Predisposition to Diabetes as Evaluated by the Cortisone-Glucose Tolerance Test in Children

A Preliminary Study

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SUMMARY

Cortisone-glucose tolerance tests with progressively increasing doses of the steroid were performed in healthy children born to diabetic parents belonging to different mating types. The results suggest that predisposition to diabetes can be detected in younger offspring by using a critical dose of cortisone.

Predisposition to diabetes seems to be a constitutional state governed by heredity. This assumption is supported by studies on overt familial diabetes.[1-6] It is generally accepted that the diabetic constitution is inherited as a recessive pattern in which about 20 per cent of the homozygotes develop overt diabetes;[7] but there is also evidence suggesting that diabetes may be genetically heterogeneous since certain pedigrees appear to be compatible with dominant inheritance.[4] However, it would be astonishing if a clearly deleterious gene were found to have a population frequency many times higher than the known mutation rates unless a heterozygous state more advantageous than the corresponding homozygous state were postulated.

Phenotypic manifestation of the diabetic predisposition is too variable to permit segregation analysis to be conducted properly. Presently, the diabetic state can be detected as a slightly diminished tolerance for a glucose load, but a simple way to relate the subclinical state of the disease to overt diabetes is not available. Since the change of subclinical to overt diabetes can depend on a constellation of physiological and environmental factors[8] operating during the whole life span, the age of the patient is an important determinant. A large fraction of predisposed genotypes are never detected as they are eliminated by premature death.[7,9] In addition, the subclinical state or "prediabetes" may never change into clinical or overt diabetes even in predisposed subjects belonging to the old age group.

Sensitization by cortisone prior to a glucose tolerance test may indicate predisposition to diabetes[10,11] and uncover a subclinical defect in carbohydrate metabolism. However, no optimal dose of steroid which would permit us to make feasible segregation analysis has been found. Recently it has been shown that the discriminant value of cortisone in the detection of subclinical diabetes can vary among different age groups.[11,12]

The purpose of this communication is to report preliminary data on the effect of varying doses of cortisone on the cortisone-glucose tolerance test applied to young offspring with one or more diabetic parents.

MATERIAL AND METHODS

The present investigation is based on 189 tests performed in children born to different parental groups: (1) thirty-nine tests were done in eleven children (four years to twenty years of age) with both parents affected with overt diabetes; (2) 138 tests were done in thirty-five children (four years to twenty-one years of age) with one diabetic parent; (3) twelve children (from two to twenty years) with no diabetic parents were used as controls.

All the subjects were proved to have normal standard oral glucose tolerance tests (GTT) and were then tested for glucose tolerance (1.75 gm. glucose/kg. ideal body weight) with previous sensitization by different doses of cortisone (CO.GTT), namely 70, 140, 280, 350 and 420 mg. cortisone per m^2 of body surface*

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*As an example, for subject L.S., six years old, 104 cm. (3 feet, 5 inches) tall, weighing 15 kg. (33 pounds) and having 0.65 sq. m. of body surface the actual dose of cortisone at the level of 280 mg. per sq. m. of body surface would amount to about 182 mg.

until a positive test was obtained. The interval between testing was more than one week. Half of the dose of cortisone was given eight and one-half and the other half two and one-half hours prior to the oral glucose overload. Blood glucose was determined according to the Nelson modification of the Somogyi method.[13] A test giving a two-hour blood glucose level of 140 mg./100 ml. or above was considered to represent a "positive response" in accordance with the criterion of Fajans and Conn.[10]

RESULTS

Table 1 shows the frequency of positive responses for different doses of cortisone applied to children up to sixteen years and to subjects between sixteen and twenty-one years of age.

It is apparent from table 1 that age has a marked influence upon responses of the subjects to the cortisone. As a whole, the frequency of positive responses within the younger group (up to sixteen years of age) was lower than that of the older one (sixteen to twenty-one years of age) but the first group responded much less uniformly to the different doses of cortisone.

The differences between these two age groups were more marked for 280 mg. of cortisone per m^2 of body surface, if allowance is made for the smallness of the number of tests for 420 mg. cortisone.

Table 2 shows the percentage of positive responses for different doses of cortisone applied to children of different parental types, as discussed above.

In table 2, a correlation is seen between parental diabetes and the percentage of positive response of the children. Again, this association is comparatively greater for the dose of 280 mg. of cortisone per m^2 of body surface. The children with no diabetic parents were tested only for a single dose (280 mg. of cortisone for m^2 of body surface), the parents being appreciably less cooperative due to their healthy state.

DISCUSSION

In spite of the smallness of the sample tested, table 2 suggests that the dose of cortisone administered prior to the GTT may be critical in revealing a tendency to diabetes. Doses of 280 mg. of cortisone per m^2 of body surface seem to discriminate more efficiently between young offspring of different mating types, a result consistent with the postulation that there may be a critical sensitizing dose of cortisone associated with the hereditary diabetic state.

SUMMARIO IN INTERLINGUA

Predisposition a Diabete, Evaluate in Juveniles per le Test del Toleration pro Glucosa con Cortisona: Un Studio Preliminari

TABLE 1

Frequency of positive tests for different doses of cortisone in children of diabetic parents belonging to different age groups

Age group	Cortisone dose (mg.) per m^2 of body surface																	
	70				140				280				350				420			
	1 parent		2 parents		1 parent		2 parents		1 parent		2 parents		1 parent		2 parents		1 parent		2 parents	
	No.*	Per cent†	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Up to 16	23	0	5	0	23	13	5	0	22	9	5	60	9	22.2	2	50	6	16.6	1	0
16 to 21	12	25	6	20	10	30	6	50	10	40	6	80	2	5	2	50	1	100	1	100
All ages	35	8.5	11	9	33	18.8	11	27.3	32	27.3	11	50	11	25.7	4	50	7	25.7	2	50

*Number of tests
†Percentage of positive tests

TABLE 2

Percentage of positive tests for different doses of cortisone among subjects classified according to the mating type of their parents

Mating type	Cortisone dose (mg.) per m^2 of body surface					All doses	
	70 per cent	140 per cent	280 per cent	350 per cent	420 per cent	No. of tests	Per cent
Both parents diabetic (11 children)	9.0	27.5	63.3	50.0	50.0	39	35.9
One parent diabetic (35 children)	8.5	18.8	18.7	27.3	25.7	138	14.5
No parent diabetic (12 children)	—	—	0	—	—	12	0

Tests del tolerantia pro glucosa esseva executate con progressivemente augmentate doses de cortisona in normal juveniles con parentes diabetic de diverse combinationes copulatori. Le resultatos suggere que un predisposition genetic pro diabete pote esser detegite in un progenie de juvene etate per le uso de un dose critic de cortisona.

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Carbohydrate in Low Protein Diets

High carbohydrate, low protein diets have been known to cause fatty metamorphosis and increased reticulin in the liver, gradual weight loss, and death in rabbits. The possibility that excess carbohydrate may in some way disturb metabolism in the animal led Macdonald to investigate this hypothesis further (J. Physiol. *160*:306, 1962).

Four groups of animals were studied. Group D represented the normal series, eating a diet consisting of 26.8 per cent protein. Group A rabbits consumed a diet consisting in parts by weight of: green food 25, dried yeast 2, salt mixture 5, and carbohydrate 68; these rabbits were fed ad libitum. The protein represented 6.7 per cent of the diet. Group B ate the same diet but was fed only three quarters, by weight, the amount eaten by Group A. Group C animals were fed, by weight, only one half the daily consumption of group A animals.

All animals had similar protein intakes, but the caloric intake of group B was three quarters that of group A and that of group C was one half of group A. These proportions were arranged by decreasing the weight of carbohydrate in the diets of groups B and C. The animals in the three groups were of equal weight. The amounts to be fed to groups B and C were determined from the amount eaten ad libitum by group A. A series of diets using sucrose, glucose, and starch as the carbohydrate source was studied. The weight of the animals was determined weekly. Oxygen consumption of those on the glucose and starch diets was also studied. Rabbits were sacrificed after they had lost one third of their control body weight. The liver was examined histologically and liver lipid and nitrogen were determined, as was muscle nitrogen.

The mean weight of the animals of groups A, B, and C declined in a similar fashion. Group A animals lost as much weight as the animals on the more restricted diets. No reducing substances were found in the urine to account for this loss. The metabolic rate, however, was lower in the latter groups since oxygen consumption decreased as caloric intake decreased.

Perirenal fat and yellow livers were seen in animals in group A but were absent in those in group C. As carbohydrate intake increased liver lipid increased, although for the glucose and starch series all livers except one had less fat than normal. In the sucrose series, the livers of four of five rabbits had higher lipid content than those of controls. Therefore, for a given protein intake, the amount of liver lipid appeared dependent

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