

## TWO CASES OF DIABETES MELLITUS

One with Myxedema and one with Addison's Disease

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For a long time it has been recognized that glucose tolerance is increased in patients with hypothyroidism and that diabetes mellitus is aggravated by coexisting hyperthyroidism.<sup>1, 2</sup> Attention also has been called to the fact that diabetes is more common in the presence of hyperthyroidism than in its absence.<sup>3</sup> The mechanism by which hyperthyroidism produces diabetes-like metabolic changes appears to be as follows: The rate of oxidation of carbohydrates by the tissues of the body is increased. This results in a rapid flow of stored sugar from the liver into the blood stream tending to deplete the liver stores.<sup>4</sup> Because the absorption rate of glucose from the intestine is accelerated, the post-prandial rise of blood sugar is further exaggerated.<sup>5</sup> Meanwhile, the liver is further depleted because of an increased rate of oxidation within its cells. Thus the whole picture rather closely simulates that found in diabetes mellitus. For the same reasons latent diabetes may manifest itself, and existing diabetes may become more severe in the presence of hyperthyroidism.

In myxedema the whole process is reversed. The ameliorating effect of thyroidectomy upon diabetes mellitus has been tested clinically<sup>6</sup> and has not been found to be of practical therapeutic value. Cases of diabetes and myxedema thus present an unusual and interesting metabolic picture. They prove that thyroidectomy cannot be expected to have a curative effect on diabetes mellitus. Diabetes and myxedema have coexisted in five cases which have come under my supervision. One of these is reported here.

*Case 1.* The patient, a 62 year old white woman, had been well and active until three years prior to examination. Since that time she had noted a gradually increasing sense of fatigue and an increased need for sleep. Her face, eyelids, arms, hands, and ankles had become puffy, and her skin and hair were dry. Her memory was diminished. She became intolerant to cold, and her hands and feet were often numb. There was mild dyspnea on exertion. Repeated urinalyses had failed to show any evidence of kidney disease. Her weight had increased 15 pounds in the preceding year. Menopause had occurred at the age of 50 and had been accompanied by few symptoms.

Glycosuria had been discovered 12 years previously and had been observed occasionally since. No insulin had been used, and no dietary regimen had been followed for three years. She had never had the cardinal symptoms of diabetes nor any of the symptoms of common complications.

One brother had died of pernicious anemia and one sister of diabetes. The patient had had two pregnancies, and her two normal children were living and well. She had had no surgical operations.

*Physical examination.* The patient's height was 65½ inches; weight 199½ pounds; temperature 98.4° F.; pulse 66; blood pressure 140 mm. systolic and 92 mm. diastolic. Her appearance was typical of myxedema. The face was puffy and sallow, and there were practically no eyebrows. The skin, especially on the face and backs of the hands, was dry and somewhat scaly. The subcutaneous tissues had a doughy feeling, and there were well marked supraclavicular pads. The relative cardiac dullness did not appear to exceed normal. The heart sounds were clear but distant. Occasional extrasystoles were present. There was crepitation and stiffness of the knees. The reflexes in the arms and legs were physiological, except that the patellar reflexes and the Achilles tendon reflexes were sluggish and exhibited a peculiar, slow recovery rate. There was a slight sensory impairment in both feet and lower legs to perception of heat, cold, touch, and sharp-dull differentiation. The dorsalis pedis pulse was not detected.

### LABORATORY TESTS

*Blood chemistry and serology* revealed fasting blood sugars of 258 and 227 mg. per cent; urea 39 mg. per cent; cholesterol 272 mg. per cent; and CO<sup>2</sup> combining power 53.8 volumes per cent. Serum proteins totalled 7.3; albumin 5.0; and globulin 2.3 grams per cent.

*Blood count* disclosed 4,310,000 red blood cells; 5,500 white blood cells, with 54 per cent neutrophiles, 39 per cent lymphocytes, 1 per cent eosinophiles, 5 per cent monocytes, and 1 per cent basophiles; the volume of packed red blood cells was 87 per cent of normal, with an hematocrit level of 39 cc. per 100 cc.; volume index 1.01; hemoglobin 84 per cent of normal or 13 grams per 100 cc. (Haden-Hauser); color index 0.98; and icterus index 6.0.

*Urinalyses* revealed a specific gravity which varied from 1.018 to 1.026; a faint trace of albumin in some specimens; no sugar.

*Urea clearance* evidenced 65 and 60 per cent excretion in each of two hours.

*Hippuric acid liver function test* was 130 per cent of expected normal.

*Basal metabolic rates* were minus 29 per cent and minus 27 per cent.

The electrocardiogram showed changes commonly recognized as being due to myxedema: rate 76, sinus rhythm, slurring of the QRS complexes, T<sub>2</sub> iso-electric, T<sub>3</sub> inverted, left axis deviation, and ventricular premature beats. Parts of the electrocardiograms before and after nine months of treatment are shown. (Fig. 1) The second tracing shows a complete return to normal.

*Course of the myxedema.* Desiccated thyroid was prescribed at once in doses of 2 grains per day orally. The dosage was raised to 3 grains daily in a week and has been maintained there for 22 months to the present time. The basal metabolic rate rose to +6 per cent in a month, was ±0 per cent in 8 months, and -9 per cent in 18 months.

In one month there was a slight increase in energy but only slight clinical improvement otherwise. The skin remained very dry. The pulse rate had increased to 86. The

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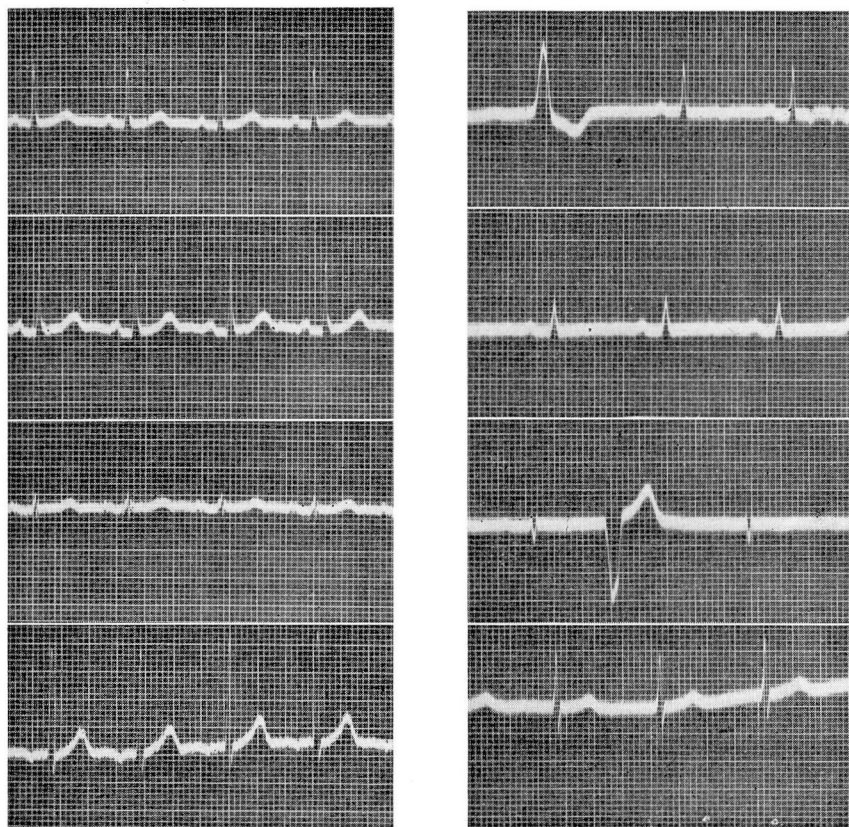


FIG. 1

blood pressure apparently had dropped somewhat and was 120 systolic and 60 diastolic. The tongue, meanwhile, had become quite smooth, and there was deep pitting edema of the ankles. Multi-vitamin capsules and 50 mg. of nicotinic acid t.i.d. were added to her program of treatment. The blood cholesterol already had fallen to 122 mg. per cent.

In two months there was further improvement in strength and energy, the extremities were warmer, and there was less need for sleep. The doughy feeling of the subcutaneous tissues had disappeared, but the skin remained dry. The tongue edges were red, and the pitting edema of the ankles persisted. Her weight had decreased 31 pounds. Thiamine chloride 10 mg. per day was added to her regimen.

In six months almost all the symptoms and signs of myxedema had disappeared. The skin had a normal texture; the blood pressure remained the same; the edema had disappeared; sensory perception in the feet had returned to normal. The tongue remained abnormally red. Her weight was 156 pounds. The memory continued to improve.

There was little further change except that the blood pressure was 136/70 after 9 months and 154/90 after 18 months of treatment. The weight loss was due in part to

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the low caloric intake. A mild hypochromic anemia which appeared in the course of treatment responded to iron therapy.

*Course of the diabetes.* The diet during the first three months supplied carbohydrate 100 gm., protein 50 gm., and fat 60 gm. per day; total calories 1140. At the beginning of treatment the original diet was followed for four days without insulin. During this time the fasting blood sugar varied from 113 to 246 mg. per cent. Glycosuria was not present, but a further elevation of sugar levels was anticipated because of the action of thyroid. Therefore, protamine zinc insulin was begun in doses of 10 units daily before breakfast. From the third to the eighteenth month, the daily food intake approximated C 160, P 62, F 80, total calories 1752. After 18 months because of an increase in weight from 156 to 169 pounds, the original diet was again prescribed.

In two months blood sugar levels before each of three meals were 165, 164, and 155 mg. per cent. The protamine zinc insulin dose was increased to 15 units daily. Subsequent blood sugar levels before meals were as follows:

	A. M.	Noon	Supper Time
3 months.....	119	104	125
6 months.....	130	103	103
8 months.....	119	106	116
18 months 168 (7 hrs. p.c.).	143 F.	...	171

The rise in blood sugar levels at the eighteenth month examination was subsequent to a period of dietary indiscretion. It indicated that the mild diabetes was still present and had not been changed materially during that period of treatment. The increase in severity of the diabetes due to thyroid probably was balanced by fundamental improvement due to weight loss.



FIG. 2

## DIABETES ASSOCIATED WITH ADDISON'S DISEASE

That hypoglycemia occurs in Addison's disease and in adrenalectomized animals has been reported by Bierry and Malloizel in 1908<sup>7</sup> and Porges in 1909.<sup>8</sup> Since then the importance of the adrenal in the regulation of carbohydrate metabolism has been demonstrated by Silvette and Britton<sup>9</sup> in extensive studies on adrenalectomized animals. Long and Lukens<sup>10</sup> have reported experiments on a depancreatized-adrenalectomized dog, which demonstrated the important interrelationship of the adrenals and the pancreas in the regulation of carbohydrate metabolism. After the removal of all adrenal tissue there was a marked decrease in the amount of insulin required to one fourth to one fifth the previous amount. The dog was receiving unfractionated adrenal extract.

Grattan and Jensen demonstrated that the convulsions produced by insulin could be counteracted by the crystalline hormones of the adrenal cortex.<sup>11</sup>

Kendall<sup>12</sup> stated that in pancreatectomized-adrenalectomized dogs a high degree of glycosuria existed as long as compound E (11-dehydro-17-hydroxycorticosterone) was given. When the administration of this material was stopped, the glycosuria declined to relatively low levels. Attention was directed to the fact that the high degree of glycosuria under these conditions was not associated with extra nitrogen excretion, indicating that the extra glucose did not arise from endogenous protein. This was considered evidence that compound E can suppress the utilization of glucose.

Recent studies of liver glycogen stores in rats treated with various crystalline adrenal cortical preparations have demonstrated an extreme variation in effect. No increase in liver glycogen was observed following treatment with very large doses of desoxycorticosterone acetate, while a marked increase occurred following very much smaller doses of corticosterone, 17 hydroxy-11-dehydrocorticosterone and 17-hydroxycorticosterone. The injection of unfractionated adrenal extracts in large doses also resulted in a marked increase in liver glycogen.<sup>11</sup>

Only a few of the many interesting interrelationships of adrenal cortical hormones and carbohydrate metabolism have been mentioned. Clinically, the types of cases which represent the diabetic tendency associated with adrenal cortical hyperactivity are Cushing's syndrome, adreno-genital syndrome, Achard-Thiers syndrome (diabetes of bearded women), and some cases of adrenal cortical tumor.

The reported cases in which diabetes and Addison's disease have been coexistent are very few. Bloomfield<sup>13</sup> reviewed the cases up to 1939

(4 cases) and reported a case of diabetes which subsequently developed Addison's disease. During the development of the Addison's disease the insulin requirement decreased from 40 units to 4 to 6 units. Treatment with desoxycorticosterone acetate did not modify the diabetic state, but treatment with adrenal extract (Eschatin) was followed by a greater hyperglycemia and increased glycosuria.

*Case 2.* (Patient referred by Dr. W. A. Klann, Wellington, Ohio) On May 4, 1942 a pale thin young man presented himself complaining chiefly of weakness, persistent left abdominal and epigastric pain, anorexia, and a loss of 30 pounds in six months.

The presence of diabetes had been known for seven years. It had been ushered in with cardinal symptoms and had been treated with diet and insulin. In 1940 he had been taking 40 units of protamine zinc insulin daily. This had been discontinued for several months but had been started again because of increasing symptoms.

Since January 1942 he had spent from several days to several weeks in three hospitals where attempts had been made to control his diabetes. The diet had varied, and insulin doses sometimes had been as low as 40 units, at times as high as 120, and recently 80 units of protamine zinc insulin per day.

As long as three years ago peculiar reddish areas had begun to appear on both shins. In the late summer of 1940 following a minor injury to his right shin a very large painless ulcer had appeared involving two-thirds of the length of his right shin. About January, 1942 a similar large ulcer formed on the left shin. In addition there were several yellowish purple areas of smaller size and irregular shape which appeared for a time on the verge of necrosis but did not ulcerate. The large ulcers healed completely following periods of improved diabetic control.

In January, 1941 he had begun to notice soreness and dull pain in the epigastrium and at times pain in the left groin extending downward toward the testis. The epigastric pain was somewhat relieved by bowel movement, but was not related to meals or to urinary symptoms. The appetite had become increasingly poor, amounting almost to a disgust for food, and he had lost 30 pounds in weight during this time. He was very constipated.

*Physical examination.* The patient was thin and pale. He appeared weak, dehydrated, somewhat drowsy, and obviously was very ill. His height was 69¾ inches; weight 120 pounds clothed; temperature, 98.6° F.; pulse 80; blood pressure 100 systolic and 70 diastolic. Except for evident malnutrition and dehydration, there were few noteworthy physical findings. The skin was dry and scaly, and the mucosae were dry. There were a few shotty glands in the inguinal regions. There was mild tenderness to pressure in the region of the mid-epigastrium and the sigmoid colon. No pigmentary changes of the skin were noted. Rectal examination was normal, and the reflexes were intact. Retrospective examination of the skin and mucous membranes showed no abnormal pigmentation of the buccal mucosae nor skin and no black freckles, although the patient believes that many small moles have become darker than they had been previously. The large reddish or brownish red atrophic scars of the legs, because of their peculiar relationship to the diabetes, are described below in more detail.

Because the patient was very ill and because relatively severe diabetic acidosis was strongly suspected, he was admitted to the hospital at once for treatment, and further investigation considered not immediately necessary was postponed.

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*Immediate course.* Urinalysis for sugar and acetone was ordered, and the immediate determination of blood sugar and CO<sub>2</sub> combining power. Arrangements were made for one of the technicians to stay on duty all night in the event that the CO<sub>2</sub> combining power were found to be below 30. We were astonished to find that the urine contained no ketone bodies, and the CO<sub>2</sub> combining power was 55.7 volumes per cent. The blood sugar level was 348 mg. per cent. A liquid diet was ordered to supply C 100, P 50, F 60 within 24 hours. One thousand cc. of 1 per cent normal saline intravenously, and 50 units of protamine zinc insulin and 40 units of regular (amorphous) insulin were given. After four and a quarter hours the blood sugar was 89 mg. per cent. The following morning the blood urea was 36 mg. per cent, cholesterol 189, CO<sub>2</sub> combining power 38.5 volumes per cent.

The diet, blood sugar, and insulin doses for the next three days are shown in the following table. The four periods of the day represent periods before meals and at bedtime, and blood sugar levels are fasting or approximately four hours after food unless otherwise stated. 'P' designates protamine zinc insulin, and 'R' regular (amorphous) insulin.

TABLE 1

Date	Blood Sugar mg. % (Hr. P.C.)	Insulin	Diet Taken			
			C	P	F	Cal.
May 5						
1	78(F)	30 P				
2	227(4)					
3	208(4)	4 R				
4	202(4½)		198	60	95	1887
May 6						
1	128(F)	30 P 5 R				
2		5 R				
3	92(4)	5 R				
4			193	54	86	1682
May 7						
1	50(F)	30 P 5 R				
2						
3	70(4½)	6 R	190	74	120	2136
4						

During the next few days the patient improved markedly but remained weak. He ate the prescribed quantities of food with much difficulty and continued to complain of epigastric pain. The diet was concentrated, of smooth quality, and increased in caloric value. He was given phenobarbital and tincture of belladonna to tolerance,

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almost continuous heat to the abdomen, and small saline enemas after breakfast if necessary.

It soon was apparent that the diabetes was extremely erratic. We were now obliged to devise a scheme whereby the patient might hope to control his diabetes at home. For this purpose urine specimens secreted during the half-hour before meals and before bed-time were tested, and regular insulin was added at various times of day in amounts of 6, 10, or 12 units for yellow, orange, or red Benedict's qualitative reactions respectively. Such a plan improved his control, but frequent blood sugar determinations clearly demonstrated its relative inefficiency in this case. Some of the diabetic data from the 11th through the 15th hospital days are shown below.

TABLE 2

Date	Blood Sugar mg. % (Hr. P.C.)	Insulin	Diet Taken			
			C	P	F	Cal.
May 15						
1	56(F)	34P 10R				
2						
3	240(4)					
4	375(4 $\frac{1}{4}$ )	4R	245	42	105	2109
May 16						
1	309(F)	34P 4R				
2		10R				
3						
4			227	62	114	2182
May 18						
1	92(F)	34P 3R				
2	103(4)					
3	146(3 $\frac{3}{4}$ )	3R				
4	108(4 $\frac{1}{4}$ )		230	46	109	2085
May 19						
1	73(F)	34P 3R				
2						
3	300(4)	6R				
4	254(4 $\frac{1}{4}$ )	3R	240	47	97	2021

The patient was dismissed on the 20th hospital day.

*Special examinations and laboratory reports.* (Dermatological, Dr. E. W. Netherton) During the past three years small red lesions had appeared without trauma on both lower legs. Some had enlarged slowly, some rapidly, by peripheral extension to form rounded and irregular brownish red areas of variable size. The larger lesions were ulcerated. There was a long band-like, indolent, brownish red, well-defined plaque  $9\frac{1}{4}$  by  $2\frac{1}{4}$  inches on the anterior surface of the right leg. This extended from just be-



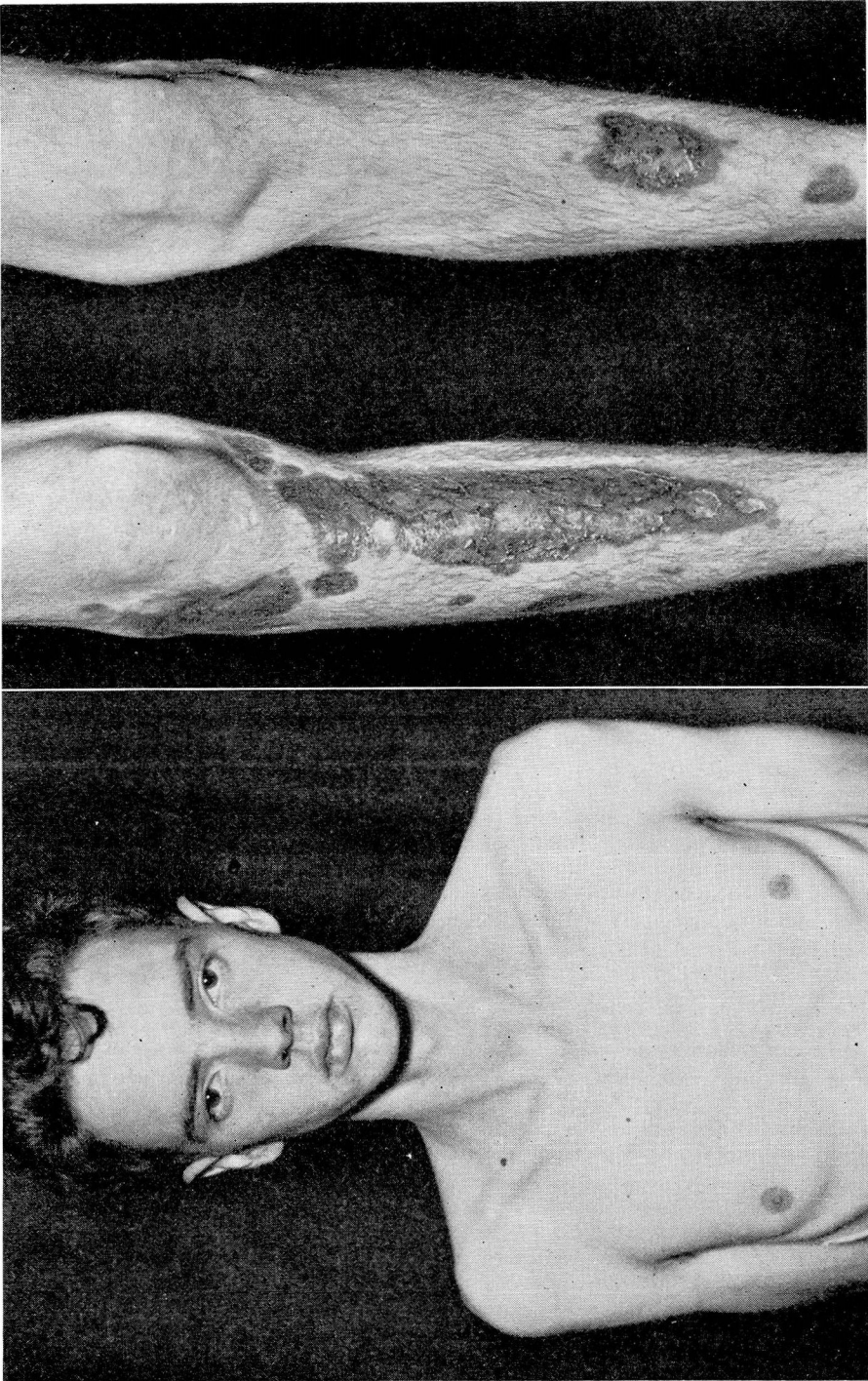


FIG. 3

low the knee to about the junction of the 2nd and 3rd third of the leg and was located over the anterior portion of the tibia. The central portion of the lesion was an atrophic scar, while the periphery was slightly thickened by a yellowish or xanthomatous deposit in the skin. There was telangectasia over the margin of the lesion, and fairly large, thin, brown, adherent scales were scattered over the lesion. There were smaller rounded or irregular lesions of a similar nature on the lateral surfaces of the right leg and also a few lesions on lateral and anterior surfaces of the left leg. There were no lesions above the knees. The striking features were the atrophic scarring (tissue destruction), chronicity, and the xanthomatous deposit in the lesions. Diagnosis: necrobiosis lipiodica diabetorum.

*X-rays.* An intravenous urogram was normal. Gastrointestinal x-rays revealed a normally functioning gallbladder without stones. The stomach was large and showed a 15 per cent retention after four and one-half hours. The third portion of the duodenum was dilated. Partial duodenojejunal obstruction possibly due to congenital bands was suspected.

The blood counts were normal; blood urea 30 mg. per cent; Wassermann and Kahn tests negative; serum proteins totaled 7.2; albumin 4.9; globulin 2.3 grams per cent. Fractional test meal showed normal gastric acidity.

Continued rest, smooth diet, heat to the abdomen, the use of sedatives and antispasmodics, and regular emptying of the bowel failed to bring more than the slightest symptomatic relief. Five days later the patient returned to the office with the same complaints, having lost an additional seven pounds in weight since his first admission. Extenuating circumstances rendered further gastrointestinal investigation impossible, and, although neither gastrointestinal nor surgical consultants were at all enthusiastic, exploratory laparotomy was prescribed.

*Second hospital admission.* On June 1st the patient was readmitted to the hospital. His preoperative preparation included 10 to 20 grams of sodium chloride intravenously daily. On June 5th laparotomy was performed. No duodenal obstruction could be found. Many small hypertrophied lymph nodes were seen at the root of the mesentery. Those removed showed hyperplasia but no evidence of tuberculosis. The appendix was removed, and since no cause could be found for the abdominal distress, cholecystostomy was performed.

The postoperative course was relatively smooth. One thousand cc. of 5 per cent glucose in saline was given intravenously on the day of operation and on the following day. Considerable glycosuria and mild ketonuria appeared on the second, third, and fourth postoperative days. Blood sugar levels during this period varied from 150 to 256 mg. per cent. Blood pressure remained about 110 systolic and 80 diastolic, the pulse approximately 120. Intravenous glucose in saline was not given from the second to the fifth postoperative day. The patient appeared unusually listless and could be persuaded to take nourishment only with considerable difficulty.

On the sixth and seventh days 5 per cent glucose in 1 per cent saline was given intravenously, and the patient seemed to show a more marked symptomatic response than usual. Blood sodium was 354 and potassium 16.0 mg. per cent. On examination of the daily chloride excretion, we suspected that he was retaining blood chlorides with abnormal difficulty. It was at this point that Addison's disease was seriously suspected, and Kepler's adrenal function test was ordered.

## DIABETES MELLITUS

The amounts of urine excreted were as follows:

10:30 p. m. to 7:30 a. m.....	605 cc.
8:30 a. m.....	62 cc.
9:30 a. m.....	143 cc.
10:30 a. m.....	313 cc.
11:30 a. m.....	386 cc.
12:30 p. m.....	94 cc.

Because the highest volume of any of the morning specimens was exceeded by the night specimen, this part of the test ("the water test") was positive and favored adrenal failure. The blood chloride level during the test fell to 495 mg. per cent. There was a trace of sugar in the urine at bedtime on the evening the test was begun, and none the next day at noon. Diabetic polyuria, therefore, was not a factor.

On June 19th, the 16th day postoperative, the patient was given 15 cc. of adrenal cortical extract subcutaneously in three doses, 1000 cc. of 5 per cent glucose in 1 per cent saline intravenously, and 5.0 mg. of desoxycorticosterone acetate intramuscularly. Subsequently, he was given 6.0 gm. of NaCl in enteric coated pills daily and 5.0 mg. of desoxycorticosterone acetate daily which later was reduced to 2.5 mg. The response was dramatic. Within two days his strength had improved markedly, and within the next few days his appetite was good. Within about 10 days the abdominal distress disappeared. Blood sodium on July 15, 1942 was 354 and potassium 16.0.

After the treatment had been followed for fifteen days it was discontinued for three days and Kepler's test was repeated. The water excretion was as follows:

10:30 p. m. to 7:30 a. m.....	222 cc.
8:30 a. m.....	6 cc.
9:30 a. m.....	9 cc.
10:30 a. m.....	21 cc.
11:30 a. m.....	64 cc.
12:30 p. m.....	55 cc.

The second procedure was calculated as follows:

$$\frac{\text{Urinary urea } 225 \text{ mg. } \%}{\text{blood urea } 57 \text{ mg. } \%} \times \frac{\text{Blood chlorides } 495 \text{ mg. } \%}{\text{urinary chlorides } 808 \text{ mg. } \%} \times \frac{\text{Largest 1 hr. vol. day urine } 64 \text{ cc.}}{\text{volume night urine } 222} = 6.9$$

Any factor below 25 is considered positive.

At the end of this test the blood urea had risen to 57 mg. per cent, and the blood chlorides had fallen to 495 mg. per cent. The blood pressure was 80 systolic and 60 diastolic. He was very weak, and he found it difficult to stand or walk. The anorexia had returned. Again following intravenous saline, cortical extract and "desoxy" he was almost completely rehabilitated overnight. At present his progress is excellent. X-rays of the adrenal areas showed no evidence of calcification. Chest x-rays demonstrated no signs of tuberculosis.

*Final diagnoses.* Diabetes mellitus, necrobiosis lipoidica diabetorum, Addison's disease.

The subsequent treatment in this case will include, firstly, a determination of the optimum dose of desoxycorticosterone acetate by continued use for an additional three weeks. After that it is planned that he will receive an implantation of pellets of "desoxy." If Schering's pellets are used, he will receive approximately 1.0 mg. per day from each 300 mg. implanted, and each 1.0 mg. per day absorbed from the implant has the approximate value to the patient of 2.0 mg. by injection. If the implant proves to be delivering too much hormone and abnormal retention of water is indicated by edema or by blood dilution (hematocrit, proteins, calcium, etc.), the amount of salt will be reduced. If it proves insufficient, more salt will be given.

Later we hope to study the possible stabilizing effect of adrenal cortical extract in this type of diabetes.

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