The Concomitance of Diabetes Mellitus and Addison's Disease

Brief Review of the Literature and a Case Report

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The occurrence of diabetes mellitus and Addison's disease in the same person is unusual. In a review of the literature, Stanton[1] in 1954 tabulated forty-six cases of the simultaneous occurrence of the two diseases; fifteen cases have been reported subsequently. These make a total of sixty-one cases reported in the literature, and they are summarized in table 1.

Diabetes mellitus precedes the development of Addison's disease in the majority of these combinations. Among the sixty-one patients, diabetes mellitus preceded adrenal insufficiency in forty-one instances; adrenal insufficiency appeared first in fifteen cases; and there was the simultaneous occurrence in only three individuals. The dual diagnosis was not made during life in five instances. Only twenty-eight of the cases were substantiated by autopsy. Twenty-six were living at the date reported.

In the series of sixty-one cases, there were thirty-four males and twenty-seven females. The ages ranged from ten to seventy-six years with the greatest number, eighteen, being in the two decades twenty to thirty-nine.

The duration of life following the dual diagnosis has been short in most cases. Nine lived less than one year; seven lived about one year; four lived two years; two survived three years; one, five years, and one lived eight years. The remainder were not determined except one was reported living after eight years,[2] and one after twelve years.[1]

Among the twenty-eight cases with post-mortem reports, the pancreas was found to present either fibrosis, atrophy, hyalinization, or fatty infiltration. Table 2 summarizes the pathology of the adrenal glands in this series. In this group, twenty-one represented atrophy, fibrosis, hypoplasia, or absence of the adrenals, or combinations of one or more of these. The etiology was tuberculosis of the adrenal glands in only six cases. Thyroid hypertrophy was noted in two patients. Pulmonary tuberculosis was present in five, abdominal tuberculosis in one, and positive tuberculin tests were described in only three.

Adrenal insufficiency alters coexisting diabetes mellitus in a number of ways. There is an unusual sensitivity to insulin, marked changes occur in the carbohydrate metabolism in the two diseases, and severe repeated hypoglycemic reactions occur. Although the therapeutic use of desoxycorticosterone acetate may not significantly alter the diabetic condition, there are diversified opinions on this point.[3, 4] The recognition of the diminution in insulin requirement, the frequent hypoglycemic reactions, the occurrence of Addisonian crises, and the dramatic electrolyte changes are demonstrated in the following protocol.

The rarity of the simultaneous existence of diabetes mellitus and Addison's disease would seem to justify the reporting of the present case, the diagnosis of which was corroborated by the findings at necropsy of tuberculosis of the adrenals and atrophy of the pancreas.

CASE REPORT

The patient, W.C., a forty-two-year-old cab driver, had enjoyed good health until approximately three months after his entrance into the United States Army in 1943. At this time he allegedly fell during mass calisthenics and sustained a back injury. Thereafter he remained hospitalized for several months until he was separated from the service because of "nervousness." Following discharge from the army he was hospitalized at a veterans' hospital where the diagnosis of probable schizophrenia was made. A review of both his army and veteran's hospital records revealed normal blood counts, urinalyses, fasting blood sugars, serologic tests for syphilis and X rays of the heart and lungs.

The patient was first seen by the senior author as an outpatient. In February 1947, he had multiple complaints of increased nervousness, severe frontal headaches, "fluttering of the heart," slight exertional dyspnea, aching over the left kidney area at times, frequency, nocturia and enuresis. Other history was not remarkable except for an entirely negative family history which included fifteen siblings who were living and well. Physical examination yielded normal findings except for obesity. He weighed 192 lb. and was 5 ft. 6 in. in height. All labora-

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tory data, which consisted of complete blood counts, serology, fasting blood sugar, and nonprotein nitrogen, urinalysis, electrocardiogram, basal metabolism test, radiograms of the chest and skull, were within normal limits. The impression at this time was psychoneurosis and moderate obesity.

The patient did not return again until March 1949. There had been a further gain in weight of fourteen pounds since the previous visit. There were no new abnormal physical findings except for acute bursitis. Complete blood counts and urinalysis were again normal.

About fourteen months later he returned complaining chiefly of frontal headache, nausea, dizziness and back ache. There was some suggestion of mental confusion. Weight was 201 lb.; blood pressure 130/86 mm. Hg. Physical examination was again within normal limits. The following normal laboratory data were obtained: hemoglobin 14.8 gm., normal urinalysis, fasting blood sugar 114 mgm. per 100 ml., nonprotein nitrogen 34 mgm. per 100 ml., carbon dioxide 25 mEq. per L., serum chloride 104 mEq. per L. A lumbar puncture was done with the finding of a normal opening and closing pressure, dynamics, cell count, protein, sugar, chloride, smear, culture and Wassermann test. The diagnostic impression was severe psychoneurosis. Psychiatric care was advised but refused.

In June 1951, he returned seemingly improved. Physical examination was nonrevealing. Weight was 200 lb., blood pressure 130/80 mm. Hg., hemoglobin 13.2 gm. per 100 ml., and urinalysis negative.

The diagnosis of diabetes mellitus was first made in May 1952, when the patient sought attention because of increasing weakness, drowsiness, weight loss, nocturia, urinary frequency, muscle soreness and increased nervousness. Appetite had remained good. In the eleven-month period since his previous visit there had been a loss of 11 lb. in weight. Blood pressure was 136/82 mm. Hg. No abnormal physical findings were recorded. The urinalysis revealed a four-plus sugar, no acetone or diacetic acid. Blood sugar was 502 mgm. per 100 ml. The patient was placed on 1,545 calorie diabetic diet with carbohydrate 150 gm., protein 90 gm., and fat 65 gm. divided in equal portions. Globin insulin 20 units daily was prescribed. The blood sugars thereafter varied from 156 mgm. to 250 mgm. per 100 ml. His weight remained stable.

In August 1952, he developed herpes zoster over the left posterior thorax. Weight was 190 lb. and blood pressure 128/72 mm. Hg. Urinalysis was normal and the blood sugar 170 mgm. per 100 ml. Approximately eighteen months later, January 1954, he returned because of a small infected sebaceous cyst on the posterior thorax which was removed. On questioning he revealed that he had taken no insulin for the previous seventeen months. The weight was 186 lb. The fasting blood sugar was 146 mgm. per 100 ml. A glucose tolerance test confirmed the diagnosis of diabetes mellitus.

In December 1954, he was seen again because of pronounced weakness, weight loss and anorexia present for the preceding four to five months. His weight was 166½ lb. and blood pressure 136/80 mm. Hg. There were no abnormal physical findings except that his face appeared somewhat tanned. Hemoglobin was 14.4 gm., packed cell volume 40 per cent, urinalysis negative, fasting blood sugar 158 gm. per 100 ml. and the serum electrolytes as follows: sodium 134 mEq. per L., chloride 94 mEq. per L., potassium 5.4 mEq. per L., and carbon dioxide 23 mEq. per L. Radiograms of the heart and lungs were within normal limits. Tuberculin, histoplasmin and brucellergin skin tests were negative. During the next few days there was a rapid progression of symptoms with increasing weakness and the appearance of nausea and intermittent vomiting. There was continuing gradual weight loss and possibility of adrenal insufficiency was now entertained for the first time. However, the blood pressure remained normal and there was no evidence of buccal pigmentation or other abnormal physical findings. Within the period of one week there had been a 7½ lb. weight loss. Twenty-four hour urine volumes on two occasions were 1,830 and 2,210 cc. An eosinophile count was 246 per cu. mm. Sedimentation rate was 8 mm. an hr. Serum electrolytes were repeated with values as follows: sodium 138 mEq. per L., chloride 100 mEq. per L., potasium 4.6 mEq. per L., and carbon dioxide 22 mEq. per L. The fasting blood sugar was 118 mgm. per 100 ml. The patient was persuaded to enter St. Thomas Hospital for further evaluation. Daily fasting blood sugars varied from 112 to 170 mgm. per 100 ml. Blood counts, urinalysis, nonprotein nitrogen, VDRL, electrocardiogram, radiograms of the heart and lungs, gastrointestinal series and barium enema were reported as normal. A subnormal concentration of test dye was noted in the gall bladder during cholecystography. There was symptomatic improvement during his eleven-day hospitalization and no additional weight loss during this interval. He was discharged on a 1,680 calorie diabetic diet.

During the one and one-half months following discharge from the hospital, however, there was an additional weight loss of 15 lb. and he had developed some "sinking spells" and difficulty in swallowing. The weight now was 141 lb. Physical examination was again normal except for brownish appearance of the face, neck and thorax. The fasting blood sugar was 116 mgm. per 100 ml., serum sodium 132 mEq. per L., chlorides 66 mEq. per L., and potassium 5.2 mEq. per L.; eosinophile count was 246 per cu. mm. Intravenous pyelogram, packed cell volume, liver function studies, serum amylase, serum cholesterol, protein bound iodine, L. E. cell preparations, urinary porphyrins and stool examination were all within normal limits. Determination of 17-ketosteroids was 8.2 mgm. per twenty-four hours. The Robinson-Kepler-Power water test showed prompt water excretion. There was no hormone or other specific therapy at this time.

For the next four and one-half months there was continuing anorexia, intermittent nausea and vomiting and gradual weight loss. In May 1955, he was admitted to a Veterans Administration Hospital with the only new outstanding finding of a persistently low blood pressure ranging between 80/60 and 92/64 mm. Hg. On admission the serum sodium was 122 mEq. per L., chloride 79 mEq. per L., and potassium 5.3 mEq. per L. There were persistently low serum sodium and chloride until sodium chloride tablets were given. The initial eosinophile count was 381 per cu. mm. Two twenty-four hour determinations of urinary 17-ketosteroids were 7.1 mgm. and 10 mgm. Two other determinations were about of the same order; a twenty-four-hour fast and a Thorn test were done in an effort to rule out Addison's disease. There were no adverse effects following the fast. Eosinophiles numbered 1,000 per cu. mm. and the fasting blood sugar 87 mgm. per 100 ml. The eosinophile count dropped to 300 per cu. mm. following the intravenous Thorn test. This was interpreted as reasonably good evidence against the diagnosis of Addison's disease. The patient was then seen by a psychiatric consultant who was of the

TABLE 1

Summary of additional dual diagnoses of diabetes mellitus and Addison's disease

Reference and case number	Year reported	Sex	Age in years			Autopsy findings	Remarks
			Onset of diabetes mellitus	Onset of Addison's disease	At death		
47 Rogoff[5]	1936	M	20	25	25	Died 5 months later.	Addison's disease following adrenal denervation.
48 McCullagh[6]	1942	M	—	7 years later	Living	Living at report.	Listed as young man. Chest film negative.
49 Balfour[7] & Sprague	1949	F	29	37	40	Atrophy of adrenal cortices, fatty infiltration of pancreas.	Previously treated for hyperthyroidism.
50 Balfour[7] & Sprague	1949	F	29	30	31	None.	Died at home of hypoglycemic reaction.
51 Breslow,[8] Lashof, & Klein	1953	F	48	52	Living	Living at report.	Tuberculin positive.
52 Jersild[9]	1953	M	21	29	Living	Living at report.	Many hypoglycemic reactions.
53 Markovitz[10]	1954	F	28	32	Living	Living at report.	Tuberculin negative.
54 Markovitz[10]	1954	M	17	26	32	No autopsy.	Died of hypoglycemia; X-ray chest suggested pulmonary tuberculosis.
55 Gurling,[11] Rockow, & Smith	1954	F	27	24	Living	Living at report.	Associated pregnancy. X-ray of chest negative.
56 Baird & Munro[12]	1954	F	23	42	Living	Living at report 3 years later.	Chest film negative.
57 Teichmann[13] & Leupold	1954	M	3 months after Addison's	48	Living	Living at report.	
58 Porteus[14]	1955	M	23	31	Living	Living at report.	
59 Gilbert,[15] Dreyfus, Siquier, Zara, Prunier	1955	M	53	51	Living	Living at report.	Poly-tuberculosis.
60 Krauter[16]	1955	F	42	46	Living	Living at report.	
61 Gould[17] & Shlevin	1955	M	10	15	15	Atrophy of adrenals, hypoplasia of pancreas.	Tuberculin test negative; chest film negative.

TABLE 2

Autopsy findings of twenty-eight reported cases of diabetes mellitus and Addison's disease occurring concurrently

Pathology of adrenal gland	Number of cases
Atrophy	9
Absence, atrophy and fibrosis	1
Atrophy and absence	1
Fibrosis and atrophy	5
Absence and hypoplasia	2
Absence and fibrosis	1
Fibrosis	2
Tuberculosis (present case included)	7

opinion that the case was probably that of schizophrenia in remission and hypotension. No specific treatment other than an increase in sodium chloride intake was prescribed.

In July 1955, approximately two months after his discharge from the Veterans Hospital, the patient returned complaining of continued weight loss, dizziness, occasional nausea and vomiting, cramping upper abdominal pain, negativism and occasional episodes, described by his wife, as being "unable to swallow" or "move a muscle." The weight had now diminshed to 129½ lb. Blood pressure was 90/60 mm. Hg. There was slight right upper quadrant tenderness, some tenderness over the right testicle and diminished knee jerks. Serum sodium was 104 mEq. per L., potassium 5.4 mEq. per L. The eosinophile count was 450 per cu. mm. and the fasting blood sugar 114 per 100 ml.; 17-ketosteroid excretion was 0.8 mgm. and 1.4 mgm. per 24 hr. Hospitalization was advised. He was admitted to the hospital at which time the serum sodium was 126 mEq. per L., potassium 5 mEq. per L. The 17-ketosteroid excretion varied from 0.7 to 1.8 mgm. per 24 hr. prior to adrenocorticotrophin stimulation. The highest figure observed after intravenous adrenocorticotrophin was 4.6 mgm. per 24 hr. This was considered as evidence of some response on the part of the adrenal cortex, but not a completely adequate one. Eosinophile count varied from 250 to 1,075 per cu. mm. and was considered to be compatible with the diagnosis of Addison's disease. The diagnosis of adrenal cortical insufficiency was further corroborated by the fact that he improved with the use of oral cortisone, 12.5 mgm. twice daily. This was apparent in his gain of weight and the return of his blood pressure and laboratory values to normal limits. However, after approximately one month he again complained of anorexia and appeared apathetic and discouraged although there had been no weight loss. His cortisone dosage was increased to 50 mgm. daily and he was instructed to take an additional sodium chloride tablet daily. He was referred to the mental hygiene clinic because of his depression. Because of the possibility that his continuing emotional reaction was related to too much rather than too little cortisone, the dose was reduced to 12½ mgm. daily and the dose of sodium chloride established at 4 gm. a day. On this lower dosage of cortisone he apparently did poorly and was seen four days later with most of the outstanding features of adrenocortical crisis. The serum sodium was 115 mEq. per L., potassium 6.3 mEq. per L., blood sugar 115 mgm. per 100 ml. and nonprotein nitrogen 72 mgm. per 100 ml. He was given 100 mgm. of cortisone intramuscularly and 1,000 cc. of 5 per cent glucose in normal saline and discharged on Aug. 19, 1955, with the hope that he would resume his normal eating habits. He continued to do poorly, however, and attempts to get him to go to local hospitals were unsuccessful.

On Dec. 18, 1955, the patient was admitted to St. Thomas Hospital approximately one hour after having taken a sleeping capsule; he was unable to move any part of his body and too weak to talk. Temperature was 98.6° F., pulse 76 a min., respirations 24 a min. and blood pressure was 88/60 mm. Hg. The skin appeared rather diffusely tanned and there were a few dark freckles over the upper chest, shoulders and back with some questionable increase in pigmentation in the palmar creases. No deep tendon reflexes could be elicited. There was no retinopathy. The physical examination otherwise was not remarkable. Hemoglobin was 14.5 gm., white blood count 12,150 per cu.mm., differential 42 per cent polymorphonuclear leucocytes, 6 per cent monocytes, 2 per cent eosinophiles and 1 per cent basophiles. The eosinophile count was 549 per cu. mm. The serum sodium was 121 mEq. per L., chloride 94 mEq. per L., potassium 8.7 mEq. per L., and carbon dioxide 21 mEq. per L. The nonprotein nitrogen was 74 mg. per 100 ml. and blood sugar 116 mg. per 100 ml. The electrocardiogram showed changes compatible with hyperpotassemia. Hypertonic saline intravenously and cortisone 50 mgm. every twelve hours and epinephrine in oil, 1 cc. intramuscularly as needed for hypotension, were started as emergency therapy. He responded to this initial treatment with a gradual gain in strength and ability to talk although he remained mentally clouded and confused. In an effort to restore electrolyte balance more completely and also with the idea of possibly reducing the cortisone dosage, desoxycorticosterone 2 mgm. daily was started. The sodium chloride dosage was continued at 3 gm. daily. On this regime there was a gradual weight gain and symptomatic improvement although he remained extremely withdrawn and negativistic with continuing evidence of a primary psychiatric disturbance. During twenty-seven days of hospitalization the serum potassium varied from 8.7 to 4.2 mEq. per L., sodium from 121 to 134 mEq. per L., and the carbon dioxide from 19 to 25 mEq. per L. Eosinophile counts ranged from 549 to 349 per cu. mm. and the fasting blood sugar from 110 to 170 mgm. per 100 ml. on admission to 35 mgm. per 100 ml. The serum amylase remained mildly elevated with values ranging from 120 to 180 units (normal 40-110). The PPD skin test for tuberculosis was 1+ at 72 hours. X rays of the heart and lungs and skull showed no abnormality. He was discharged improved Jan. 9, 1956.

Six days after discharge he returned having continued to gain weight, a total of 22 lb. in slightly less than a month, and with relatively few complaints. The blood pressure remained within normal limits. However, because of a serum sodium of 128 mEq. per L. and a 24-hour urinary sodium of 6.4 gm., desoxycorticosterone was increased to 5 mgm. daily and cortisone maintained at 100 mgm. daily. On Jan. 31, 1956, the patient expired, apparently after discontinuing the previously prescribed cortisone and desoxycorticosterone.

AUTOPSY REPORT

The body appeared well-developed, somewhat poorly nourished and there was a brownish mottled pigmentation of the forehead, face, neck and anterior and posterior thorax. Relevant findings were limited to the abdomen.

Pancreas: The pancreas appeared essentially normal in size and shape. There was a moderate increase in interlobular and intralobular connective tissue. The acinar tissue appeared essentially normal. There was moderate hypoplasia of the islets of Langerhans on microscopic study.

Adrenals: Both adrenals were markedly enlarged. One adrenal measured 9x8x7.5 cm. and the other adrenal measured 7x5x4.5 cm. On section the normal architecture of both glands was found to be completely replaced by caseous necrotic material. Multiple microscopic sections revealed almost complete replacement of the adrenal tissues by caseous necrosis. The few cortical cells that remained were swollen and vacuolated. Acid-fast stain revealed the presence of acid-fast organisms.

Kidneys: The kidneys each weighed 180 gm. The capsules

stripped with only slight difficulty, exposing a few small vascular scars. The cortices, medullary portions, calyces and pelves appeared grossly normal. Microsopic sections were not unusual. No intercapillary glomerulosclerosis was seen.

Examination of all other organs revealed no remarkable changes. The pituitary gland was not examined.

Final pathological diagnosis was: Caseous tuberculosis of the adrenal glands.

DISCUSSION

The present case illustrates the occurrence of diabetes mellitus and Addison's disease in the same individual. This was confirmed by post-mortem findings of tuberculous caseous necrosis of the adrenal glands with almost complete disappearance of the adrenal cortical tissue. Only six similar cases of this dual occurrence caused by proven tuberculosis of the adrenals are previously recorded in the literature. The antecedent diabetes mellitus in this patient became less severe and required no insulin after the appearance of Addison's disease. Even after the administration of cortisone, no insulin was required. The patient finally expired in adrenal crisis four years after the diagnosis of diabetes mellitus and six months after the dual diagnosis.

This instance of the simultaneous occurrence of these diseases in the same individual represents a rare occurrence of disturbed function in two closely interrelated endocrine systems. Although tuberculosis occurs commonly in poorly nourished diabetics, it rarely produces such adrenal destruction. The effect of the adrenal insufficiency produces the expected effect of lowered blood sugar and hypersensitivity to insulin. Moreover, special interest lies in the group where diabetes mellitus follows Addison's disease where it is least expected. An increased number of these dual combinations are being reported. As better knowledge of the variations in carbohydrate metabolism and the typical courses are recognized, the antemortem diagnosis should be made more frequently.

SUMMARY

Review of the medical literature reveals sixty-one cases of the concomitance of diabetes mellitus and Addison's disease. Of these, diabetes mellitus appeared first in forty-one instances, Addison's disease occurred first in fifteen, and the two diseases appeared simultaneously in three. Only twenty-eight cases have been confirmed by autopsy.

An additional case of the dual occurrence of diabetes mellitus (present four years) and Addison's disease (six months' duration) due to tuberculosis of the adrenal glands in a forty-two-year-old white male with autopsy findings is reported. Post-mortem diagnosis of bilateral adrenal destruction caused by tuberculous caseous necrosis has been previously reported in only six other cases.

SUMMARIO IN INTERLINGUA

Concomitantia de Diabete Mellite e Morbo de Addison

Le revista del litteratura medical revela sexanta-un casos de concomitantia de diabete mellite e morbo de Addison. Inter istos, diabete mellite appareva primo in quaranta-un casos, morbo de Addison appareva primo in dece-cinque casos, e diabete mellite e morbo de Addison appareva insimul in tres casos. Solmente vinti-octo del casos esseva confirmate per necropsia.

Es reportate un caso additional del occurrentia combinate de diabete mellite (de quatro annos de durantia) con morbo de Addison (de sex menses de durantia), causate per tuberculose del glandulas adrenal. Le patiente esseva un masculo blanc de quaranta-duo annos de etate. Le constatationes del necropsia es reportate. Un diagnose post morte de bilateral destruction adrenal causate per caseose necrosis tuberculotic se trova reportate in le litteratura in solmente sex casos additional.

REFERENCES

[1] Stanton, Eugene R., Jones, H. Water, Jr., and Marble, Alexander: Coexisting diabetes mellitus and Addison's disease. A.M.A. Archives Int. Med. 93:911-20, 1954.

[2] Thorn, G. W., Forsham, P. H., Frawley, T. F., Wilson, D. L., Renold, A. E., Tredrickson, D. S., and Jenkins, D.: Advances in the diagnosis and treatment of adrenal insufficiency. Am. J. Med. 10:595-611, May 1951.

[3] Crampton, Joseph H., Scudder, S. T., and Davis, C. D.: Carbohydrate metabolism in the combination of diabetes mellitus and Addison's disease, as illustrated by a case. J. Clin. Endocrinol. 9:245-54, 1949.

[4] Knowlton, Abbie I., and Kritzler, Robt. A: The development of diabetes mellitus in Addison's disease—case report with autopsy. J. Clin. Endocrinol. 9:36-47, 1949.

[5] Rogoff, J. M.: Addison's disease following adrenal denervation. J.A.M.A. 106:279-81, Jan. 1936, in a case of diabetes mellitus.

[6] McCullagh, E. P.: Two cases of diabetes mellitus: one with myxedema and one with Addison's disease. Cleveland Clin. Quart. 9:123-34, July 1942.

[7] Balfour, William M., and Sprague, Randall G.: Association of diabetes mellitus and disorders of the anterior pituitary, thyroid and adrenal cortex. Am. J. Med. 7:596-608, 1949.

[8] Breslaw, Leonard; Lashof, Joyce; and Klein, Charles: Diabetes mellitus and Addison's disease in one patient. Annals of Int. Med. 38:338-42, 1953.

[9] Jersild, M.: Diabetes mellitus o.g.mb. Addisonii (diabetes mellitus and Addison's disease). Ugesk. f. laeger (København) 115:1303-06, Aug. 27, 1953.

[10] Markovitz, Meyer: Coexisting diabetes mellitus and Addison's disease. Report of two cases. Metabolism 3:268-73, 1954.

[11] Gurling, R. J., and Rockow, F.: Addison's disease complicated by pregnancy and diabetes mellitus. Lancet 267:316-18.

[12] Baird, I. M., and Munro, D. S.: Addison's disease with diabetes mellitus; a case treated with cortisone. Lancet *1*:962-64, May 8, 1954.

[13] Teichmann, G., and Leupold, H.: Kombination von Morbus Addison und Diabetes Mellitus. Endokinologie (Leipzig) *32*:160-64, 1954.

[14] Porteous, W. M.: Diabetes mellitus with Addison's disease. A case treated with cortisone. New Zealand M. J. *54*:18-22.

[15] Gilbert-Drefus, Siguier, F., Zara, M., and Prunier: Sur un cas d'association diabète sucré et maladie d'Addison. Bull. Soc. méd. hop. Paris: *71*:86-88, Jan. 28-Feb. 4, 1955.

[16] Krauter, S.: Koinzidenz von Diabetes Mellitus mit Morbus Addison. Ztsch. f. inn. Med. Wien. *36*:322-28, July 1955.

[17] Gould, K. S., and Shlevin, E. L.: Addison's disease complicating diabetes mellitus in adolescence. Ann. Int. Med. *43*:1092-99, Nov. 1955.

MECHANISM OF INSULIN REACTIONS

The mechanism of insulin reactions is poorly understood. Formerly all insulin reactions were considered to be the result of hypoglycemia; however, experience has shown that the severity of the symptoms is not always proportional to the degree of hypoglycemia. In fact, symptoms such as hunger, tremulousness, sweating, and palpitation have frequently been observed in patients with normal or slightly elevated blood sugar. In general these symptoms are mild, but they may be very troublesome to the patient and even prevent good control of his diabetes.

Although Joslin states that no member of his group has observed an insulin reaction associated with a blood sugar level above 80 mg. per 100 cc., he further states that a rapid fall to a level slightly below 100 mg. per 100 cc. might give rise to symptoms that would hardly be felt under normal circumstances. Most observers believe that it is the rapid fall in blood sugar rather than the final level reached that brings about this apparent paradox of hypoglycemic symptoms without hypoglycemia. In sharp contrast with the above is the apparent absence of symptoms in the presence of severe degrees of hypoglycemia. Blood sugar levels as low as 40 to 50 mg. per 100 cc. have frequently been reported in individuals who apparently do not have symptoms. The wording "apparently do not have symptoms" has been used advisedly, since signs of hypoglycemia may often be found after a careful search. A slight increase in physical or intellectual activity may often quickly reveal the true situation and bring on more obvious symptoms. This type of reaction has become fairly frequent following the use of long-acting insulins.

The obvious similarity between such symptoms as sweating, tremulousness, palpitation, etc., produced by an injection of epinephrine, and those that occur in hypoglycemia was first pointed out by Boothby and Wilder in 1923. The theory that the symptoms of hypoglycemia might be due to an increase in circulating epinephrine was then further strengthened by the actual demonstration of an increase in circulating vasoconstricting substance, presumably epinephrine, in the presence of hypoglycemia. It was also shown that epinephrine not only brought about the release of glucose from the glycogen of the liver but also reduced the demands of the peripheral tissues on the circulating glucose. Epinephrine was thus shown to be an effective agent for elevating the blood sugar in the presence of hypoglycemia.

The association of the symptoms of disturbances in behavior, vision, speech, and consciousness early implicated the central nervous system in the causation of insulin reactions. In 1929 Joslin suggested that the effect of hypoglycemia on the central nervous system might be related to depressed activity of certain oxidative processes similar to that occurring in asphyxia. The demonstration that carbohydrate was the chief or only source of energy for nerve tissue tended to substantiate this theory. Studies by Himwich and others indicated a correlation between the degree of hypoglycemia and a reduction in activity of various centers of the brain. The higher centers were the first to fail, while a successive failure of lower centers occurred as the blood sugar continued to fall.

This theory and the supporting observations are fairly satisfactory in explaining the phenomena observed in hypoglycemic states rapidly induced by shock doses of fast-acting insulin. It does not explain the apparently contradictory nature of the central nervous system's reaction to the more gradually induced hypoglycemia seen in patients receiving long-acting insulins for the treatment of diabetes mellitus. The absence of symptoms in the presence of a blood sugar of 40 mg. per 100 cc. also remains a mystery.

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