following values were obtained:

	Control	Day 1	Day 2	Day 3
Urine 17-hydroxy corticoids	0.2	0.2	1.2	--
Plasma 17-hydroxy corticoids	1.0	2.5	1.2	0.7

Skull x-rays showed a normal sella turcica and flat plate of the abdomen revealed no adrenal calcification. A tensilon test was attempted but evaluation was inadequate because of an allergic response to the drug.

The patient was started on replacement therapy with hydrocortisone, intermittent 9-α-fluoro-hydrocortisone and l-thyroxine. She improved dramatically and has resumed a normal life. All symptoms were alleviated and skin pigmentation decreased to normal.

TABLE 1

Incidence of Common Signs and Symptoms

in Addison's Disease (86 patients)*

Sign or Symptom	Insufficient Information	Number	Precent
Tiredness and weakness	--	86/86	100
Loss of weight	24	62/62	100
Skin pigmentation	--	80/86	97
Systolic B.P. <110 mm	--	78/86	91
Gastrointestinal symptoms	10	66/76	87
Early morning hypoglycemia	30	40/56	72
Buccal pigmentation	--	61/86	71
Reactive hypoglycemia	39	20/47	43

* Dunlop, Brit. M. J. 2:887, 1963. All patients had primary adrenal failure and were under the personal care of the author.

TABLE 2

Causes of Decreased Blood Pressure and Shock

in Addison's Disease

1. Decreased myocardial contractility.
2. Volume depletion and hyponatremia.
3. Decreased vascular responsiveness to norepinephrine.

TABLE 3

Maintenance of Blood Sugar by Adrenal Hormones

Hormone	Action and Result
Epinephrine	1. Inhibits insulin release from pancreas. a. ↑ Gluconeogenesis b. ↑ Glycogenolysis c. ↑ Free fatty acid release from fat stores d. ↓ Peripheral utilization of glucose 2. Activates hepatic and muscle phosphorylase. a. ↑ Glycogenolysis 3. Activates free fatty acid release from fat stores. a. ↓ Peripheral utilization of glucose
Hydrocortisone	1. Induces gluconeogenic enzymes. a. ↑ Gluconeogenesis 2. Activates free fatty acid release from fat stores. a. ↓ Peripheral utilization of glucose

TABLE 4

Normal Steroid Values*

Test	Condition	Value
Plasma cortisol	Early morning	6-26 µG/100 ml
	Afternoon	2-14 µG/100 ml
Cortisol secretion rate		15-30 mg/24 hours
Urinary 17-hydroxy steroids (Porter-Silber)	Male	3-12 mg/24 hours
	Female	2-10 mg/24 hours
Urinary 17-ketogenic steroids	Male	8-22 mg/24 hours
	Female	7-19 mg/24 hours
Urinary 17-ketosteroids	Male	8-22 mg/24 hours
	Female	5-15 mg/24 hours

* These values may vary slightly from laboratory to laboratory.

TABLE 5

Prevalence of Addison's Disease in a Metropolitan Population*

Age	Tuberculous		Non-tuberculous		Est. population	
	M	F	M	F	M	F
					x10^{-3}	
0-24	1	0	2	3	528	528
25-44	9	3	5	25	424	448
45-64	4	7	4	15	393	449
65-69	0	0	2	0	59	89
> 70	0	1	0	1	86	164
All ages	14	11	13	44	1490	1678
Prevalence	15	10	13	41	28	51

* Mason, et al, Lancet 2:744, 1968. Indicates the number of known cases of Addison's disease in a population of approximately 3,200,000. Prevalence rate is calculated as number of cases per million population. Calculated annual death rate from Addison's disease in a 5 year period was 1.4 per million.

TABLE 6

Associated Diseases in 118 Cases of Idiopathic Addison's Disease*

Disease	Number	Percent
Thyroid (hyper or hypo)	30	25
Hypoparathyroidism	18	15
Diabetes mellitus	10	12
Pernicious anemia	7	6
Moniliasis	7	6
Premature menopause	4	3
Alopecia	3	3
Cirrhosis	1	< 1

* From Blizzard, et al, Clin. Exper. Immun. 2:19, 1967. Fifty-one of 118 patients had one or more associated diseases.

TABLE 7

Antibodies to Parathyroid, Thyroid, and Gastric Tissues in 67 (of 118) Patients with Idiopathic Addison's Disease Alone*

Tissue	Antibody	Percent
Hypoparathyroid	27	40
Thyroid	9	13
Gastric	16	24

* From Blizzard, et al, Clin. Exper. Immun. 2:19, 1967. In 118 cases of idiopathic Addison's disease the percentage of patients with associated disease or its antibody in the absence of the disease was: Hypoparathyroid-45%; Thyroid disease-38%; Pernicious anemia-30%.

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