DIABETOGENIC ACTION OF PITUITARY

Clinical Considerations

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CLINICIANS are becoming aware that knowledge of the various factors affecting carbohydrate metabolism is important to a better understanding and better control—perhaps eventually the cure—of diabetes in the human being. Although the faulty carbohydrate metabolism that characterizes diabetes mellitus most frequently is traceable to dysfunction of the pancreas and resultant deficiency of insulin, other factors also play important roles in carbohydrate metabolism and their action sometimes causes diabetes or affects an existing diabetes.

Pituitary hormones and other hormones related to pituitary and to adrenal function are parts only of a total complex having intimate connection with carbohydrate metabolism and with hyperglycemia. It appears that hyperglycemia, if sufficiently great or sufficiently long-lasting, in some people may precipitate lasting diabetes and eventually true insulin deficiency; very rarely, hyperglycemia may produce diabetes that is severe and temporary, as in the case reported by Del Greco and Scapellato.[1] The purpose of this paper is to review from the clinical aspect, relationships of pituitary and adrenal factors related to carbohydrate metabolism, in order to reveal some of the complexities of that metabolism and perhaps to gain more insight into means of reversing diabetes.

THE PITUITARY

The pituitary hormones that we think of as being responsible for the onset and persistence of some cases of diabetes in patients are: *growth hormone*, which operates in acromegaly; *adrenocorticotropic hormone* (*ACTH*) at fault in rare cases of pituitary tumor associated with Cushing's disease; and possibly another, "*the Cori factor*" that has bearing on hexokinase activity—it may be neither ACTH nor growth hormone.

Hyperpituitarism and Diabetes

Acromegaly: The diabetes of acromegaly is the clinical counterpart of experimental diabetes that is caused in animals by giving growth hormone. It

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is not possible to state with certainty in a given case whether an excess of growth hormone is the sole responsible factor, or whether this acts together with some excess of ACTH with excess of corticosteroids. Large adrenal cortices commonly have been found in acromegaly, and the studies by Venning and Browne[2] indicate that increased excretion of corticosteroids may occur. If excess ACTH is produced in acromegaly, one would expect the frequent development of Cushing's syndrome, but the two conditions rarely coexist. One case is reported by McCormick and associates.[3] Most observers are dissatisfied with the methods currently available for the estimation of excess corticosteroids, and those methods most recently developed have not yet been fully evaluated for acromegaly. It is to be hoped that the new methods of Sydnor and Sayers[4] for the determination of ACTH in blood will help to solve this part of the problem.

The incidence of diabetes in acromegaly has been variously estimated. The most frequently quoted figure is that of Coggeshall and Root[5] who reported that of 153 acromegalic patients, 35 per cent had glycosuria and 17 per cent had diabetes. We think it is fair to assume that many more than 17 per cent would have been classed as diabetic if glucose tolerance tests had been performed for all. It may be pertinent, however, that ACTH and cortisone cause glycosuria before hyperglycemia occurs as a result of their action.[6] Certainly it is not easy to relate the experimental facts with the low incidence of diabetes in acromegalic patients.

In our series of 76 acromegalic patients, 21 (28 per cent) were classified as diabetic. From the higher incidence it seems evident that mild diabetes, disclosed only by a glucose tolerance test, is present in many acromegalic patients or becomes clinically manifest.

The time lapse between the development of the first signs of acromegaly and the development of those of diabetes varies widely according to available figures. In Coggeshall and Root's[5] series, the time lapse ranged from 1 to 22 years and the findings of Goldberg and Lisser[7] are similar. Of the Clinic series of 21 acromegalic diabetic patients, in one patient the two conditions were diagnosed simultaneously, and in another there was a time lapse of 15 years between the diagnosis of acromegaly and that of diabetes; in the remainder, the time lapse ranged between these extremes.

Diabetes is said to occur much more commonly in women with acromegaly than in women in general. In our series there were 9 women and 12 men who were diabetic and acromegalic. In Coggeshall and Root's[5] series, the diabetes was much more common in those acromegalic patients who had family histories of diabetes.

Usually the diabetes that occurs in acromegalic patients is mild (Table 1), but severe diabetes does occur. In Coggeshall and Root's series, of the 16 patients who died, three died in diabetic coma. None in our series have had diabetic coma. Insulin resistance seems to occur more frequently in acromegalic diabetic patients than in the average diabetic patient; however, there are no accurate statistics to support this impression. We have under observation one acromegalic patient, a 48-year-old man, who requires a maintenance dose of

160 units insulin per day. Two other patients have required 220 and 175 units daily for brief intervals, but the usual requirement is in the range of 60 to 80 units.

Table 1.—*Blood sugar levels in 20 acromegalic diabetic patients*

Patient no.	Blood sugar, mg./100 ml.		Insulin,* units	
	Fasting	P.C.		
1	224	—	110 PZI	30 R
2	348	—	120 PZI	100 R
3	152	—	10 PZI	
4	285	—	—	
5	147	—	—	
6	188	—	10 PZI	
7	234	—		98 R
8	182	—	—	
9	—	294 (1 hr.)	—	
10	143	—	—	
11	165	—	65 PZI	10 R
12	366	213 (1 hr.)	—	
13	—	202 (1 hr.)	—	
14	—	168 (3 hr.)	—	
15	212	—	—	
16	234	—	—	
17	—	246 (2 hr.)	—	
18	342	—	66 PZI	10 R
19	186	—	—	
20	147	—	—	

**PZI—protamine zinc insulin; R—regular insulin.*

The muscular wasting of acromegaly and the signs simulating amyotrophic lateral sclerosis do not parallel the severity of diabetes. The muscular weakness may be extreme, or actual amyotrophic lateral sclerosis may be present with

very mild or no diabetes, or diabetes may be severe with no evident muscular wasting or weakness.

Diabetic retinopathy has been reported as occurring in acromegaly.[4] We have seen typical diabetic retinopathy in 3 of 21 acromegalic diabetic patients. One of the patients was a man who had had acromegaly for 12 years and diabetes for 8 years at the time retinal changes were first seen. His blood pressure was 160/100 mm. Hg. In another patient a few punctate hemorrhages were found; he was known to have had diabetes for only two years. His blood pressure was 110/60. The third patient was a 28-year-old man who had retinal hemorrhages that were actively recurring; he had been acromegalic for 10 years. He had had improvement in visual fields and apparent slowing of acral growth after removal of a pituitary tumor in 1944. However, he developed diabetes two years later —which was five years before retinopathy was found. His blood pressure was 120/90 mm. Hg. The type of renal failure seen in chronic diabetes, if it occurs, has not been recognized in our acromegalic patients. The paucity of cases of generalized vascular disease with renal failure may be related to the fact that most acromegalic patients die before their primary disease has lasted 15 years and that diabetes in them usually has existed for a much shorter time.

It is mentioned frequently in the literature that there is unusual variability in the severity of acromegalic diabetes. In a sense this is true, but in my own experience in watching the progress of acromegaly for years I have been more impressed by the fact that in most such patients the diabetes is mild and peculiarly stable—vastly different in this respect from the diabetes of so many patients in whom we struggle daily to try to attain adequate control. It is equally true, however, that diabetes may show ingravescence during maintained pituitary hyperfunction, and slow or sudden amelioration with decline in hypophyseal function. However, Darragh and Shaw[8] reported the development of diabetes in acromegalic patients despite the apparent arrest of the acromegaly subsequent to roentgen treatment of the pituitary.

Almy and Shorr[9] reported the development of mastoiditis and basilar meningitis in a 40-year-old man who had had diabetes and acromegaly for five years. He had required 60 units of insulin daily. When evidence of pituitary failure developed, the glucose tolerance became normal and remained normal for five years. John[10] reported the spontaneous disappearance of diabetes in a patient having acromegaly.

Balfour and Sprague[11] reported the case of an acromegalic patient who had had blood sugar levels as high as 384 mg. per hundred milliliters and had required 62 units of insulin daily. Following roentgen therapy directed at the pituitary, an acute episode occurred that was thought to have resulted from rupture of an intrasellar tumor. Subsequently, 10 units of insulin daily controlled the blood sugar at a level of 147 mg. per hundred milliliters.

Recently, Gurling[12] in London reported the case of a 49-year-old acromegalic man who had diabetes with blood sugars as high as 740 mg. per hundred milliliters and mild acidosis with severe coma and fever. The hyperglycemia was controlled with therapy. The temperature continued to rise, the coma continued,

and the patient died. Hypoglycemia in this instance apparently did not develop, although death was associated with pituitary necrosis.

In our own experience[13] reversal of diabetes in acromegaly has been seen to follow long-continued therapy with estrogen. Of six acromegalic women, five had diabetes mellitus. In all it was mild, according to glucose tolerance tests. Very large doses of estrogen were used. Stilbesterol was given in doses of 10 to as much as 50 mg. per day or ethinyl estradiol 1.0 to 5.0 mg. per day, which is 20 to 100 times the usual dosage. The changes were slow, taking months to occur. Although the patients were not on carefully regulated diets we believe that the changes are significant because they were progressive; they were consistent in all five patients and in addition, after the glucose tolerance had become normal or nearly normal during therapy, cessation of treatment was followed in three cases by a recurrence of abnormal glucose tolerance (Fig. 1). That

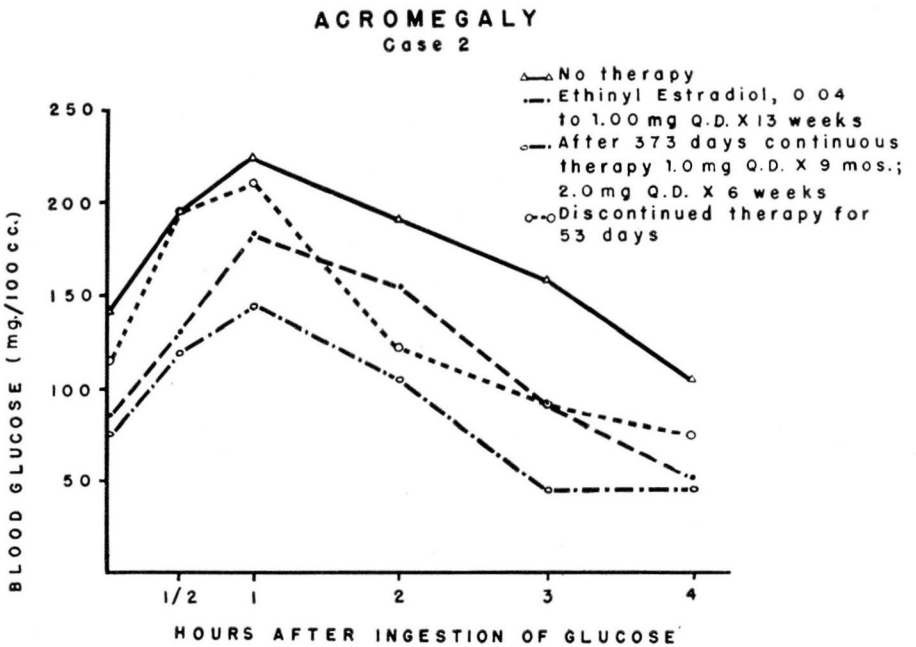

Fig. 1

estrogen suppressed growth hormone production was indicated by soft-tissue shrinkage and a sustained lowering of blood phosphorus levels. The change in glucose tolerance, I believe, was due in part at least to diminished production of growth hormone and the sequence of events tends to confirm animal tests by a clinical experiment.

The effect of growth hormone upon diabetes in the human being has been studied in one patient by Kinsell, Balch, and Michaels.[14] A "highly purified" growth hormone preparation was used. Under controlled conditions this caused

an increase in hyperglycemia and glycosuria and there were minimal evidences of ketonuria. The nitrogen balance changes also were minimal. The authors thought that these findings favored the idea that the effect of growth hormone was one that resulted more from interference with the utilization of insulin than from gluconeogenesis from protein breakdown.

In our laboratories we currently are measuring growth hormone by a method that measures purified pituitary extract in amounts as small as 5 micrograms. The test object is a hypophysectomized rat. The animal is given a standardized dose of radioactive sulfur, the theory being that sulfur is incorporated as sulfated chondroitic acid in the growing epiphysial cartilage. By this means it is hoped that we may study conditions in which an excess of growth hormone occurs, and that such a test may elucidate the relationship of growth hormone to clinical diabetes. Segaloff and associates[15] have recently reported success in measuring growth hormone by another procedure in small amounts of human plasma.

Studies along this line have been reported by Randle[16] in England. He has measured plasma-insulin activity in acromegaly. In regard to an assay for insulin, he points out that if the alloxan-diabetic hypophysectomized adrenalectomized rat is used, one actually is measuring a balance of effects of insulin versus insulin antagonists. For example, when an excess of glucagon, or some other substance that causes a relative insulin-immunity, is present, the assay indicates less insulin than actually is in the solutions tested. Randle[16] believes that if the glucose uptake of the rat diaphragm is used as a test object, glucagon, if present, will not interfere with the insulin measurement. Using this method, he measured insulin-like activity in normal persons, in diabetic and in acromegalic patients. He showed that a diabetic patient receiving insulin had more measurable insulin in the plasma than had a normal person. Plasma from acromegalic patients showed great insulin activity; in fact, measurably more than that usually found in normal plasma diluted up to 100 times. Randle substantiated his findings by showing that he could measure amounts as small as 2 milliunits of insulin as such and, moreover, that he could measure an increased insulin effect in normal plasma diluted four times and collected two and one-half hours after oral administration of glucose. At that stage the plasma contained not only more insulin than it did in the fasting state, but about as much as was measured as 2 milliunits.

Daughaday, Perry, and MacBryde[6] reported an increase in urinary "cortin" as determined by the formaldehydrogenic method in their acromegalic patient having insulin-resistant diabetes.

Hypopituitarism and Diabetes

It is now 32 years since Olmsted and Logan[17] called attention to the fact that pituitary activity has a striking effect on animal sensitivity to insulin, and it is nearly 20 years since Houssay[18] reported his now-classical experiments on carbohydrate metabolism. Severe anterior pituitary failure superimposed on diabetes in the human being is a rare occurrence: perhaps a dozen outstanding cases have been reported.[19-27] It is remarkable that although the general effects

Table 2.—*Summary of results of hypophysectomy in 26 patients having severe retinal and renal disease of diabetes mellitus*

Author	No. of patients	Length of postop. follow-up (mo.)	Deaths (no. of patients)	Hypertension		Albuminuria		Insulin required		Retinopathy	
				Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
Kinsell et al.[29,30]	6	up to 18	2(?)	Present	Absent	+	less	+	much less	4+	4+(?)
Luft et al.[31,32]	20	3—43	7	Present	Absent	+	less	to more than 60 U.	less than 15 U.	4+	Visual acuity improved in 7 patients

of Simmonds' disease were severe in all of the patients, the effects on pre-existing diabetes differed markedly. In one patient a glucose tolerance, previously diabetic in type, became normal[23]; and in another the insulin requirement decreased from 60 to 43 units per day.[24] At the other extreme, there are those who develop hypoglycemia. In one patient "excessive glycosuria" disappeared after acute pituitary necrosis[25]; blood sugar levels fell to 31 and finally to 20 mg. per hundred milliliters. Another patient who had been taking 35 units of insulin daily, discontinued this dosage as pituitary cachexia developed; she died in hypoglycemic crisis.[19] Another patient who had required 60 units of insulin daily, had a similar course: after pituitary necrosis, hypoglycemic crisis developed; she died despite the intravenous administration of 60 grams of glucose.

In instances of severe pituitary deficiency, sensitivity to insulin is very much greater than that seen in Addison's disease. This extreme sensitivity is dramatically illustrated in the case reported by Herstmann.[28] His patient was given intravenously a test dose of 8 units of insulin; she developed hypoglycemic coma and died, despite intravenous administration of glucose. Patients with hypopituitarism may have hypoglycemic reactions from as little as one unit of insulin given intravenously.

Hypophysectomy: Much interest centers about the effect of hypophysectomy on diabetes mellitus since Poulsen[21] observed the disappearance of all evidence of diabetic retinopathy in a 37-year-old woman after she had developed Simmonds' disease. The ocular signs consisted of punctate hemorrhages as well as larger retinal hemorrhages appearing as spots or stripes. There were a few remaining evidences of retinopathy four years after the development of cachexia. After seven years all evidences of that complication seemed to have disappeared.[21] Since that time, hypophysectomy has been performed upon some patients with diabetes, in an attempt to halt the progress or to alleviate degenerative disorders, particularly retinopathy. To date, the results have not been very encouraging.[29-32] A brief summary of the results that have been reported in some patients is presented in Table 2.

Cobalt Teletherapy: Recently we have attempted to produce hypopituitarism in patients having diabetes associated with severe retinopathy, by irradiation (exceeding 10,000 r) to the pituitary. Cobalt teletherapy was used. As yet, we have produced no measurable pituitary deficiency. Except in patients having acromegaly, there has been no significant fall in insulin requirements, blood sugar levels, or urinary steroid titers (Figs. 2 and 3).

PITUITARY-ADRENAL FUNCTION AND DIABETES

Three types of diabetes seen clinically are traceable to adrenocortical action: (1) that which begins with pituitary hyperactivity, such as in cases of pituitary tumor, excess adrenal stimulation, and Cushing's disease; (2) that which is seen in Cushing's syndrome or after exogenous cortisone—it appears to be identical with the first type except that it originates in the adrenal itself,

BLOOD SUGAR AND INSULIN DOSE AFTER COBALT TELETHERAPY 12,000 r TO THE PITUITARY IN DIABETES MELLITUS

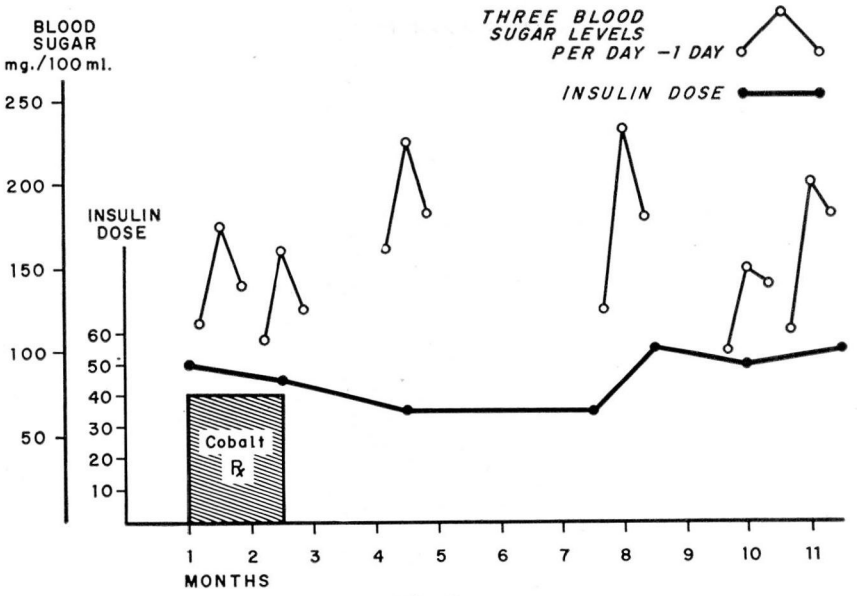

Fig. 2

COBALT TELETHERAPY 12,000 r TO THE PITUITARY IN DIABETES MELLITUS

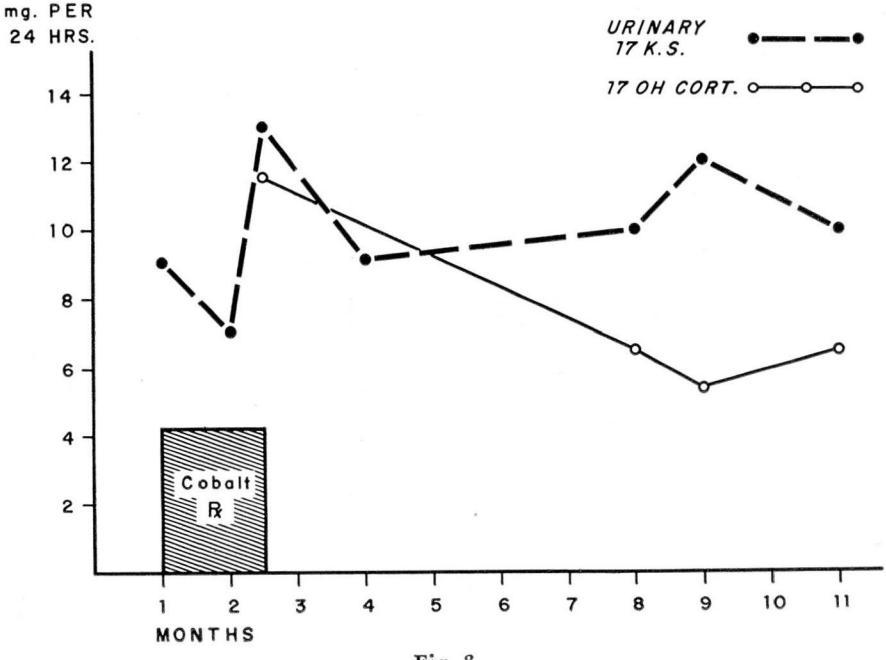

Fig. 3

and in most cases the diabetes is reversible; (3) that caused by an aldosterone-producing tumor. This latter is apparently rare: my associates and I have observed three patients with proven aldosterone-producing tumor. Two of these patients had mild diabetes and after removal of the tumor, the glucose tolerance became normal. There is no clear evidence that pituitary function controls the production of aldosterone.

Cushing's Disease Emanating from Pituitary Tumor: Figure 4 is a chart of glucose tolerance curves in a patient who had typical Cushing's syndrome associated with adrenocortical hyperplasia and who recovered after subtotal adrenalectomy. The reversal of the hyperglycemia is shown by repeated glucose tolerance curves (Fig. 4). Instances of this type in which the disease emanates

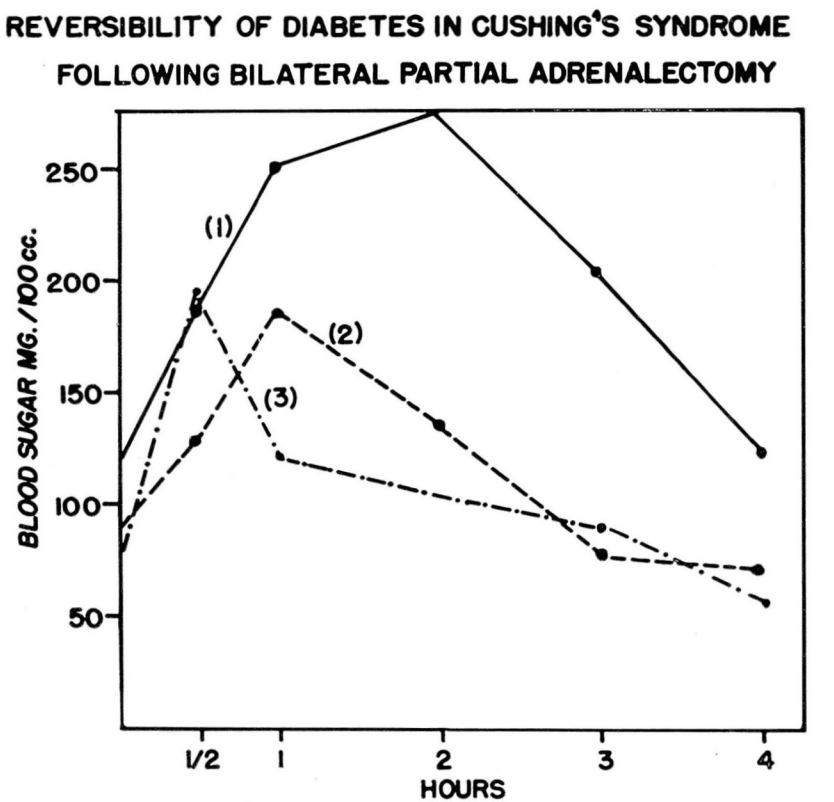

Fig. 4

from pituitary tumor usually are classified as *Cushing's disease*; however, they are rare. One of our patients had typical clinical Cushing's disease with pituitary tumor; the tumor was visualized roentgenographically and was proven at surgery. Presumably the diabetes, which was very mild, was caused by an excess of ACTH. The diabetes disappeared after local application of radioactive cobalt to the pituitary gland. Results of glucose tolerance tests before and six months after cobalt irradiation are presented in Table 3. Diabetes subsequently recurred and adrenalectomy was performed, but the patient died. He had a malignant adenoma of the pituitary.*

Table 3. — *Results of glucose tolerance tests before and after cobalt teletherapy*

Relation to treatment	Blood sugar, mg./100 ml.					
	Fasting	Time, hours p.c.				
		½	1	2	3	4
Before treatment	138	240	370	275	116	—
Six months after treatment	137	208	149	110	75	86

Hyperglycemia after Administration of ACTH: Dustan, Corcoran, Taylor, and Page[33] have shown that in patients with essential hypertension the injection of ACTH may cause hyperglycemia. Cohn and Kolinsky[34] have shown that temporary diabetes mellitus may appear after the use of relatively large doses of corticotropin.

In 1953, Zimmerman, Parrish, and Alpert[35] reported the effects of injections of 40 to 100 mg. of ACTH daily for 5 to 12 days in 17 patients with various conditions, only one of whom had diabetes mellitus. The responsiveness to insulin was measured by the glucose-insulin tolerance test. In this group there were only four patients in whom there was a significant loss of insulin sensitivity.

Recently Martin and Pond[36] cited a case of pituitary insufficiency in diabetes and showed that here, where apparently ACTH was lacking, as judged by extremely low levels of urinary steroids, the administration of ACTH caused a striking increase in insulin requirement and a considerable increase in glycosuria.

The administration of ACTH may have caused lasting diabetes in the case reported by Bishop and Glyn.[37]

Spontaneous Steroid Diabetes: Steroid diabetes arising spontaneously is due to excessive production of hydrocortisone-like compounds by the adrenals. Those hormones cause glycosuria partly by decreasing the ability of renal tubules to reabsorb glucose.[38] They also interfere with the action of insulin, and cause glycosuria and hyperglycemia by impairing carbohydrate utilization and by augmenting the breakdown of protein. Clinically, such diabetes is relatively mild and insulin-insensitive, and is associated with a negative nitrogen balance

**A patient of George J. Hamwi, M.D., Columbus, Ohio.*

that is not fully corrected by insulin. The diabetes usually disappears after the steroid excess has been corrected.

It is a remarkable fact that diabetes does not always occur in patients having severe Cushing's syndrome of long standing. Evidently, important protective homeostatic mechanisms are functioning in these cases and prevent the development of diabetes. We also have seen one patient who clinically had the adrenogenital syndrome with severe alkalosis but without diabetes.

Of 34 of our patients having Cushing's syndrome, 21 (15 women and 6 men) had diabetes. Insulin in dosages ranging from 8 to 90 units daily was prescribed for 7 of the 21 patients.

In patients having Cushing's syndrome it is difficult to ascertain a diabetic origin of vascular complications since the hypertensive disease is an integral part of the condition.

Among our 21 patients with Cushing's syndrome, three had retinopathy. One of the three patients had a hemorrhagic retinopathy not typical of diabetes, and the blood pressure was 175/120 mm. Hg. The remaining two patients had what was classified as *diabetic retinopathy*.

The possibility that certain chemical features of the diabetes associated with Cushing's syndrome are different from those in the average case of clinical diabetes has been studied by Hills, Power, and Wilder.[38] They found that in 34 patients having typical mild diabetes without Cushing's syndrome, the blood lactate and pyruvate levels were not distinctly abnormal. In contrast, in four of six patients having diabetes mellitus and Cushing's syndrome, the blood lactate and pyruvate levels were markedly elevated before the administration of glucose for a glucose tolerance test and rose still further after the administration of glucose. Two of the six patients had hypokalemic hypochloremic alkalosis.

As mentioned previously, long-standing steroid diabetes may not cause permanent diabetes. For example, in one of our patients who had a glucose tolerance of diabetic type before adrenal surgery, the diabetes not only disappeared postoperatively when adrenal insufficiency supervened but the glucose tolerance became that typical of Addison's disease. (Two of our patients in whom adrenal surgery provided complete clinical recovery from severe Cushing's syndrome, developed severe myocardial infarction ten years postoperatively.)

The fact that the steroid diabetes of Cushing's syndrome has *not* been shown to cause diabetic retinopathy more frequently than do other types of diabetes, may be partially attributable to variations in duration of diabetes: when diabetic retinopathy develops in a patient having Cushing's syndrome, the duration of the diabetes usually has been shorter than when diabetic retinopathy develops in a patient who does not have Cushing's syndrome.

It is unlikely that adrenocortical hyperfunction is a common cause of diabetes mellitus. The correction of steroid excess and/or the "cure" of Cushing's syndrome almost invariably result in the disappearance of diabetes, and those patients who have been known to have adrenal deficiency superimposed on diabetes mellitus have persistent diabetes.

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