Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Addison's Disease

Volume XIV | Friday, June 11, 1943 | Number 29

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Volume XIV | Friday, June 11, 1943 | Number 29

INDEX

Published for the General Staff Meeting each week
during the school year, October to June, inclusive.

Financed by the Citizens Aid Society,
Alumni and Friends.

William A. O'Brien, M.D.

I. LAST WEEK

Date: June 4, 1943

Place: Recreation Room, Powell Hall

Time: 12:15 to 1:15 p.m.

Program: "The Mechanism of Muscle Spasm in Poliomyelitis"
Herman Kabat
Miland E. Knapp

Discussion
A. V. Stoesser
Herman Kesting
Durval Vianna

Attendance: 103

Gertrude Gunn,
Record Librarian

\- - -

II. TODAY

With this meeting we complete the 1942-1943 series. This is the fourteenth consecutive year of Hospital Staff Meetings of this type. Because of War conditions there was a 20% reduction in the number of bulletins published each week. The number in attendance decreased slightly in excess of this amount largely because the practice of inviting groups from the Center for Continuation Study to the meetings has been discontinued. There was also a decrease in the number in discussion for reasons which are not obvious. In spite of these shifts the year's program has been outstanding. Interest in our meetings extends throughout the city and state and to many of the adjoining states. Our bulletins have been read by those in foreign service as well as those in army camps in the states. There have been many changes in the staff during the year. Interns and fellows have come and gone. In most instances no record has been made of these fluctuations. Largely because it seemed that it is in the order of things to be at your post of duty no matter where it happens to be. Many of the Staff Meeting Bulletins have appeared in the teaching manuals of those in attendance at the courses in the Center for Continuation Study. It is good to know that the various clinical contributions are of interest to others. Critics tell us they enjoy our way of trying to find the truth without discovering something which has dramatic value. In other words, we have nothing to sell. It is difficult to single out any one for special mention without omitting others whose contributions are of equal merit.

May I at this time thank everyone who in any way contributed to the success of these meetings. They would not be possible without the endorsement and support of the University administration represented by the dean of the Medical Sciences and the superintendent of the University Hospitals, and the various departmental and divisional heads and directors. Powell Hall has graciously permitted us to use their facilities each week. The Housekeeping department has set up the room, the Dietitotic department has served the buffet luncheons, the Record Room has been responsible for the mail service in connection with the bulletins, keeping roll and with administrative details. The stenographic section has taken care of the notes, Visual education has supplied equipment and personnel. Most of all one or more physicians have prepared the manuscript each week and have delivered it before a discriminating audience. To them should go our thanks. Hope to see you next year! Thank you!

William A. O'Brien, Editor

III. ADDISON'S DISEASE

G. T. Evans
E. B. Flink
L. Hoilund

The provocation of this discussion has been the recent reviewing by us of 9 Addison's cases studied on the Medical Service during the past 3 years.

History of Treatment of Addison's Disease[1,2]

Opinion must always be involved in the naming of pivotal points in our knowledge of disease, but many will agree that the combination of surprise and simplicity which entered into the demonstration by Robert Loeb in 1933[3] that common table salt constituted effective substitution therapy in Addison's disease was sufficient to make it a dramatic turning point. In the brief 10 years that have elapsed since then much has been added to the knowledge of the nature and treatment of Addison's Disease.

It would be misleading to imply that significant work on the treatment of Addison's Disease had not preceded the above mentioned demonstration by Loeb. Soddu in 1899 had demonstrated that the symptoms in the adrenalectomized dog were alleviated by saline injections. Lucas in 1924[4] had noted a low blood chloride level in adrenalectomized dogs as did also Rogoff and Stewart[5] in the same year. A year later Bauman and Kurland[6] noted low blood sodium and elevated serum potassium in adrenalectomized animals. Stewart and Rogoff in 1925[7], Corey in 1926[8], Banting and Gairns in the same year[9] and Marine and Bauman in 1927[10] had shown a beneficial effect of intravenous saline in adrenalectomized animals. Harrops, Soffer, and their co-workers[11,12] in 1933 confirmed the observations by Loeb in 1932[13] that there was an outpouring of sodium and chloride in the urine of Addison's patients with an elevation of blood potassium, and these investigators[11] suggested the use of a low salt diet as a provocative test in the diagnosis of Addison's Disease.

In 1936 Wilder, Snell, Kepler, Rynearson, Adams, and Kendall[13a] demonstrated the advantage of a low potassium intake combined with high sodium chloride intake in the control of Addison's disease.

Also, there had been attempts, some quite successful, to treat Addison's disease with extracts. Addison's original paper was presented in 1849 and in 1867 Stockman attempted extract therapy; however, without success. Adams in 1903[14] collected a total of 97 cases in which organotherapy of one kind or another had been tried. Some of these had apparently been moderately successful, a notable one being reported by Osler in 1896 of a patient who received a glycerol extract of fresh sheep adrenals by mouth and hypodermic injections, and who on discontinuation of the extract went into acute adrenal insufficiency and died. The proven toxic nature of crude adrenal cortical extracts and the inclusion of epinephrine when whole adrenals were used permits one to doubt that these were anything but the most rugged form of therapy.

Early in this century the false hope offered by the isolation of pure epinephrine hydrochloride had been explored and abandoned. In 1927 Rogoff and Steward[15] prolonged the survival period of adrenalectomized animals with the use of a saline extract of whole adrenal glands, and Hartmand and his co-workers[16] described a similarly effective extract. In 1929 Pfiffner and Swingle[17] described the successful use of an alcoholic adrenal extract in adrenalectomized dogs. In 1930 Hartman and co-workers[18] described dramatic results obtained in a patient in Addisonian crisis by the use of their extract given subcutaneously and intravenously. In 1931 Rowntree, Green, and Swingle and Pfiffner[19] gave a good account of satisfactory results obtained in Addison's patients treated with extract prepared according to the method of Pfiffner and Swingle. Since that time constantly improved extracts have appeared, notably those of Kendall and of several pharmaceutical houses. In 1936 and 1937 Mason, Myers, and Kendall[20] and deFremery et al.[21] isolated corticosterone and dehydrocorticosterone in crystalline form from extracts of adrenal cortex. Other crystalline materials notably the compound E of Kendall have been prepared. Steiger and Reichstein in 1937[22] prepared desoxycorticosterone synthetically using stigmasterol as the starting substance and Reichstein and von Euw[23] recovered some of this compound from an extract of adrenal cortex. Early successful applications of "DOCA" were made by Levy, Simpson[24], Thorn, Engel, and Eisenberg[25], Thorn, Howard and Emerson[26], Ferrebee, Ragan, Atchley, and Loeb[27], Soffer, Engel and Oppenheimer.[28] In 1939 Thorn, Howard, Emerson and Firor[29], taking their clue from Deansley and Parkes[30] who had implanted pellets of estrogens and androgens subcutaneously, prepared pellets of DOCA and implanted them subcutaneously in 6 patients with Addison's Disease.

Essential Disturbances in the Adrenalectomized Animal

The adrenalectomized animal has been the subject of considerable study since the middle 1920's. It cannot be said that the fundamental disturbance has been elucidated any more than is the case for insulin in diabetes or for liver extract in pernicious anemia, but the search has narrowed down considerable. Among satisfactory reviews of the subject are those of R. F. Loeb[31], E. C. Kendall[32,33], Hartman,[34] Kepler and Wilson,[35] Long, Katzin, and Fry,[36] Lewis, Kuhlmann, Delbue, Koepf, and Thorn.[37] Taking the rat as a typical example the adrenalectomized animal remains apparently normal in respect to appetite and behavior for the first few postoperative days and then manifests weakness, loss of appetite, lowering of temperature, diminution of the metabolic rate, hemoconcentration, weight loss and dies in 5 to 9 days. None of this sequence of events takes place if only the medulla has been removed. Even before the general decline in the animal's condition is obvious, it is hypersusceptible to heat, cold, anoxia, small doses of toxic substances, exercise and stress in almost any form. With all due allowance for its brevity the fundamental disturbances in adrenalectomized animals are approximately as shown in the following table:

Table I

1. Handling of water and electrolytes:		
a. Excretion (kidney)	Sodium Chloride	Increased excretion despite low blood levels
	Potassium Urea	Deceased excretion despite elevated blood values.
b. Absorption	Diminished rate of absorption particularly shown for glucose solution.	
c. Distribution of fluid and electrolytes within the animal	Still a matter for debate, but evidence favors a defect separate from a. and b.	
2. Muscle weakness		
a. DeFremery Test	Immediate defect on first stimulation.	
b. Ingle Test	Eventual inability to respond to brief often-repeated stimuli.	
3. Carbohydrate metabolism.	Enhanced oxidation. Decreased storage. Failure of gluconeogenesis.	

Maintenance with Sodium Chloride

If adrenalectomized animals are maintained with 1% sodium chloride as drinking water they appear normal in respect of growth, appetite, and activity and have normal fluid contents and distribution of electrolytes as far as can be shown. They resist various forms of stress definitely better than untreated animals. By the exercise test of Ingle, and by inability to resist the deleterious effects of hemorrhage on glucose absorption, they can be shown still not to be normal animals. The carbohydrate defects are still fully manifest. They are still deficient in their resistance to anoxia, cold, and toxic materials.

Maintenance with DOCA

Animals maintained with desoxycorticosterone acetate, live indefinitely, and are vigorous. With an overdose of DOCA they retain more than an ordinary amount of sodium and water, and the serum potassium may be lowered. They are now remarkably resistant to the usual forms of stress. The defect, however, in respect to carbohydrate metabolism is not at all repaired and coupled with this the prolonged exercise test of Ingle shows them to be abnormal.

Maintained with Whole Cortical Extract

If the animals are maintained with whole adrenal cortical extract complete replacement therapy seems to have occurred. The carbohydrate defect is remedied, they tolerate the prolonged exercise test very well. The absence of the medulla would seem to be of minor consequence.

Compound E and dehydrocorticosterone are examples of steroids having an oxygen on carbon 11 (compare corticosterone and desoxycorticosterone). Desoxycorticosterone, the synthetic substance, differs from dehydrocorticosterone in the absence of an oxygen at carbon 11.

The following table modified from Kendall states the differential effects which have been shown for the main groups of compounds:

Table II

Physiologic actions of adrenal steroids

Compounds with oxygen on C 11	Maintains apparent vigor well	++
	Prepotent for carbohydrate and Ingle effect	++++
	Maintains electrolytes - not selectively	+
DOCA	Maintains apparent vigor well	++
	No carbohydrate effect and little Ingle effect	0
	Prepotent for retention of water and electrolytes and deFremery effect	++++
Amorphous fraction	Maintains apparent vigor - very well	++++
	Little action on carbohydrate and Ingle effect	(+)
	Maintains electrolytes	++
	Prepotent for kidney function	++++

(Modified from Kendall)

So far as investigation has gone Compound E would appear to be the most generally potent compound. It is typical of those compounds which have an effect upon the carbohydrate mechanism. It is possible by injection of compound E in a normal animal to cause protein to be converted into carbohydrate which is stored to super normal levels. Although not particularly potent in respect to maintenance of electrolyte levels and in its effect upon the kidneys it nevertheless has definite activity in these respects. Its synthetic preparation would undoubtedly represent a great advance in the treatment of Addison's Disease and would reopen investigation in directions in which desoxycorticosterone acetate has been tried and found wanting.

Clinical Addison's Disease

Limitation of time prevents the supplying of detailed references to cover the various points discussed. Current knowledge of the disturbance and of its diagnosis has been discussed by Kepler and Willson[35]: Thorn, Dorrance and Day[37a]: Loeb[31]: Ferrebee, Ragan, Atchley and Loeb[27]: Soffer, Engel and Oppenheimer.[28]

Etiology

The traditional belief that Addison's Disease was due to tuberculosis of the adrenals has undergone severe modification. Conybeare and Millin[38] in 1924 found on autopsy in 29 cases of Addison's Disease that 24% were nontuberculous. Rowntree and Snell[39] found 16% to be nontuberculous in 39 autopsies. Kepler and Willson[35] commenting on autopsy records that had accumulated between the years

1930 and 1937 say that "cortical atrophy now accounts for about half of the cases of fatal Addison's disease, whereas formerly tuberculosis was the etiologic factor in 90% of the cases." Thorn et al.[40] in 89 cases diagnosed 60% as being nontuberculous: they had 14 autopsies showing 100% accuracy in the etiologic diagnosis and of these 14, 50%, were nontuberculous. In our 9 cases, however, 8 were tuberculous of which one was confirmed at autopsy, 1 was of doubtful etiology possibly tuberculosis, and 1 was nontuberculous. The literature contains no very positive suggestions to account for the increase in the non-tuberculous variety. It is, however, now being more clearly recognized (Tepperman, Engel, and Long[41]: Selye[42,43] that the adrenal cortex is a fluctuant organ responding readily to many different stimuli.

Diagnosis

Thorn[4] has given an analysis of the frequency of symptoms in 64 patients with Addison's disease which he studied at the Johns Hopkins Hospital (Table III).

Table III

Analysis of Symptoms in 64 Patients with Addison's Disease

	Number	Per Cent
Weakness and fatigability	64	100
Increasing pigmentation	60	94
Anorexia	58	91
Nausea	55	86
Vomiting	48	75
Constipation	21	33
Abdominal pain	20	31
Diarrhea	10	16
Salt craving	10	16
Muscle pain	8	13

A number of recent reviewers give but little attention to the changes in axillary and public hair. In our series it has been quite consistent to find either that the hair in these regions was scanty or had markedly diminished. This deserves comment because of the obvious relationship to masculinizing function resident in the adrenal cortex. It contrasts with the hirsutism characteristic of adrenal cortical tumors and with those cases of Addison's Disease occurring in pseudohermaphroditism associated with hyperplasia of the adrenal cortex.

Blood Pressure

Barring crisis it is not found with any degree of regularity that the blood pressure in Addison's disease is under 90/60 and since blood pressure levels such as these are frequently seen in patients who do not have Addison's disease, the low blood pressure unless associated with other characteristic signs and symptoms is not of much diagnostic aid. The difficulty of obtaining good blood pressure readings by the auscultation method in uncontrolled Addison's is such as almost to constitute a useful diagnostic sign. The character of the pulse is much altered. In crisis when the blood pressure is unobtainable by auscultation the method of palpation may reveal a systolic pressure of 70 to 80. Our experience with blood pressure findings is shown in Table IV.

Table IV

Initial Blood Pressure and Pigmentation in 9 Cases of Addison's Disease

Case	Pigment	Blood Pressure	
HB	+	122/90	°
EJ	?	78/52	
MF	+	110/68	°
EB	?	96/68	
KH	+	105/60	°
FZ	+	98/74	
AG	+	94/65	
MH	+	94/72	
CW	+	100/70	

° Hypertensives as judged by history and course.

If the diagnosis of Addison's Disease were to depend upon 1. weakness, 2. a suggestively low blood pressure, and 3. gastrointestinal symptoms, the diagnosis would be risky in many instances. The frequent association of pigmentation (7 of our 9 cases) renders the diagnosis safe in the majority of cases. Before proceeding with a brief review of chemical features and tests which have been investigated in recent years, one might reasonably inquire why all the effort has been made. In the first place the 94% occurrence of pigmentation quoted by Thorn is from a series of cases from which all doubtful cases have been excluded. According to experience at the Mayo Clinic laboratory diagnostic aids are required in about 20% of cases. In the second place the disease is a serious one carrying a heavy prognosis, the extent of the disease needs quantitation and the clinician usually desires extra assurance before starting the patient out on a long, expensive troublesome therapy. In the third place the desire has been to see whether the diagnosis can be of value in borderline asthenic states. The chief value of the more recent tests is in the exclusion of Addison's disease. Thus, Willson, Robinson, Power and Wilder[44] (Archives of Internal Medicine 69:460, 1942) were able to exclude Addison's disease in 20 of 44 patients who came to the Mayo Clinic carrying a diagnosis and being treated for Addison's disease.

Blood Chemistry

In Table V average values of the significantly altered blood chemistry as culled from the literature are shown as compared to the average and range of normal.

- - - -

Table V

Serum electrolytes in Addison's Disease

Milliequiv/L

	Normal Average	Normal Range	Average in Addison's	Relative Diagnostic Value
Na	142	137-147	132.3	+++
K	5	4.5-5.7	5.7	+(+)
Ca & Mg.	8	small	N	
Total Base	155	150-160	146	+++
Cl	103	99-108	97.5	+
CO_2	27	23-31	24.2	+
$HPO_4''+SO_4''$	3	small	N	
Organic	6	small	N	
Protein	16	± 1.5	N±	
Total Anion	155		146.7	

The relative importance of altered values for given constituents has been rated. When it is considered that the diagnosis of Addison's disease must be made in a person who has not been eating well or who has had vomiting or diarrhea, it is perhaps not to be wondered at that the blood chemical findings are frequently not sufficiently characteristic as to make a diagnosis much more certain. Although the blood sugar in Addison's disease is frequently low and the blood urea nitrogen occasionally elevated, these findings together with that of the basal metabolic rate cannot be relied upon too greatly in view of other possible causes.

In our 9 cases the blood chemical findings deserve brief comment as follows:

Tablo VI

Initial Blood Chemistry in Cases of Addison's Disease

Case	Na	K	Total Base	Cl	CO_2	B.U.N.	Glucose	Remarks
	milliequiv/L					Mg.%		
Normal Aver.	142	5	155	103	27	15	90-95	
Range	137-147	4.5-5.7	150-160	99-108	23-31	8-22	80-100	
	136°	6.8°		101	22	32°	81	
	142			103	24	19	114	
		5.0	142°	108		6	66°	Mild crisis
				101		19		
		9.1°		103				
				101	18°	37°		
						51°	82	Near crisis
			146	108	28	12	78	
			133°	102		13	62°	
		5.0		100		16	72°	
		6.8°		92°	14°	21		Crisis
		5.1		98		59°		
		7.7°	148	100	23	17	71°	Crisis
				102		8	71°	Some re-cent
				98	25	9	91	treatment
		4.3	136°	104	22			

° Instances in which blood chemical findings typified Addison's disease.

Special Tests and Diagnostic Devices

1. A provocative test consisting of a 6-day period of restriction of salt for the production of Addisonian symptoms was proposed by Harrop, Weinstein, Soffer, and Trescher[45]. This undoubtedly was a very good test but proved so dangerous that it has been abandoned.

2. Growing out of the above salt restriction test a 52-hr. test was devised by Cutler, Power, and Wilder.[46] This is the so-called Wilder test employing a low sodium, high potassium diet, with added potassium citrate and forced fluid. It is a measure of the ability of the normal individual to retain sodium and chloride despite attempts at potassium and water diuresis. The Addison's patient fails in this respect. The test is conducted as follows:

On the day preceding the first day of the test the patients received a general diet, without extra sodium chloride or adrenal cortical extract. If patients had been receiving desoxycorticosterone acetate, the use of this substance was discontinued at least forty-eight hours prior to the test in the examination of all except 3 of the patients who had Addison's disease.

On the first day of the examination and daily thereafter until its completion, a standard weighed diet was served which, by calculation, provided 0.95 Gm. of chloride, 0.59 Gm. of sodium and 4.1 Gm. of potassium. The fluid intake was not measured on the first day, but the free drinking of water was encouraged.

On the afternoon of the first day 33 mg. of potassium per kilogram of body weight (15 mg. per pound) was administered in the form of potassium citrate dissolved in a glass of water (1 Gm. of potassium citrate provides 362 mg. of potassium).

On the second day the intake of fluid was maintained at 40 cc. per kilogram of body weight distributed over the waking hours. The same dose of potassium citrate that had been administered on the previous day was repeated on the morning of the second day.

On the third day 20 cc. of fluid per kilogram of body weight was administered before 11 a.m. Urine was collected between 8 a.m. and 12 noon on the third day. At 12 noon blood was drawn for analysis. The patient was weighed daily.

These studies have been conducted in the hospital in order that the patients might be under constant observation for the development of signs of impending crisis. In those instances in which crisis did develop blood was drawn for analysis and 1,000 cc. of a special solution was administered intravenously. This solution consisted of 5 per cent dextrose and 0.85 per cent sodium chloride to which had been added approximately 5 Gm. of sodium citrate (ampules of sterile sodium citrate utilized as an anticoagulant for blood transfusions are convenient) and 20 cc. of an active extract of the adrenal cortex.

- - -

Diet Employed in the Standardized Diagnostic Procedure°

	Breakfast	Dinner	Supper	Potassium	Sodium	Chloride
Vegetables						
Canned tomatoes		90		0.27	0.01	0.034
Lettuce		10	10	0.06	0.005	0.015
Canned Peas			100	0.125	0.013	0.024
Baked potato		100	100	1.000	0.042	0.076
Fruit						
Peaches		100		0.125	0.022	0.004
Oranges	100			0.2	0.012	0.006
Grapefruit			100	0.2	0.004	0.005
Bananas			100	0.400	0.034	0.125
Bread, salt free	50	30	30	0.110	0.073	0.127
Jello		150				
Butter, salt free	10	10	10	0.003	0.012	0.049
Cream, 20 per cent	25	25	75	0.158	0.044	0.1
Milk			200	0.3	0.102	0.212
Coffee, medium	300	200		0.5		
Eggs	1			0.07	0.071	0.053
Beef, lean (weight before cooking		75	50	0.465	0.131	0.117
Jelly	20	20	20	0.076	0.008	0.002
TOTAL				4.062	0.592	0.949

° All quantities are measured in grams.

The authors followed the changes in sodium, chloride, and potassium in blood and urine in cases of Addison's Disease and in control series of normals, patients with tuberculosis, and in cases of asthenia without Addison's disease. It developed that the Addison's cases separated themselves clearly from the others in respect to the concentration of sodium per 100 cc. in the urine during the last four hours of the test. Fortunately for analytical ease, the concentration of chloride in this specimen of urine had almost equal diagnostic significance. Expressed in terms of sodium chloride the concentration of chloride in this last 4 hours of urine ranged in the cases without Addison's disease from 28 to 232 mg.%: for the Addison's cases the values ranged from 378 to 587 mg. per 100 cc. Further application of this test has been reported in a second paper by Willson, Robinson, Power, and Wilder[47]. To date, of 16 patients with Addison's disease, only 1 patient has responded atypically but this was in a patient whose blood sodium was so depressed as to be diagnostic in itself. Of 44 patients examined who did not have Addison's disease only 1 gave results which suggested Addison's disease and in this patient, prolongation of salt restriction without precipitation of crisis aided in exclusion of Addison's disease. A number of patients with Addison's disease but treated with DOCA subjected to the test gave results similar to those of normal subjects. The chief value of the test would seem to lie in the exclusion of Addison's disease in many cases in which the diagnosis has been found troublesome. Our experience with this test is summarized as follows:

The 52-hour salt deprivation test of Cutler, Power, and Wilder for adrenal insufficiency was carried out twenty-five times in 22 patients. Entirely normal tests were obtained in 13 patients with asthenia in whom the diagnosis of Addison's disease was considered; in these the urine NaCl concentration ranged from 220 mg. to 40 mg.% for the final period. There were 3 patients with other diseases used as control material.

The test was carried out 8 times in 5 patients with Addison's disease. In 3 instances the test had to be discontinued because of symptoms and signs of impending crisis. In the 5 instances in which the test was completed unequivocally abnormal results were obtained: the final urine NaCl concentration ranging from 272 mg.% to 576 mg.%. The test was not carried out on the other 5 patients either because of clear-cut signs of Addison's disease, definitely positive water test (2 patients) or the supervention of crisis (3 patients).

In one patient in whom the diagnosis of Addison's disease was not made, the test was positive. This patient besides having nephritis was, at the time of the test, febrile with bronchopneumonia. There was visible calcification of the upper pole of one kidney. He was operated and an adenocarcinoma of the kidney was found; nephrectomy was done. He subsequently died and an autopsy was not obtained.

3. It was obvious from the study referred to immediately above that on the average the Addison's cases responded with a far smaller diuresis to the administration of forced fluid than did the normal and control subjects. Robinson, Power and Cutler[48] have explored this lead and devised a test much simpler than the above but which has approximately the same diagnostic capacity. The test divided into two parts called procedure 1 and procedure 2. Procedure 1 is a simple <u>observation of diuresis</u> on a fixed regime. Procedure 2 applies a correction to procedure 1 by taking advantage of the tendency of the kidney in Addison's disease to retain urea and spill chloride. The tests are conducted as follows:

"The water test." On the day before the test the patient eats 3 ordinary meals but omits extra salt. He is requested not to eat or drink anything after 6 o'clock in the evening. Until this time he may drink water as desired. At 10:30 p.m. he is requested to empty his bladder and discard the urine. All urine which is voided from then on until and including 7:30 a.m. is collected. The volume of this urine is measured and saved for chemical analysis if this should be necessary later. Breakfast is omitted. The patient is asked to void again at 8:30 a.m. and immediately thereafter he is given 20 cc. of water per kilogram of body weight (9 cc. per pound). He is asked to drink this within the next 45 minutes. At 9:30, 10:30, 11:30 a.m. and 12:30 p.m. he is requested to empty his bladder. In order to eliminate the effects of exercise and posture on urinary excretion, he is kept at rest in bed except when up to void. Each specimen is kept in a separate container. The volume of the largest one of these four specimens is measured.

Under these conditions some patients having Addison's disease will excrete so little urine that they are unable to void more than once or twice during the entire morning. In such instances the amount of urine excreted per hour may be calculated; frequently however, such calculations are unnecessary because of the very low urinary output throughout the entire morning.

Inferences that may be drawn from procedure 1.-- These are as follows:

(1) If the volume of any single hourly specimen voided during the morning is greater than the volume of urine voided during the night, the response to the test is negative, that is, such a response indicates the absence of Addison's disease. Thus far we have not encountered any exceptions to this rule. (2) If the volume of the largest hourly specimen voided during the morning is less than the volume of urine voided during the night, the response to the test is positive, that is, Addison's disease may or may not be present. To establish the diagnosis procedure 2 should be instituted.

Procedure 2 (Based on Chemistry of Blood and Urine)

To carry on with this procedure blood is drawn (preferably under oil) while the patient is still fasting, and the plasma analyzed for its content of urea and chloride. The specimen of urine which was voided during the night is also analyzed for urea and chloride. From these four determinations and from the results obtained from Procedure 1 the following equation is solved:

$$A = \frac{\text{Urea in urine (mg. per cent)}}{\text{Urea in plasma (mg. per cent)}} \times \frac{\text{Chloride in plasma (mg. per cent)}}{\text{Chloride in urine (mg. per cent)}} \times \frac{\text{Volume of day urine (c.c.)}}{\text{Volume of night urine (c.c.)}}$$

The term "day urine" applies to the largest of the hourly specimens voided during the day; "night urine," to the entire amount which was voided from 10:30 p.m. to 7:30 a.m. It is immaterial how these values are expressed provided that the same method be used throughout the equation. For example, if the concentration of plasma chloride is expressed as milligrams of sodium chloride per 100 c.c. the concentration of urinary chloride should be expressed in the same manner.

Inferences that may be drawn from Procedure 2.-- These are as follows: (1) If the value of A in this equation is greater than 30, the patient probably does not have Addison's disease. (2) If the value for this equation is less than 25, the patient probably has Addison's disease provided that nephritis has been excluded.

If the results of procedure 2 are at all equivocal or if they are not indicative of Addison's disease when there is strong clinical evidence to the contrary, the test devised by Cutler, Power and Wilder may be conducted. This can be instituted immediately. When this is done, none of the patient's time is wasted since the day of the "water test" constitutes the first day of the provocative test. Thus far we have encountered only two instances in which it was necessary to resort to the Cutler, Power, Wilder test and in these cases it also yielded indecisive results.

Our experience with this test has been more limited than with the 52-hour Wilder test. However, we have found it to be positive in cases of Addison's disease, to be negative in cases of Addison's disease which was being treated and to check with the results obtained by the 52-hr. Wilder test.

4. Blood Volume and Heart Size

The result of the disturbances in salt and water control are such that the Addison's patient becomes relatively dehydrated. This dehydration is not severe but it is long continued and makes itself manifest not only in the interstitial fluid but also in the contraction of blood volume. This reduces blood volume and hemoconcentration has been conceded by all investigators to be of regular and early occurrence in adrenalectomized animals and in Addison's disease. As a consequence of this contraction in blood volume and possible also as a result of vascular asthenia the heart size diminishes: this has received the particular attention of McGavack[51]. We have found observation of these two points to be considerable help in the diagnosis, and together with observations of weight change they have been particularly helpful in regulating therapy. As a result of their consistent use the one-sided nature of the action of DOCA has been called to particular attention and as a consequence we find that we share with Engel, Cohn and Soffer[52] a belief in the more conservative use of DOCA than has been generally advocated.

In 6 of the 9 patients in whom Dr. Rigler found the measurement to be applicable the cardiac thoracic rations were: .32, 137°, .36°, 137), .31, .35. In conformity with McGavack's findings these values for Addison's cases are all under 0.4. The cases marked with an asterisk are those whose history or subsequent course indicated that there had been a preceding hypertension.

The observations on blood and serum volume are shown in Table VII.

Table VII

Serum Volume and Total Blood Volume in Addison's Disease

Deviation from normal - %		
Untreated		
	Ser. Vol.	Bl. Vol.
	-9	-16..(recent therapy)
	-33	-38
	-28	-40
	-23	-18
	-21	-27
	-16	-19
Treated		
	- 6	-16
	- 1	-15
	+ 2	-12

The total blood volume is the most depressed in the untreated cases since it reflects both the hemoconcentration and the anemia frequently seen in Addison's disease. On the basis of a few cases it would appear that the return of serum volume to normal is a useful guide in following treatment.

These points will be touched on again in connection with the discussion of therapy and in presenting charts showing the detailed findings in certain patients who have particularly studied.

5. 17 - ketosteroids

The 17-ketosteroids are a chemically characteristic group which derive in large part from the adrenal and to a lesser extent from certain fractions of the gonadal hormones. In severe hypogonadism they are decreased although by no means abolished[49]. We have examined four of the present cases of Addison's disease and find that the total 17-ketosteroids are at such low levels that the amounts found might represent merely the error of the method. This accessory observation may well prove to be a valuable diagnostic point. They have been particularly followed in studies with Dr. Samuels and Dr. McKelvey in three women, in two throughout the menstrual cycle, and in one during the course of pregnancy and successful parturition. This work has already been published (Samuels, Evans and McKelvey Endocrinology[5]) and has shown contrary to previous supposition that the ovary and placenta exhibit normal cycles of steroid function in the absence of significant adrenal function and without any rhythm being obvious in the ketosteroid function of the adrenal. The symptoms, signs and positive tests of Addisons' disease were abolished during pregnancy only to return undiminished in the puerperium. It was interesting therefore to observe in one of the other women that progesterone, which has been reputed to have salt and water regulating properties, when administered in daily doses of 10 mg. allowed the patient to go slowly into Addisonian crisis.

Diagnosis - Summary:

The traditional clinical signs of Addison's disease do not suffice in all instances to permit an accurate diagnosis. Accessory methods have greatly improved the diagnosis, and permit more intelligent control of therapy and study of the cases.

Treatment

There have been many papers presenting the advantages and disadvantages of various forms of management in Addison's disease. A very satisfactory therapeutic symposium has been presented by Thorn, Wilder, Thompson, and Cleghorn.[53] This together with the earlier paper by Thompson, et al[54] covering their experience with adrenal extracts, and the later papers by Thorn, Dorrance and Day[40] and Engel, Cohn, and Soffer[52] present a comprehensive picture of current practice. Time does not permit a full discussion, but the following summary including comment based on recent experience here may be helpful.

Treatment of Crisis is summarized in Table VIII.

Table VIII

Treatment of Crisis

If necessary
- 2 L 5% glucose saline) I.V.
- 20 cc. Adr. Cort. Ext.) I.V.
- 5 gm. Na Citrate (?)
- 10 cc. A.C.E. Subcut. rep. q.h., q2H, prn.
- 10 cc. DOCA in oil I.M.
- 0.2-0.5 cc. 1/1000 epinephrine
- Moderate heat
- Care in withdrawing glucose

If impending only
- Glucose saline or A.C.E. or both

Sharp prompt therapy is necessary to prevent fatality.

Maintenance Management may be summarized as follows:

1. Sodium chloride alone. Supplementary sodium chloride is conveniently given as 1 gm. enteric-coated tablets or may be given in the form of the "elixir" devised by Wilder which consists of 10 gms. of sodium chloride, 5 gms. of sodium citrate with sugar, fruit juice and water to 1 liter. In gauging the amount of sodium chloride which a person receives, the following remarks are pertinent: The average American intake of sodium chloride is stated to be 9 gms. If so, it would appear that most of this comes out of the shaker at mealtime for we have examined the salt intake repeatedly in this hospital for patients on full diet and find that such diets contain, when the usual amount of salting is done in cooking, approximately 4 gms. In regulating salt intake, therefore, we count the basic diet cooked with salt to be 4 gms.; the patient is then given a shaker containing a weighed amount of salt and instructed to notice how many days it takes to consume this amount; added sodium chloride as tablets is then given to a predetermined total. If 9-12 gms. of salt added to the diet or a total of approximately 16-18 gms. does not produce definite results, more specific therapy is indicated. It should be noted that the maximum ability of the

kidney to concentrate sodium chloride is about 3 times which means, therefore, that 1.8% is the maximum concentration in the urine. It follows that urine volume is a useful observation in salt therapy. The salt treatment without any other therapy is occasionally successful in mild cases. An annoying complication may be a diarrhea.

2. Low sodium chloride, high potassium diet. This was introduced by Wilder and gave excellent results. One patient of ours was much better on this therapy than on any other form. The chief and very valid objection to this form of treatment is the very unappetizing character of the diet.

3. Adrenal Cortical Extract

a. Tablets by mouth. This is an inefficient form of therapy but if the price of cortical material were to be reduced would probably be a quite satisfactory one.

b. Adrenal cortical extract in oil. This is a new preparation which so far has had no extensive trial.

c. Watery extract subcutaneously (or intravenously). Thompson who has had the most experience with this form of therapy states that "10-20 cc. are sufficient to maintain life without other therapy." He remarks that more than 20 cc. is necessary for optimal control. For maximum effect adrenal cortical extract should be injected more than once a day; this is usually not done. The inconvenience together with the great cost has limited its use; at 15 cc. a day the cost of annual maintenance would be approximately $2,200. There is some indication that a resistance is built up to this extract. We have reserved its use for periods of emergency.

4. Desoxycorticosterone acetate. The relative effectiveness of different routes of administration has been studied by Thorn, Grief, Coutinho, and Eisenberg.[55] The average daily maintenance doses as found by him are: (1) pellets, 1.2 mg. (2) dissolved in oil, 2 mg. (3) in propylene glycol sublingually, 6 mg. (4) orally, 15 mg. Low potassium diet is contraindicated in any form of DOCA therapy.

a. DOCA in oil. This is given once daily in amounts from 1-7 mg. usually from 2-5 mg. I.M. Amounts greater than this are rarely necessary if the sodium chloride intake reaches 12 gms. This method is inconvenient because of the need for intramuscular injection but it is subject to varied control. The average yearly cost of maintenance, assuming 3.5 mg. to be the daily dose, is approximately $230 a year.

b. Pellets containing 125 mg. of DOCA are implanted subcutaneously. They last approximately for one year and the yearly cost of maintenance would approximate $65. One disadvantage of this form of therapy is that it is not recallable. It is necessary, therefore, to gauge the dose during a period in which DOCA in oil is administered. Thorn determines the number of pellets by assuming that each pellet is equivalent to 0.3 to 0.5 mg. of DOCA in oil. He does not add salt to the diet as a usual procedure, but counts on adding it in a period in which the need for treatment is increased. We have found pellets to be a very satisfactory form of treatment but have followed a more conservative estimate of the number needed. This has been brought about because a relatively high intake of sodium chloride has been used. We have been impressed with the dangers of

DOCA therapy and therefore like to have the salt therapy for recall in times of apparent overtreatment. In emergencies we require that the patient be under medical management and adrenal cortical extract be employed, this being the only entirely safe form of therapy.

c. DOCA in propylene glycol can be administered three or four times a day by placing the appropriate number of drops of a 1% solution under the tongue. We have found it particularly useful in tiding patients over the period immediately preceding a second implantation of pellets.

d. Linguets of DOCA. Particularly because these cause excessive salivation we have not found them to be a satisfactory form for oral absorption as is DOCA in propylene glycol.

5. A combination of high salt intake with (3) or (4). With high salt intake (12-16 gms.) we believe that the requirement of DOCA in oil is under 4 mg., the requirement of pellets is 4 or less, and the requirement of adrenal cortical extract under 10 cc. McGavack and coworkers[56] have shown a reciprocal relation between the requirements of NaCl and DOCA and have found that with an intake of 12 gms. of sodium chloride approximately 3 mg. of DOCA in oil was effective, with an intake of 4 gms. of salt, 12 mg. was necessary, and with the intake below 2 gms. of salt, 23-30 mg. were necessary.

6. Hypothyroidism occurs fairly frequently in Addison's disease and if marked should be treated.

7. The hypoglycemia of Addison's disease is not at all prevented by DOCA and measures, such as frequent feeding, are indicated.

8. A low plasma protein increases the chances of early edema with DOCA therapy. Dietary measures to correct this should be instituted.

9. Anemia is a common feature of Addison's disease and should receive appropriate therapy.

10. Intercurrent infection, operations and pregnancy call for special and energetic management. The presence of a hydropneumothorax in tuberculous patients constitutes a contraindication to full DOCA therapy. Untreated patients are particularly liable to sudden collapse for the most trifling reasons.

REASONS FOR CAUTION IN DOCA THERAPY

The literature has recorded many deaths in patients too energetically treated with DOCA. Thus Loeb with 20 patients receiving 1-7 mg. of DOCA had 6 deaths; one death was due to undertreatment, one to an overwhelming t.b. infection, and 4 were sudden deaths with evidences of cardiac insufficiency. The difference between 3 and 4 mg. seems so small that the percentage change is frequently neglected. Just as 40 mg. of protamine insulin may be dangerous when 30 is the correct dose, so 4 mg. of DOCA can be dangerous when 3 mg. is the correct dose. DOCA is a very powerful but one-sided agent. It can produce edema and lower serum potassium at times when the general well being of the patient gives no indication of overtreatment. The very important carbohydrate defect is not at all remedied by it. In one of our cases with a slow weight gain of 5 pounds, with a heart of normal size, and without any evidences of edema in the eyes, extremities or lungs as judged clinically, a rather surprising lung edema was noted. In another patient without significant edema or marked gain in weight a hypertension was manifest. Our conservatism in the use of DOCA is reflected in the aphorism that it is potent, partial, and perilous.

A Summary of Criteria for Gauging Treatment follows:

1. Improved appetite and improved well-being of the patient.

The literature is full of warnings

of the danger of using this criterion alone; many sudden deaths have been reported when desoxycorticosterone acetate (DOCA) has been the therapeutic material.

2. Increases in blood pressure readings are of course a sign of improvement, but when DOCA is used, the danger of allowing blood pressure to rise too sharply cannot be overemphasized.

3. Edema usually seen first beneath the eyes is to be taken as an indication for a check on therapy. It is usually wise to measure the plasma proteins at such a time.

4. Observation of heart size.

5. Serial hemoglobin determinations used as a measure of changing blood volume.

6. The water test can be repeated as a gauge of therapy.

7. Electrocardiographic changes should be watched. The characteristic EKG changes of Addisonian crisis and of overtreatment with DOCA have not been sufficiently outlined, but deviations from normal do occur and if seen should be used as an indication for caution.

8. Sharp gains in weight will foretell subsequent edema.

9. Any sign of increased venous pressure even to the upper limit of normal indicates that therapy should be reduced.

10. The discharge instructions to the patient should require him to have his blood pressure taken at regular intervals, to follow his weight twice weekly, to reduce therapy or to report back when there has been a sudden gain of 5 lbs. in weight or a total gain of 10 lbs; on the first sign of infection or illness he should increase the salt intake and report promptly.

Results of Therapy

It is too early to give any long time evaluation. Thorn states the yearly mortality in pellet-implanted patients to be 9% as compared to approximately 30% on earlier forms of therapy and 43% before specific therapy was used. With an average time of observation of two years in our 9 patients, one death has occurred, but one other patient has not been heard from and when last seen was in very poor condition.

We are indebted to Dr. C. J. Watson for providing the opportunity to make these studies. The generosity of Dr. Max Gilbert of the Schering Corporation, and of Dr. Ernst Oppenheimer of the Ciba Company for pellets and other preparations of desoxycorticosterone is acknowledged.

The Case Summaries will be included in a special supplement.

It is not the purpose to recount them in detail as such.

\- - -

References

1. Soffer, Louis J. and Engel, Frank L. J. of Mount Sinai Hospital, 9:11,'42.
2. Wilder, R. M. Proc. Staff Mtgs. Mayo Clinic, 15:273,'40.
3. Loeb, R. F. Proc. Soc. Exper. Biol. & Med., 30:808, '33.
4. Lucas, G. W. H. Am.J.Physiol., 77:114, '26.
5. Rogoff, J. M. and Stewart, G. N. Am.J.Physiol. 78:711, '26.
6. Bauman, E. J. and Kurland, J. J. Biol. Chem., 71:281, '27.
7. Stewart, G. N. and Rogoff, J. M. Proc. Soc. Exper. Biol. & Med., 22:394, '25.
8. Corey, E. L. Proc. Soc. Exper. Biol. & Med., 24:206, '26.

9. Banting, F. G. and Gairns, S.
Am. J. Physiol., 77:100, '26.
10. Marine, D. and Bauman, E. J.
Am. J. Physiol.,81:86, '27.
11. & 45. Harrop, G. A., Weinstein, A.,
Soffer, L. J. and Trescher, J. H.
J.A.M.A., 100:1850, '33.
12. Harrop, G. A., Soffer, L. J.,
Ellsworth, R. and Trescher, J. H.
J. Exper. Med., 58:17, '33.
13. Loeb, R. F.
Science, 76:420, '32.
14. Adams, E. W.
Practitioner, 71:472, '03.
15. Rogoff, J. M. and Stewart, G. N.
Science, 66:327, '27.
16. Hartman, F. A., MacArthur, C. G.,
and Hartman, W. E.
Proc. Soc. Exper. Biol. & Med.,
25:69, '27.
17. Pfiffner, J. J. and Swingle, W. W.
Anat. Rec., 44:225, '29.
18. Hartman, F. A., Aaron, A. H.,
and Culp, J. E.
Endocrinology, 14:438, '30.
19. Rowntree, L. G., Greene, P. H.,
Swingle, W. W. and Pfiffner, J. J.
J.A.M.A. 96:231, '31.
20. Mason, H. L., Myers, C. S. and
Kendall, E. C.
J. Biol. chem., 116:267, '36.
21. De Fremery, P., Laqueue, E.,
Reidistein, T., Spanhoff, R. W.,
Uyldert, I. E.
Nature, London, 139:26, '37.
22. Steiger, M. and Reichstein, T.
Helvet, Chem. Acta, 20:1164, '37.
23. Reichstein, T. and Von Euw, J.
Helvet. Chem. Acta, 21:1197, '38.
24. Levy-Simpson, S.
Lancet, 2:557, '38.
25. Thorn, G. W., Engel, L. L., and
Eisenberg, H.
J. Exper. Med., 68:161, '38;
Endocrinology, 25:39, '39.
26. Thorn, G. W., Howard, R. P., and
Emerson, K., Jr.
J. Clin. Investigation, 18:449, '39.
27. Ferrebee, J. W., Ragan, C., Atchley,
D. W., and Loeb, R. F.
J.A.M.A., 113:1725, '39.
28. Soffer, L. J., Engel, F. L., and
Oppenheimer, B. S.
J.A.M.A., 115:1860, '40.
29. Thorn, G. W., Howard, R. P., Emer-
son, K., Jr., and Firor, W. M.
Bull.Johns Hopkins Hosp.,64:339,'39.
30. Deansley, R. and Parkes, A. S.
Lancet, 2:607, '38.
31. Loeb, R. F.
J.A.M.A., 116:2495, '41.
32. Kendall, E. C.
J.A.M.A., 116:2394, '41.
33. Kendall, E. C.
Arch. of Pathology, 32:474, '41.
34. Hartman, F. A.
J.A.M.A., 117:1405, '41.
35. Willson, Donald M. and Kepler, Edwin J.
Arch. of Int. Med., 68:979, '41.
36. Long, Katzin, and Fry
Endocrinology, 26:309, '40.
37. Lewis, Roger A.,Kuhlmann,Daniel, Del-
bue, Carlos, Koepf, George F., and
Thorn, George W.
Endocrinology, 27:971, '40.
38. Conybeare and Millis
Guy's Hospital Report, 74:369, '24.
39. Rowntree and Snell
"A Clinical Study of Addison's Disease"
Mayo Clinic Monogram, '31.
40. Thorn, G. W., Dorrance, and Day
Annals of Int. Med., 16:1053, '42.
41. Tepperman, Engel, and Long
Endocrinology, 32:373, '43.
42. Selye, Hans
British J. of Exper. Path., 17:234,'36
43. Selye, Hans. J.A.M.A. 115:2246,'40.
44. Willson, Robinson, Power and Wilder
Arch. of Int. Med., 69:460, '42.
45. Harrop, Weinstein, Soffer and Trescher
J.A.M.A., 100:1850, '33.
46. Cutler, Power and Wilder
J.A.M.A. 111:117, '38.
47. Willson, Robinson, Power and Wilder
Arch. of Int. Med., 69:460, '42.
48. Robinson, Power and Cutler
Proc. of Mayo Clinic, 16:577, '41.
49. Fraser, Forbes, Albright, Sulkowitch
& Reifenstein, J.Clin.Endocr.1:234'41.
50. Samuels, Evans and McKelvey
Endocrinology, 32:422, '43.
51. McGavack, T.H., Am.Heart J.21:1,'41.
52. Engel, Cohn and Soffer
Ann.Int.Med., 17:585, '42.
53. Thorn, G.W., Greif, R.L.,Coutinho, S.O.
Eisenberg, H.,J.Clin.End.1:967,'41.
54. Thompson, W.O.,Thompson,P.K.,Taylor,
S.G.,Hoffman,W.S.,Endoc.24:774,'39.
55. Thorn, G.W.,Greif,R.L.,Coutinho,S.O.,
Eisenberg,H., J.Clin.Endoc.1:967,'41.
56. McGavack, T.H., Charlton, G.Paul, and
Klotz,Solomon, J.Clin. End.1:824.'41.
57. McCullagh, E. Perry
J.A.M.A., 114:2530, '40.

IV. CASE REPORTS

Case 1.

, female, age 23. A young woman who first noted symptoms of Addison's disease during the later part of her first pregnancy in 1938. She went through a second pregnancy uneventfully in 1941 and her history is given in some detail.

First Admission, May 3, 1939 to June 23, 1939.

History: During a first pregnancy in 1938, she began to have increased pigmentation of her skin, weakness, and fatigability. Following delivery she continued to have vaginal bleeding for 3 months and later a profuse vaginal discharge. The weakness persisted and progressed. Early in April, 1939, after some loss of weight, she suddenly developed a marked anorexia, became so weak and faint that she had to go to bed, and was hospitalized at a tuberculosis sanitorium with a diagnosis of active pulmonary tuberculosis. Definite haliphagia began in 1937.

Past History: Diagnosis of healed pulmonary tuberculosis by x-ray during school days. Family history of tuberculosis. Menstrual history normal until pregnancy.

Physical Examination: On admission there was evidence of malnutrition, chronic illness, diffuse pigmentation of the skin with accentuation in the folds and over extensor surfaces, and patchy pigmentation of the buccal mucosa. Her temperature was 101° on admission and usually rose above 99° daily. The pulse averaged 100/minute. The blood pressure was 100/70 on admission and averaged 90-110/60-70. General physical and neurological examinations were negative except for the lungs where there were a few inconstant fine rales and dullness in the right interscapular area. Pelvic examination showed retroversion of the uterus and cervical erosion.

Laboratory Examination: Wassermann, negative. Routine urinalysis negative. Hemoglobin, 12.2 gms.%. Erythrocytes, 3,700,000; leukocytes, 12,400; N. 58%; L. 37%; M. 2%; E. 3%. The electrocardiograph showed diminished amplitude of the complexes in all leads. Plasma chlorides were 568 mg.% on admission and 544 mg.% 24 hours after starting the 52-hour salt deprivation test of Cutler, Power and Wilder which was discontinued because of near crisis with nausea, vomiting, abdominal cramps, and a fall of blood pressure to 82/56.

Course in Hospital: Prompt relief was obtained from the above symptoms by administration of 15 cc. of cortical extract given intravenously. There was considerable improvement in her general condition on a high sodium-low potassium diet, and she was discharged on this regime after successful institution of pneumothorax resulting in adequate collapse of the right lung.

X-Ray: Bilateral apical pulmonary tuberculosis more marked on the right side. Calcified area in both adrenals. "Drop" heart, cardiothoracic ratio, 0.33.

Interim Course:
She returned to a tuberculosis sanitorium (July, 1939 to April, 1940). During 1940 she had constant symptoms of Addison's disease: diarrhea, some nausea frequent abdominal cramps, and weakness. She was then seen in the Outpatient Department and given desoxycorticosterone acetate in oil intramuscularly daily for 6 weeks; 5 mg. were given per day for 10 days and then 10 mg. per day for the rest of the time. During this time she was in a rest home eating a general diet without any prescribed addition of salt. On this regime there was definite and prompt symptomatic improvement with a weight gain of 13 lbs., no edema, no gastrointestinal symptoms, regular menstrual periods, blood pressure 100-120/68-84. On 11/20/40 six pellets of desoxycorticosterone acetate (450 mg.) were implanted subcutaneously, and on a general diet without added salt this resulted in continued improvement.

Second Readmission: 3/5/41 to 12/23/41.

In early January, 1941 she became pregnant (L.M.P. Dec. 25, 1940) and was admitted for the present study. Her spontaneous intake of NaCl while the pellets were in place had been judged by urinary excretion of chloride, 12 gm. daily. The pellets were then removed for purposes of evaluation, and she was put on a measured intake of 12 gm. of NaCl daily. During 18 days on this regime there was no manifestation of Addison's disease as judged by symptoms including a standardized test of fatigability, chloride balance, blood pressure, weight changes, heart size, blood volume, and the absence of hemoconcentration. As a further test she was allowed to go home for 4 days during which time no therapy was prescribed; she returned well and without change in the above stated criteria of cortical insufficiency. It appeared, therefore, that pregnancy was accompanied by a definite improvement of her Addison's disease. To check this judgment further she was treated for 22 days with 4 mg. of desoxycorticosterone acetate in oil by intramuscular injection together with an increase of NaCl up to 16 gm. and for 4 days of this time with 2.5 cc. of Wilson's cortical extract subcutaneously. This resulted in a weight gain of 5 lbs., minimal edema, an initial slight positive balance of chlorides, a minimal hemodilution, but her blood pressure, heart size, and state of well-being and strength showed no significant change. A low potassium, high sodium diet for 5 days also was without apparent effect on her condition. At the conclusion of these tests, she was transferred to the obstetrical service of Dr. J. L. McKelvey and for the rest of her pregnancy was placed purely as a precautionary measure on 6 mg. DOCA in propylene glycol sublingually with a general diet including 10 gm. NaCl daily; on this regime she continued well and ambulatory. On her admission in 1939 she weighed 113 lbs., during the present admission when under satisfactory treatment for Addison's disease both before pregnancy and during the early months of pregnancy she weighed 125 lbs. Her weight before delivery was 152 lbs.

On 10/22/41 she was delivered spontaneously (4 hrs. labor) of a normal male child. In addition to the continuance of DOCA in propylene glycol and NaCl as last stated she was given intramuscularly 25 cc. of Wilson's cortical extract during labor and 9 cc. daily for 4 days thereafter, followed for 10 days by 5 mg. of DOCA in oil intramuscularly. Severe follicular tonsillitis (streptococcus haemolyticus) occurred on the 8th day post partum but was successfully treated. Her weight during the second month post partum was 135 lbs. down to 130 lbs. She was transferred back to the metabolic service on the 15th day postpartum when therapy was stopped, and she was subjected to the 52-hr. salt deprivation tests of Cutler, Power and Wilder which was positive for Addison's disease and chloride of the 48-52 hr. urine being 395 mg.% expressed as NaCl. The daily dose of 5 mg. of DOCA in oil intramuscularly was then resumed but reduced to 3 mg. a day due to the elevation of blood pressure to 134/90 with slight edema. The water test of Robinson, Cutler, and Power done at this time was negative for Addison's disease, the "night-day" ratio of urine volume being 180/270. On 12/13/41 four 75 mg. pellets of DOCA were implanted.

Additional Laboratory Data: Laboratory data were: repeated fasting blood sugar varied from 57-100 mg.%. A blood sugar tolerance test done in the third month of pregnancy while the pellets were still in place, showed fasting, 90 mg.%; $\frac{1}{2}$ hr., 168; 1 hr., 148; 2 hr., 125; $2\frac{1}{2}$, 50 mg.%. Blood sugar tolerance in the eighth month of pregnancy was flat: fasting, 76; $\frac{1}{2}$ hr., 100; 1 hr., 114; $1\frac{1}{2}$ hr., 94; 2 hr., 70 mg.%. Repeated plasma chlorides and CO_2 capacity were for the most part entirely normal and at no time markedly reduced. During the positive Wilder test done post partum after therapy was withdrawn, the CO_2 capacity fell to 51 vol.%, but the chlorides remained normal. Serum potassium was 16.2 mg.% during the third month of pregnancy while the pellets were still in place; it was 15.1 mg.% on the first day post partum and 19 mg.% during the subsequent positive Wilder. Blood volume during the fourth month of pregnancy when no therapy was given was 4.12 liters (the statistical normal for the non-pregnant women of her surface area being 4.04 liters). Basal metabolic rate at this time was +8%. Urine samples showed spontaneous specific gravity up to 1026. PSP in the last month of pregnancy was: 15 min., 35%; 1 hr., 80%. Urine for direct examination and guinea pig innoculation done during the third month of pregnancy and also one month post partum were negative for tubercle bacilli as were repeated sputums and gastric washings. Blood urea nitrogen which at no time in her course has been abnormal were 8.5-11.2 mg.% when she was not pregnant, and 4.0-6.8 mg.% when she was pregnant. Sedimentation rate in the 5th month of pregnancy showed by the Westergren technique a fall of 62 mm. in the first hour; in the first month post partum the sedimentation rate was 104 mm. Vitamin C concentration of plasma in the 3rd month of pregnancy was 0.62 mg.% and some months later was 0.37 mg.%. Plasma proteins and hemoglobin were 5.8 and 10.1 gm.% respectively at the height of test therapy in April, 1941 (4th month of pregnancy); the highest values recorded at any time were 7.9 gm.% plasma proteins and 14.6 gm.% hemoglobin and these were recorded during the positive Wilder tests. Sex hormone studies showed essentially that the function of the ovaries and placenta as judged by estrogen and pregnandiol were essentially normal. The 17-ketosteroids were practically negative during the first two trimesters and rose during the last trimester to 15 mg.% in the last month of pregnancy falling promptly after delivery.

Subsequent Course:
Since final discharge from hospital (12/23/41) her course has been irregular. This has been in part due to the development of fluid apparently sterile in the right pneumothorax which has contraindicated full DOCA therapy. She has been once reimplanted with 300 mg. (4 pellets) of DOCA two times and has received in addition 4-6 gms. added NaCl and on occasion DOCA in propylene glycol sublingually up to 2 mg. a day. Recently 5 pellets have been implanted. An estimate of the rate of rate of absorption from these pellets would indicate that the 4 pellets have yielded somewhere between 1.2-2 mg. a day, thus agreeing rather well with the figures quoted by Thorn. On the above stated regime she has varied from periods with 5-10 lbs. of weight loss below the post partum weight of 130 lbs. accompanied with weakness and amenorrhea to relatively asymptomatic periods with enough strength to assume (against advice) a large part of the care of her household and two children. With the exception of the unfortunate development of the hydrothorax, collapse therapy on the right side has been successful; she has been afebrile since discharge, and X-ray examination indicates the apical processes on both sides to be under control.

- - -

Case 2.

. is a female, age 21, whose Addison's disease was adequately controlled with desoxycorticosterone therapy, but her disease is complicated by active pulmonary tuberculosis.

History: She first noted pain in the lower back and sacro-iliac region in September, 1939, and during the winter of 1940 she tired unusually easily. In August, 1940, weakness, fatiguability, episodes of faintness, upper abdominal pains and chest pains became prominent. In December, 1940, she developed a non-productive cough. There is no family history of tuberculosis. She had lost no weight.

Physical Findings: She was a well-developed and poorly nourished white female with diffuse brownish skin pigmentation and with definite patchy mucosal pigmentation in the mouth. Pulse 80, blood pressure 90/60. Chest examination revealed dullness and bronchovesicular breath sounds and a few scattered rales in both apices more marked on the right. Heart sounds were of fair quality.

Laboratory Data: On admission to the hospital the hemoglobin was 15.2 gm.%, leukocyte count and differential normal, urinalysis negative with a specific gravity of 1027. B.U.N. was 59 mg.%; creatinine 1.5 mg.%; chlorides 579 mg.%; total protein 7.2 gm.%. The hemoglobin rose to 17 gm.% at time when B.U.N. was 59. With treatment the B.U.N. returned promptly to normal and remained normal. A glucose tolerance test was as follows: 90, 170, 192, 196, 102 at time of admission. 17 ketosteroids excretion was low. B.M.R.'s were: -16%, -8%, +5%. Gastric washings were positive for tubercle bacilli.

X-Ray Examinations: Chest--moderately advanced tuberculosis of infiltrative and nodular type involving both upper lobes. The cardiothoracic ratio was .33 shortly after admission but rose as high as .44 after therapy. Adrenal regions--calcification of both adrenals characteristic of tuberculosis.

Course in the Hospital: After 4 days of observation in the hospital she developed signs of impending crisis so 10 cc. of Wilson's cortical extract was given. A "special" diet was given from 1-20 to 3-7-41. A high salt, low potassiu, diet was given from 3-7-41 to 4-2-41, and she was maintained in fairly good health. A general diet has been given since then. NaCl in varying doses was begun on 1-23-41 in doses ranging from 8 to 18 gm. averaging about 12 gm. per day.

Cortate (DOCA) was given intramuscular-16 in a dose of 5 mg. daily 2-11 to 2-13-41 and 10 mg. daily 2-14 to 2-24-41 with the production of edema and hemodilution with a drop of hemoglobin to 9 gm.%.

Progesterone, 5 mg. daily, was given 3-28 to 3-31-41 and 10 mg. daily 4-1 to 4-7-41 but was ineffective in preventing hemoconcentration.

Wilson's cortical extract was given (2.5 cc. daily) 4-13-41 to 4-29-41 in addition to large dose of salt. During this time some edema was produced.

DOCA in propylene glycol was given in a dose of 4 mg./ day along with 8.0 gm. of extra salt. This maintained her fairly well. Cortate in oil was given intramuscularly in doses of 5 mg./ day for approximately one month with good response. However, the dose of salt had to be reduced because of edema formation at one time.

She was discharged from the hospital in August, 1941, and was maintained on a dose of 7.5 mg. DOCA in propylene glycol with 8.0 gm. NaCl daily. In October, 1941, 9 pellets of DOCA were implanted subcutaneously, the dose being calculated on the basis of the dose of intramuscular DOCA during hospital stay. In March, 1942, there was reactivation of her pulmonary tuberculosis so she was sent to the state sanitorium where she still is presukably. The last correspondence about her was one year ago.

\- - -

Case 3.

, male, age 44, has been well controlled on two forms of therapy, but has felt best on maintenance with pellets of desoxycorticosterone acetate.

History: In September, 1941, he noted a hacking cough productive of a little sputum. He was very weak and tired easily. In the mornings, especially, he had frequent episodes of vomiting. Increasing pigmentation of his skin was noted about the same time. During the month of January 1942, he lost 20 lbs. weight. He went to the Veterans' Hospital where he was given a low-potassium-high sodium chloride diet and "cortalex" tablets. He felt quite well on this regime, but the treatment was quite expensive so he was referred here for trial of desoxycorticosterone therapy.

Physical Examination: A well-developed and fairly well-nourished male. Temperature 98°, Pulse 88, Blood Pressure 94/72. There is a diffuse brown pigmentation of the skin with accentuation in the folds, areas of pressure, axilla, and perineum; the mucosa of the mouth has a large number of brown pigmented spots. Chest examination revealed slight impaired resonance over the right apex anteriorly and a few rales were audible in the supraclavicular area.

Laboratory Examinations: Urinalysis

negative. Hemoglobin 16.2 Gm.% on the day of impending collapse following withdrawal of therapy. Sputum and gastric washings negative for tubercle bac9lli. Leukocyte count and differential normal. Blood urea nitrogen 8.2 mg.%, Glucose 71 mg.%, Plasma chlorides, 606 mg.% and potassium, 18 mg.%. The water test was positive. His blood volume was 4.5 L. and plasma volume 2.73 L. before treatment (statistical normal 5.6 L.). Urinary excretion of 17-ketosteroids was 1.7 mg. and 0.55 mg. per day (very low).

X-Ray: Minimal fibroid tuberculosis at both apices, inactive. The heart size was small; the cardiothoracic ratio was 0.35. There was no calcification of the adrenal areas.

Course and Treatment: He was given a general diet, 4.0 gm. of NaCl per day, and desoxycorticosterone acetate in oil intramuscularly (DOCA) beginning with 5 mg./day and gradually decreasing it to 2.5 mg. which he received for 1 month before implantation of pellets. Four 75 mg. pellets of DOCA were implanted subcutaneously on 11-27-42. His average extra NaCl intake was 3.0 Gm./day. His average blood pressure after implantation of pellets was 125/86. About 4-20-43 it became evident that he needed additional therapy, so he was maintained on a daily dose of DOCA (2.5 mg.) for three weeks and then five 126 mg. pellets were implanted.

Diagnosis: Addison's disease, tuberculosis. Minimal fibroid tuberculosis both apices, inactive.

\- - -

Case 4.

., a middle-aged female, who has typical Addison's disease which is non-tuberculous in origin. She is being maintained adequately on daily doses of desoxycorticosterone intramuscularly.

History: This 41 yr. old white female states that she felt well until August, 1941, at which time she noted sudden abdominal pain which was diagnosed as acute appendicitis. Appendectomy was performed, but postoperatively she never recovered her strength, noted persistent weakness, etc. In Feb. 1942, she noted increasing pigmentation of her skin. This has gradually increased to the present. No gastrointestinal distress. A trial of orally administered cortical extract caused distress. Later a short trial of parenteral adrenal cortical extract gave symptomatic improvement. NaCl (6.0 Gm. a day) had given considerable symptomatic improvement during the interval from 3-25-42 to 4-18-42. There is no history of tuberculous infection and no family history of tuberculosis.

Examination: (4-18-42). The skin of the whole body is diffusely deeply pigmented - a dark brown to bronze color. No pigmentation of the oral mucosa was noted. The eyes, nose, throat, ears were normal. There was no enlargement of lymph nodes. Heart size apparently normal. Normal tones and no murmurs. Pelvic and rectal examination negative. Neurological examination essentially normal. Axillary and pubic hair was somewhat sparse.

Laboratory Examinations: Urinalysis entirely negative. Hemoglobin (3-27-42--before starting salt therapy) 16.2 Gm.%; 13.25 Gm.% on 4-12-42; Leukocytes 6,500, Neutrophils 45%, Lymphocytes 53%, eosinophils 2%. Wasserman negative. Blood urea nitrogen - 16 mg.%, sugar (fasting) 72 and 90 mg.%, Chlorides (as NaCl) 588 mg.%. Total protein 7.5 Gm.%, Potassium, 19.6 mg.%. Total blood volume - 3.57 liters, plasma volume - 1.91 liters. (Statistical normal total blood volume--4.3 liters). Mantoux test negative on several occasions. Blood urea nitrogen, 21 mg.%, Chlorides 544 mg.%, Potassium 26.6 mg.%, CO_2 32 Vol.% in Aug. '42.

Course in Hospital: Salt therapy was discontinued so that more specific tests could be carried out. A Robinson, Power, Kepler "water" test was carried out on 4-20-42 and results were equivocal. On 4-20-42 a Wilder test for adrenal cortical insufficiency was started. She slept poorly the first night, was nauseated the following morning, began having abdominal pains about 20 hours after starting the test and her blood pressure gradually dropped from 104 mm. Hg. on 4-20-42 at 11:00 a.m. to 84 mm. systolic pressure at 9:00 a.m. 4-21-42. It was necessary to stop the test and to give cortical extract and saline to which she responded promptly. Her Blood urea nitrogen rose to 23 mg.% and her potassium rose to 27 mg.% during the test.

She was discharged from the hospital receiving 3 mg. DOCA orally and 8.0 gm. NaCl. She continued to feel well until August when she ran out of DOCA for a week and developed symptoms of crisis. After preliminary therapy at home she was transferred here and was given 90 cc. of cortical extract and 5000 cc. of saline and glucose during first 30 hours and continued large dose of cortical extract for five days. Her abdominal pain and anusea remained for four days and she was very irritable. She was finally controlled on a dose of DOCA in oil i.m. (4.5 mg./day) and 6.0 gm. of extra NaCl. She has remained very well since that time. She was seen a week ago in Metabolism Clinic.

\- - -

Case 5.

\- age 56. A physician whose Addison's disease was rather easily controlled until active tuberculous infection supervened.

History: In 1938 he had noted gradually increasing pigmentation of his skin and in 1940 he first noted pigmentation of his buccal mucosa. Since 1939 he had noticed gradually increasing weakness and fatiguability. Prior to 1940 his blood pressure was 140-150/90. In 1918 he had bilateral tuberculous epididymitis, right tuberculous orchitis, tuberculous cystitis and had a right orchidectomy and left epididymectomy. In 1924 renal tuberculosis was diagnosed and a nephrectomy was performed with complete relief of symptoms of cystitis. His health had remained good in the intervening years until 1939.

Physical Examination: (1940). He was well developed, well-nourished and apparently not acutely ill. His skin was diffusely pigmented with accentuation ove bony prominences and his buccal mucosa had quite extensive pigmentation. His temperature usually rose to 99° to 99.4° each day and his pulse ranged from 70 to 90. His blood pressure was 130/90. General physical examination was essentially negative. Heart did not seem to be enlarged on examination, but on x-ray film it was evident that hart was boot-shaped. Heart tones normal. A well-healed right nephrectomy scar and bilateral scars on the scrotum from operations The left testis was normal in size.

Laboratory Examinations: Urinalysis : negative. Wasserman negative. Hemoglobin, 89%, leukocytes, 6,300, Neutrophils 50%, lymphocytes 46%, eosinophils 4%. (Repeated leukocyte counts in 1942 ranged from 3,800 to 5,050). Blood urea nitrogen 18 mg.% (ranged from 5.0 to 10.0 in 1942). Plasma chlorides 624 mg.% on admission, but dropped to 552 mg% at the end of the Wilder test. Potassium was 14.9 mg.% at time of admission. A' Wilder test in May, 1940, was strongly positive - the chloride concentration in the last 4 hour specimen was 536 mg./100 cc. of urine. The volume of urine in this 4 hour period also was in the pathological range for the so-called "water test." (185 cc. for 4 hours).

Course in interval of 1940-42. He was given a high-sodium, low-potassium diet with a total intake of 8.0 to 12.0 Gm. of NaCl. On this regime he got along fairly well, but he had to cut down on the amount of NaCl for it caused diarrhea. He gradually lost some weight, he continued to be weak so that he was unable to do a whole day's work without tiring. For a time he took 2 tablets of Upjohn's adrenal cortical extract three times a day. In December, 1941, he definitely became worse. He lost his appetite for all kinds of food, he noted increasing apathy and weakness; one of his associates stated he probably had an afternoon fever for his face would be flushed in the afternoons. He was readmitted to the hospital on January 19,1942, for an attempt at more adequate control of his Addison's disease. Two days prior to admission he had fallen down a flight of stairs with rather severe shaking-up, temporary unconsciousness, and few body bruises.

Physical Examination: (1942). Now there was evidence of malnutrition (weight loss of 20 lbs. since 1940) and considerable increase in general pigmentation of the body. There was an area of leukoplakia of the left cheek and moderate evidence of irritation from dentures. Several days after admission an acute seborrhea of the scalp developed with regional lymphadenopathy, but that subsided in a few days. Chest examination revealed a few inconstant rales at the base of right lung. The heart did not seem enlarged (M.L. 9 cm. from midline). The Blood Pressure was 122/82. The rest of the examination was negative. His temperature varied from 98.6 to 101° daily.

Course in the Hospital: A blood volume was determined and found to be 4.27 liters (statistical normal 5.02 L.), and his hemoglobin and plasma proteins showed moderate evidence of hemoconcentration. He was given a general diet, 8.0 Gm. of extra NaCl a day, and 6 mg. of DOCA in propylene glycol under the tongue daily from 1/21 to 2/6/42. Then he was given 5 mg. of DOCA in oil i.m. daily from 2/6 to 2/25. A compression fracture of the thoracic vertebrae (8 and 5th) was demonstrated by x-ray, but no specific therapy was directed at this because of location (Orthopedic consultation). He was discharged on 2/14/42.

He continued to have a fever with elevations to 103° at times. On 2/22/42 intractible hiccough started so he was readmitted to the hospital. His fever was even higher ranging as high as 102.5 daily and occasionally over 104. Therapy consisted in intravenous injection of 2000 to 2500 cc. of saline and glucose solution with 20 to 30 cc. of cortical extract daily. Lavage of stomach relieved hiccoughs temporarily. Attempted duodenal intubation for feeding was tried 2 times but was unsuccessful because of too great distress. Temporary cessation of hiccoughs and nausea occurred from 3/13 to 3/20/42 so that he again was able to take fluids by mouth and even began to eat some food. From 3/15 to 3/20 specific therapy consisted in 4 mg. DOCA in oil i.m. plus 4 to 8 Gm. of NaCl. Hiccoughing started again on 3/20 so oral medications were discontinued and intravenous injection of 1500 cc. of saline and glucose with adrenal cortical extract (15 cc.) was given daily. Gastric lavage controlled hiccoughing temporarily again. During the last two days of life he was confused mentally on frequent occasions, he had a thick speech, and he talked irrationally at times. During this second admission he had constantly a slightly lower blood pressure than on previous admission - range 100 to 110 systolic - compared with range of 110 to 120 systolic.

He expired suddenly 3/26/42 during the time he was getting an intravenous injection of saline and cortical extract.

Diagnosis: Addison's disease, etiology, tuberculosis.
Active tuberculosis of adrenals and/or of periaortic lymph nodes.

- - -

Case 6.

, female, age 38, is a patient who offers a special problem because of extreme anorexia. She is prone to develop edema from adequate therapy with DOCA. An additional complicating factor is hypothyroidism.

History: In 1925 this patient had a severe attack of scarlet fever. Since that time she has a craving for salt, has had episodes of abdominal cramps and vomiting every time she gets an infection. Her most prominent symptom has been weakness. In December, 1940, she began having more severe attacks of abdominal pain and on February 12, 1941, became semicomatose but responded immediately to intravenous injection of saline and glucose solution. For two years she had noted some increase in the pigmentation of her skin. A diagnosis of Addison's disease was made by her physician and she was treated for three weeks before hospital admission with DOCA and cortical extract.

Past History: A diagnosis of pulmonary

tuberculosis was made in 1926; apparently completely arrested by period of strict bed rest followed by period of restricted activity. (She has noted edema when she has ingested too much salt.) She has had some urinary frequency and nocturia for 20 years. Menstruation began at 13 yrs., is regular every 28 days, lasts 4 days and is quite scant. No pregnancies during 6 years of married life. Absent menses for several months.

Physical Examination: An asthenic white female with brownish pigmentation in axillary folds, groins, over bony prominences of extremities, linea alba, nipples and areola, and neck. Average pulse was 90/minute. Temperature was usually normal. General physical and neurological examinations were entirely normal except as noted above. Blood pressure 78/52 on admission. Scanty axillary and pubic hair.

X-Rays: Six-foot chest plate revealed a cardio-thoracic ratio of 0.32. During a phase of therapy when she was edematous the cardio-thoracic ratio of 0.48 was obtained, and signs of pulmonary edema (x-ray but not physical signs) developed.

Laboratory Examinations: Repeated urinalysis revealed negative findings. Blood Wasserman was negative. Mantoux (0.1 mg. O.T.) negative on several occasions. Blood volume, 2.34 liters (3.5 L statistical normal) before specific therapy (3/21/41) and 3.34 liters at height of therapy (4/30/41). Hemoglobin 10.7 Gm.%, Erythrocytes, 3,000,000, Leukocytes, 6,800, Neutrophils 38%, lymphocytes 52%, Monocytes 8%, Eosinophils 2%. Blood urea nitrogen 3.5 mg.% to 15 mg.%, Fasting blood sugar, 55 mg.% to 106 mg.%. Total proteins ranged from 6.0 Gm.% (adm.) to 4.6 Gm. %(at the time when edema was produced). Basal metabolic rate ranged from --43% to --12% during hospital stay. Estrogen and 17 ketosteroids excretion very low.

Course in the Hospital: At first no specific therapy was given. Then she was given a low potassium-high sodium diet with 10.0 Gm. of NaCl from 4/1/41 to 4/15/41. She was given a general diet with a total of 12.0 Gm. NaCl/day and from 4/17 to 4/23/41 4 mg. of DOCA i.m. per day. The DOCA had to be discontinued because of the development of edema and the x-ray signs noted above. Because of her low basal metabolic rate desiccated thyroid was started (gradually increasing the dose from gr. 1/4 to gr. iii per day over a period of 5 weeks)

Because of rapid edema formation and low plasma proteins and failure to eat adequate protein a blood transfusion was given on 5/10/41 with a near fatal reaction with temperature rise to 105., semi-coma, marked fall in blood pressure, but which responded to intravenous injection of cortical extract, glucose and saline solutions, and sodium bicarbonate solution.

DOCA in propylene glycol, 2 mg./day, was begun on 5/24/41. The dose of extra NaCl has been varied from 8.0 Gm. to 20 Gm./day. During a hospital stay of almost three months she had maintained no weight gain. Anorexia was a major problem and especially anorexia for protein foods. Adequate doses of vitamins were given to insure against concurrent deficiency. Her average systolic blood pressure at time of admission to the hospital was 70 mm. Hg. At the time of discharge average blood pressure was 90/60.

Course since 1st hospital stay: Her general condition has improved gradually with a weight gain of 8 pounds, an increase in strength, appetite, and general well-being. She is being maintained on thyroid gr. ii, and NaCl., Gm. 2, and DOCA in propylene glycol under the tongue, 2 mg./day. Her blood pressure ranges from 80 to 90 systolic. Her basal metabolic rate ranges from +4% to -7% now.

In the middle of March, 1943, she developed symptoms of crisis and was first hospitalized at Abbott Hospital and later transferred here. Extreme prostration, abdominal pain and weakness had been the chief symptoms. On admission to this hospital she was very weak, her blood pressure was 88/80, her pulse weak, hands and feet cold. She had definite hemoconcentration with a hematocrit of 50% and a hemoglobin of 16.4 gm.%. She was treated as for crisis and responded well. DOCA was given intramuscularly and extra salt, 4.0-6.0 gm./day. Now she is maintained on 3 mg. of DOCA daily intramuscularly and 4.0 gm. salt daily. She has improved a great deal.

<u>Diagnosis</u>: Addison's disease, etiology uncertain.
Hypothyroidism.

- - -

<u>Case 7</u>.

, an elderly male whose Addison's disease is quite well controlled by very small doses of cortical extract or desoxycorticosterone. He becomes careless about his care, however, and consequently had bad episodes of crisis.

<u>History</u>: In September, 1935, he developed severe occipital headache, poor appetite, nausea, and epigastric distress. The abdominal symptoms increased, his pain increased, and he was admitted to the hospital as an acute surgical emergency, but was later transferred to the medical service after subsidence of abdominal pain and tenderness and fever. The true nature of his disease was not appreciated until he went into crisis one morning with a drop in blood pressure to 0, pulse unobtainable, and stupor. Rapid response to 15 Gm. NaCl and 10 cc. Eschatin intravenously. He was discharged on a regime of 12.0 Gm. NaCl, 4.0 Gm. $NaHCO_3$, and a low potassium diet; his progress was fairly satisfactory, but he had episodes of abdominal pain so in October, 1937, he was readmitted to the hospital again.

During the 1937 hospital stay symptoms of Addison's crisis were deliberately provoked by the administration of a salt free diet. Again he became pulseless, comatose, and had an elevation of non-protein nitrogen as noted below. Treatment with eschatin and saline intravenously produced satisfactory response. At the time of discharge he again was given NaCl, and now also 5.0 Gm. of Na citrate daily. Clinic visits during 1938 revealed that he was getting along quite well most of the time. He was adhering to a low potassium diet.

On April 7, 1941 he was readmitted to the hospital at which time he had definite symptoms of adrenal insufficiency - weakness, anorexia, abdominal soreness. For a year he had failed to adhere to a diet and was careless about taking extra salt. Weakness and abdominal discomfort occurred from time to time during the preceding 6 months to a year.

<u>Examination</u>: (1941) Well-developed and well-nourished male who was somnolent, weak, apathetic about surroundings. Marked brownish pigmentation of skin, accentuated in the folds and creases, and in the buccal mucosa. Pulse barely perceptible and very slow at the time of admission. The blood pressure could not be elicited by auscultation. The temperature was subnormal. General examination revealed deafness, negative chest, normal sized heart but with markedly muffled heart tones. The liver was barely palpated at the costal margin (in 1935 and 1937 the liver was definitely palpated 4 cm. below the costal margin). The abdomen was moderately tender throughout. Neurological examination was negative except for the apathy and somnolence.

<u>Laboratory</u>: Urinalysis essentially negative on all examinations (1935) A leukocytosis on admission - 18200 - but with normal total counts on all subsequent determinations. At the time of collapse in 1935 plasma chlorides were 510 mg.%. (1937) During the provocative test non-protein nitrogen rose from normal of 27 mg.% to 101 mg.% on day of collapse and plasma chlorides dropped from 620 mg.% progressively to 476 mg.%. with rapid return to normal when therapy was given. Glucose tolerance test produced a flat type of curve with maximum value of 129 mg.%. (1941) Blood urea nitrogen was 56 mg.% on admission, but chlorides were normal. The blood urea nitrogen soon returned to normal on therapy. Gastric expression revealed presence of normal amount of hydrochloric acid.

<u>X-Ray</u>: Calcification of the left adrenal gland. Duodenal deformity due to old duodenal ulcer, which was evident in 1935, 1937 and 1941. In 1941 calcification of both adrenals was

evident in 1935, 1937 and 1941. In 1941 calcification of both adrenals was evident.

Course and Therapy (1941-1942): The crisis was treated by intravenous injection of 1500 cc. of saline and glucose with 10 cc. of Wilson's cortical extract. 10 cc. of cortical extract was also given intramuscularly and 1500 cc. of saline was given subcutaneously. The next 3 days he was given 10 cc. of corcical extract in 5 doses intramuscularly. Following this he was given 8 cc. of cortical extract for 12 days, then 5 cc./ day for several days, then 6 cc./day for 8 days and finally 9 cc./day for 2 days. He was also given 8.0 to 12.0 Gm. NaCl daily orally. His condition improved very promptly so that his strength was better than it had been for a long time. On 5/12/41 he was started on DOCA in propylene glycol under the tongue, 3 mg./day. It was found that after discharge from the hospital that this dose caused palpitation, so now he is taking 1 mg. 2 to 3 x a week. He takes 4.0 Gm. NaCl/day plus liberal salting of his food. He has not returned to clinic for 9 months.

Diagnosis: Addison's disease; etiology, tuberculosis.
Duodenal ulcer deformity.

\- - -

Case 8.

This patient, is a 57 year old male in whom the therapy has been moderately ineffectual in improving general condition appreciably though he has been able to remain active.

History: In 1938 he became drowsy, dizzy, weak and chronically fatigued. He has gradually lost 40 pounds of weight because of his constant anorexia. He continued to work until the summer of 1941 when he was forced to quit because of continued and progressing symptoms listed above. In addition to above symptoms he has noted a generalized pruritis for the past several years. In August, 1941, a diagnosis of Addison's disease was made by Dr. Hirschboeck of the Duluth Clinic and he was treated with 4.0 Gm. NaCl and 4.0 Gm. sodium citrate daily and cortical extract, but there was no noticeable benefit after rather prolonged trial.

Past History: Diphtheria, scarlet fever mumps and measles as a child. He had a chronic cough, but no hemoptysis. Family history - no tuberculosis and no history of exposure to tuberculosis. Has been impotent for past 10 years. Had gonorrhea at age 32.

Physical Examination: He was undernourished, but well developed. He had a constant irregular fever. Blood pressure difficult to obtain - has ranged from 118/76 to 90/70. Pulse usually slow and quite irregular (sinus bradycardia with extrasystoles). There was patch of brown pigmentation in the buccal mucosa on the right. Several large lymph glands are palpable in axillae and in inguinal regions. Heart tones were faint, rhythm was irregular as noted above. The spleen is not palpable. There was slight increased pigmentation of the palms of the hands. Neurological examination essentially negative. Scanty axillary and pubic hair.

Laboratory Examinations: Urinalysis negative, (sp. gr. 1018 to 1014 on routine examinations). Hemoglobin, 11.8 Gm.%, leukocytes 5,200, neutrophils 64%, lymphocytes 27%, monocytes 2%, eosinophils 7%. Blood urea nitrogen 11.5 mg.%, blood sugar, 78 mg.% chlorides 628 mg.%, potassium 19.9 mg.%. Total base 146 milliequivalents. Lymph note biopsy revealed hyperplastic tuberculosis with epitheloid cell tubercles with giant cells but no caseation.

X-Ray: Heart size was at lower limit of normal. The C.T. ratio was .36. Lungs were clear. There was no evidence of calcification of the adrenals.

Course: A "water test" of Robinson, Power, Kepler was performed and was found to be positive in that the individual specimens after ingestion of water were smaller in volume than the night volume of urine. A lymph-node biopsy was performed on 4/9/42 and on following day he was extremely weak, his blood pressure was 90/70, he was nauseated and he vomited. Consequently he was given an intravenous of 1000 cc. of saline and 5 % glucose with 10 cc. of cortical extract. His strength improved and he was able to eat his evening meal. He was given 3 mg. DOCA in oil intramuscularly daily for 6 weeks and 6.0 gm. of NaCl. After this period 3 pellets of DOCA (75 mg. each) were implanted subcutaneously. His disability remains almost at same level as before treatment. He was not given an optimal pellet dose because of ease with which his blood pressure rose on small increases of DOCA. He has not been seen for 5 months.

<u>Diagnosis</u>: Addison's disease, tuberculous, lymph node tuberculosis. Question of abdominal tuberculosis.

- - -

<u>Case 9</u>.

. . . . , elderly female, with typical Addison's disease rather poorly controlled by desoxycorticosterone therapy. Nutrition was a major problem during hospital stay.

<u>History</u>: For 5 or more years had noticed some dyspnea on exertion and ankle edema. In spring of 1941 she first noticed anorexia, malaise, weakness, and rapidly progressing pigmentation of skin. These symptoms became more severe in October 1941, at which time vomiting after meals began to occur, and at the same time she began to have vague left-side abdominal pain and epigastric tenderness. She lost at least 25 pounds and probably considerably more in 9 months. Taking salt between meals has relieved her abdominal distress from time to time. A brother and a sister died of tuberculosis many years ago. She has never had any children - in fact she has never been pregnant.

<u>Examination</u>: She was well-developed, but poorly nourished. Her skin was deeply pigmented, particularly over the extensor surfaces of the hands and arms, the areola of the breasts, and her buccal mucosa has punctate pigmented areas. The lungs were clear. The heart is normal in size and tones normal. Blood pressure was 105/60 on admission but rose to 160/84 at time of discharge from hospital. Abdominal examination is negative. Pelvic examination revealed areas of dark pigmentation of the mucosa and a senile vaginitis. During her hospital stay she had a normal temperature most of time but for a week at a time her temperature was slightly elevated. Neurological examination was non-contributory.

<u>Laboratory examinations</u>: Urinalysis was negative at time of admission, but later there was a pyuria with a positive culture of E. coli. - this was cleared satisfactorily by chemotherapy. Hemoglobin 12.3 Gm.%, leukocytes, 7,600, neutrophils 53%, lymphocytes 40%, monocytes 3%, eosinophils 4%. P.S.P. test was normal. Blood sugar was consistently low, ranging from 56 to 88 mg.% on numerous determinations. A "Wilder test" for adrenal insufficiency was strongly positive on Dec. 11, 1941 (580 mg./100 cc. urine expressed as NaCl in the last 4 hour specimen). A "water test" was strongly positive on 2 occasions. Mantoux (0.1 mg. O.T.) was positive. Blood Wasserman was negative.

<u>X-Rays</u>: No evidence of adrenal calcification. Gastrointestinal x-ray study normal. Intravenous urography negative. Plain films of abdomen revealed calcified gall stones.

<u>Course</u>: Treatment consisted of various forms of replacement. She was given DOCA in oil intramuscularly first, then DOCA in propylene glycol, then whole cortical extract and finally a return to DOCA. Her blood pressure remained in the range of 150-164 systolic during rest of her hospital stay, but edema disappeared. Her final dose of DOCA was 2 mg./day, so on 2/15/42 3 pellets of DOCA (75 mg. each) were implanted subcutaneously and she was allowed to go home. She was given 9.0 Gm. of salt/day also. Yeast powder was given as an appetite stimulator. She continued to be fairly well until 4-13-42 at which time she vomited and continued to do so until admission to the hospital. She began to cough the following day associated with generalized aching pains especially in the shoulder joints. She became definitely irritable during the week preceding admission. She has lost additional weight since last hospital stay Physical examination revealed evidence of increased emaciation. Her face was slightly puffy. Her blood pressure was

150/70 and her pulse was of good quality. There were a few rales in the bases of both lungs. Otherwise her general condition was similar to that of previous examination.

It was difficult to decide whether or not this represented a mild crisis or over-treatment in view of the puffiness of the face, the blood pressure of 150/70. Plasma chlorides were 562 mg.%, CO_2 combining power of 36 vol. %, and a blood sugar of 35 mg.%. Potassium was 19.5 mg.%. It was evident she was in need of glucose, and more substitution therapy so she was given 20 cc. of cortical extract intravenously and 10 cc. intramuscularly on night of admission along with 1000 cc. of 10% glucose in saline. Since that time she has been maintained on NaCl 8.0 Gm. a day and a general diet She has not been seen for 1 year since discharge from hospital in July, 1942.

Diagnosis: Addison's disease, probably tuberculous; cholelithiasis.

- - -