Acquired Insulin Resistance

A Case Report

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Insulin resistance, usually defined as a condition in which a diabetic requires a dosage of insulin in excess of 200 units daily, is uncommon. Most of the reported cases have been associated with diabetic keto-acidosis, allergy to insulin, or a variety of other diseases. The following case is reported because none of these conditions was present and the opportunity for detailed investigation was possible. This disclosed, among other things, the presence of an insulin-neutralizing factor in the patient's serum.

CASE HISTORY

E. R., No. 53-552, a 36-year-old married woman, was first diagnosed as having diabetes mellitus in 1943; at this time she was 5 feet in height and weighed 70 kg. Admission to another hospital at that time revealed nocturia, glycosuria without ketonuria, and a fasting blood sugar of 312 mg. per 100 cc. Her diabetes was readily controlled with crystalline insulin, and she was discharged on diet alone. Subsequently, although her diabetic control was poor, she took insulin only intermittently.

The patient was admitted to this hospital Jan. 9, 1953, complaining of lower abdominal pain, frequency of urination with dysuria, and thirst. No insulin had been taken since the summer of 1952. There was no history of allergy. Examination revealed moderate dehydration. The temperature was 99.3, the pulse 135, and the respirations, 36. The blood pressure was 125/90. There was tenderness in both costovertebral angles; the remainder of the physical examination was normal. Urinalysis and culture confirmed the presence of a urinary tract infection, which was rapidly controlled with penicillin and sulfisoxasole. Subsequent to the first three days in hospital the patient felt well, was afebrile, and had no symptoms except those described below in direct connection with her diabetes.

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COURSE OF DIABETES IN HOSPITAL

On admission, the urine contained 6.2 per cent reducing sugar and gave a positive reaction for ketones. By the next day, no ketones could be detected, and thereafter at no time was ketonuria or ketonemia present. The initial finding was probably the result of decreased food intake associated with the acute infection. The dosage of crystalline insulin* was progressively increased until on February 6, the patient was receiving 1100 units per day in five divided doses. On this date for the first time her urine became sugar free. Insulin reactions over the next two days necessitated reduction in insulin dosage to between 500 and 700 units per day, and on this amount her control was good. This is shown graphically in figure 1.

Attempts to modify the insulin resistance by intravenous administration of insulin, the use of pork insulin, or insulin which had been denatured by heat were unsuccessful. The diet, which since admission consisted of 80 gm. of protein, 50 gm. of fat, and 150 gm. of carbohydrate, giving 1400 calories, was increased on February 25, to 80 gm. of protein, 90 gm. of fat, and 172 gm. of carbohydrate, giving 1870 calories. This diet remained constant thereafter. Twenty-four hour urine specimens had been examined for sugar from admission, but a more complete study was instituted on January 28, which is called day 1. This was expanded to include nitrogen and electrolyte balances on day 29, figure 2.

On February 20, day 23 of the study, the insulin was discontinued. Thereafter until day 43 none was given except for sensitivity tests. There was a rise in the fasting blood sugar, which ranged between 305 and 424 mg. per 100 cc. The urinary sugar was about 100 gm. per day, with a peak of 167 gm. In spite of this, the patient felt well and denied thirst or polyuria. As already stated,

*All insulin used, unless otherwise stated, was beef crystalline zinc insulin prepared by Connaught Laboratories, Toronto.

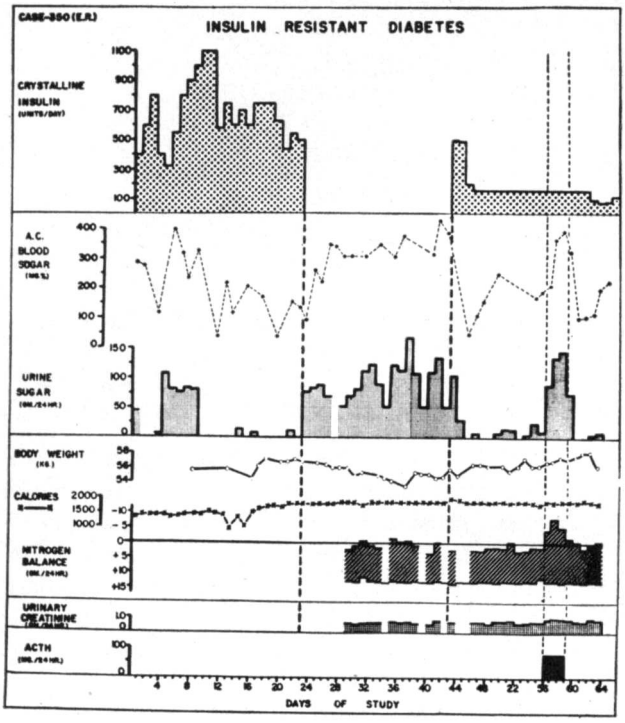

FIG. 1. The effect of insulin on blood and urine sugar.

there was no ketonuria or ketonemia. A gradual decline in weight occurred, from 56.8 to 54.7 kg.

On March 12, day 43, insulin was started again with 500 units per day in divided doses. The following day, the patient received 480 units, and the next morning she developed a severe insulin reaction. The insulin dosage was progressively reduced until on 160 units per day in four doses glycosuria was minimal and blood sugar values were within the normal range.

A course of corticotropin (Acton X), 20 units twice daily, was given from day 56 to day 59, inclusive. Although insulin and diet were unchanged, marked glucosuria up to 145 gm. per day and hyperglycemia as high as 390 mg. per 100 cc. fasting developed. After cessation of corticotropin, there was a temporary rebound effect, with insulin reactions on days 62 and 63. It is interesting that the patient complained of thirst for the first time while on corticotropin. She was discharged on April 4, day 66, on the same insulin dosage as before the course of corticotropin.

SUBSEQUENT COURSE

The patient's status remained unchanged until June 1953, when she had to be readmitted for a recurrence of the urinary infection. This again responded quickly to therapy. Diabetes was well controlled on four doses

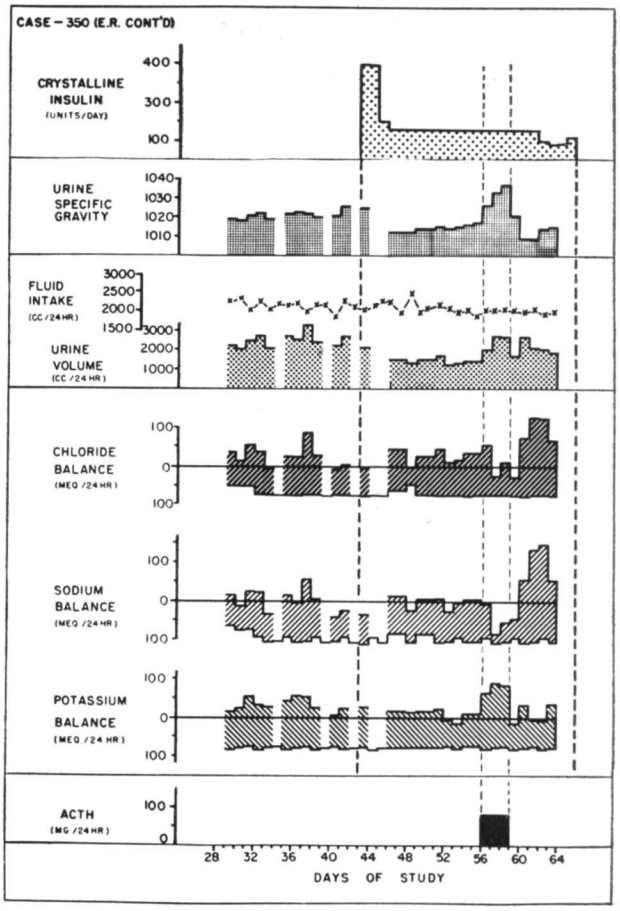

FIG. 2. Electrolyte and nitrogen balances.

of 40 units of crystalline insulin. She was discharged after two weeks in the hospital on 80 units of protamine zinc insulin and 32 units of crystalline insulin before breakfast and 32 units of crystalline insulin before lunch, with satisfactory control.

LABORATORY FINDINGS

The urine on admission contained protein graded +++ and pus in clumps. Thereafter no protein was detected and only 3 to 5 pus cells were present in a centrifuged specimen. Urine culture grew micrococci. Urea clearance was 102 per cent of normal, and ammonia, titratable acidity, and *p*H were all within normal limits.

The hemoglobin was 95 per cent and the red cell count 4,900,000. The white cell count was 7,000, with a normal differential. Eosinophils were never above 1 per cent. The sedimentation rate varied between 43 and 29 mm. in one hour. The Wassermann and Kahn reactions were negative.

Biochemical studies were as follows: nonprotein nitro-

gen 22.1 mg. per 100 cc.; serum proteins 7.08 gm.; albumin 4.58 gm., and globulin 2.5 gm. per 100 cc. Thymol turbidity was 12.1 units, and thymol flocculation was negative; the cephalin cholesterol flocculation was negative and the bromsulfalein test showed 6.8 per cent retention in thirty minutes. The serum total lipids were 700 mg. per 100 cc., fatty acids 389 mg.; phospholipids 8.8 mg.; cholesterol 209 mg.; and cholesterol esters 129 mg. These determinations were repeated at biweekly intervals, together with the serum electrolytes, calcium, and phosphorus, both when off and on insulin. All failed to show any change and except for the slightly elevated thymol turbidity were within the normal range.

Apart from the expected changes occurring with the administration of corticotropin, the electrolyte and nitrogen balances revealed nothing of note. These are shown in figure 2.

The glutathione content of ten samples of blood drawn fasting between day 25 and day 36 varied between 2.8 and 4.0 mg. (normal 3.8 mg. ± 0.7), expressed as sulfhydril groups in milligrams per 100 cc. corrected for 50 per cent hematocrit. There was no correlation between the glutathione level and the clinical course.

A galactose tolerance test was done on day 16. The patient was fasted after 8 p.m. the previous evening. The insulin requirements were 750 units at this time and the usual 4 a.m. dose of 150 units was reduced to 100 units. The results are shown in table 1. A very small rise in blood galactose is noted, indicating rapid conversion to glucose.

TABLE 1
Galactose tolerance test

Time	Blood glucose (mg. per 100 cc.)	Blood galactose (mg. per 100 cc.)
8:00 a.m.	204	
8:30 a.m.	197	
9:00 a.m.	194	
Galactose, 40 gm. orally		
9:30 a.m.	228	0
10:00 a.m.	237	2.5
10:30 a.m.	242	4.2
11:00 a.m.	212	0

Insulin sensitivity tests were performed fasting, no insulin having been given since midnight the evening before. Forty units of crystalline insulin were injected intravenously on each occasion. The results are shown in table 2.

TABLE 2
Insulin sensitivity tests

Day	0	15 min.	30 min.	60 min.	Per cent fall
22	154	128	117	117	24
37	373	339	335	309	17
50	248	216	192	159	36
58*	362	392	344	326	10
60	321	296	296	262	18

*Insulin had been boiled for 30 minutes; 48 units were used.

Tests for insulin-neutralizing activity in the patient's serum drawn on March 9, 1953, day 41, were performed using the technic described by Lowell.[1] The first series was done in March. The serum was then stored at —10° C. and a further series of tests were done in January 1954. There was no difference in the neutralizing activity of the patient's serum before and after storage.

Adult male mice fasted for sixteen hours, but with free access to water, were used. Blood sugar determinations were made by the Folin-Wu method on 0.1-ml. samples from the tail veins, using 0.26 mg. of heparin as anticoagulant. After some practice blood was obtained without difficulty. After taking the first blood sample, 0.2 ml. of the patient's serum plus 0.01 unit of crystalline insulin mixed just prior to injection were given intraperitoneally in a total volume of 0.7 ml. The serum of a diabetic responsive to insulin in usual doses was employed as a control. Both sera were dialyzed before use to make them almost sugar-free. Subsequent blood samples were then obtained at thirty and sixty minutes. As these were usually the same, a single forty-five minute specimen was later obtained. The results are shown in table 3.

TABLE 3
Tests done in March 1953 to demonstrate insulin-neutralizing activity of the patient's serum

Group	No. of animals	Average per cent change in blood sugar	Standard deviation
Patient's serum and insulin	5	+ 3.1	7.44
Control serum and insulin	6	—52.6	14.73
Patient's serum and saline	6	— 7.8	26.3
Control serum and saline	5	— 7.1	15.1

It is apparent that the patient's serum completely prevented the fall in blood sugar, which was seen when the control serum was used.

Using a method of starch electrophoresis, to be described in detail in a separate publication,[2] the patient's serum was separated into six fractions, albumin, alpha, beta, gamma 1 and 2 globulins, and the starch blank adjoining the gamma 2 globulin fraction. Each fraction was then assayed in the mice, using the same quantitative amount of material as present in the original serum. The results are shown in table 4.

TABLE 4

Tests done in January 1954 to show with which protein fraction the insulin-neutralizing factor is associated

Group	No. of animals	Average per cent fall in blood sugar	Standard deviation	P values 0	γ^2	γ^1
0 (starch blank)	14	22.6	16.15			
γ^2	12	5.5	15.75	<0.05		<0.01
γ^1	8	27.5	13.27		<0.01	
B	8	49.8	9.83			<0.01
A	7	44.6	7.62			<0.01
Albumin	6	42.4	15.23	<0.05	<0.01	<0.1
Patient's whole serum	7	6.4	10.39			
Control serum	4	48.6	6.42			

Maximum neutralizing activity is in the gamma 2 globulin fraction, with smaller amounts in the starch blank and gamma 1 globulin. These probably represent incomplete separation of the active principle.

Electrophoresis of the patient's serum in the Tiselius apparatus after storage for ten months showed it to contain albumin 51.22 per cent, alpha[1] globulin 3.61 per cent, alpha[2] 10.28 per cent, beta 15 per cent, and gamma 19.89 per cent. The beta and gamma globulins were elevated above normal.

Endocrine assays included gonadotropins (F.S.H.), positive at 13.2 mouse units per twenty-four hours and negative at 52.8 mouse units per twenty-four hours. The biologic corticoids were 46 glycogenic units per twenty-four hours and the 17 keto-steroids 4.2 mg. per twenty-four hours. The basal metabolic rate was —4 per cent. All these are within normal limits.

Allergy tests included skin testing to crystalline, protamine, and globin insulin. No difference from controls done at the same time was seen. The Prausnitz-Kustner test, using crystalline insulin, was negative. The precipitin test, using crystalline insulin, 80 units per cubic centimeter as antigen, was negative on two occasions, both at times of maximal insulin resistance.

Radiologic examination of the skull, chest, and urinary tract by excretory and retrograde pyelography was normal.

DISCUSSION

Comprehensive reviews of the literature dealing with insulin resistance have been published.[3–5] Associated conditions have included disorders of the hepatobiliary system, pancreatic disease, endocrine diseases, infections of different types, keto-acidosis, and insulin allergy, either localized or generalized. No clinical or laboratory evidence of any of these conditions was present in this patient.

Insulin, although a protein, is a very weak antigen. In some cases circulating antibody has been demonstrated by the precipitin test,[6] by insulin-neutralizing effect, and recently by using a hemagglutination technic.[7] In patients with allergic manifestations, antibody may sometimes be shown by the passive transfer test.[6] Intermittent administration of a foreign protein is an excellent way to stimulate antibody production and has been suggested as important in insulin resistance.[6] In this patient, insulin was injected at intervals over several years and may have been a factor in the development of her resistant state.

Localization of the insulin-neutralizing factor predominantly in the gamma[2] globulin fraction is compatible with the previously expressed views that it is an antibody to insulin,[8] and confirms the findings of Filippis and Iannacone.[9] The presence of cutaneous reactions or systemic anaphylactic phenomena to insulin probably depends on a separate antibody,[8] there being no necessity for both to be present at the same time, in the same protein fraction,[10] or, indeed, in the same patient.

There was no evidence that the results obtained in the mice experiments were due to a hyperglycemic principle in the patient's serum, since injection of the serum alone into mice did not produce hyperglycemia.

In view of the known action of corticotropin and adrenocortical hormones to affect some immunologic mechanisms,[11] and because of reported benefit from corticotropin administration in a case of insulin resistance,[12] it was believed that its use in this patient would be of interest. Although her insulin requirement at this time was only 160 units per day, this is considerably more than the dose known to have controlled her dia-

betes several years previously. Marked aggravation of the diabetic state occurred with corticotropin, and for this reason it was discontinued. The temporary period of increased sensitivity after cessation of the hormone may have been due to transitory depression of endogenous corticotropin with temporary adrenal insufficiency.

The ability of this patient to withstand inadequate carbohydrate utilization over a prolonged period of time without developing any apparent abnormality in fat metabolism is interesting. The distinction between the young labile diabetic who rapidly develops ketosis on insulin withdrawal and the obese elderly person in whom ketosis is uncommon comes to mind. This patient would apparently fall into the latter group, in spite of the marked hyperglycemia and glycosuria.

Maintenance of good diabetic control in patients with insulin resistance is difficult but probably worth-while, even though it necessitates the daily injection of large amounts of insulin. Often after a period of weeks or months the resistance will decrease. Although denaturing the insulin protein by heat may be of value in cases with allergic symptoms,[13] in this patient it did not seem to be of any value. If an approximate idea of the daily insulin requirement can be obtained, the administration of the full requirement after several days during which no insulin has been given may alter the degree of resistance. This seemed to occur in this patient when insulin was reinstituted on day 43. In this regard the insulin sensitivity tests, using 40 units of crystalline insulin intravenously, were a good guide to the degree of resistance present at any one time in this patient.

SUMMARY

A case of idiopathic insulin resistance in a diabetic is described. The patient's serum contained a factor in the gamma globulin fraction capable of neutralizing the hypoglycemic action of insulin.

ACKNOWLEDGMENTS

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SUMMARIO IN INTERLINGUA

Acquerite Resistentia a Insulina: Reporto de un Caso

Es describite un caso de idiopathic resistentia a insulina in un patiente diabetic. Le sero del patiente contineva in le fraction de globulina gamma un factor capace a neutralisar le effecto hypoglycemic de insulina.