

A Six-minute Test with Glucagon-free Insulin in the Classification of Diabetes and Prediabetes

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Somogyi¹ pointed out that conventional tests for insulin tolerance are not adequate for determining sensitivity or responsiveness to insulin, since blood glucose below the fasting level rapidly initiates counter-regulatory mechanisms which promptly mask the degree of response to insulin.

The uncertainty of the period of action of the hyperglycemic factor existing in presently available crystalline insulin makes it quite impossible to appraise satisfactorily the primary influence of the administered insulin on blood glucose in respect to the promptness of initiation of action ("latent period" of Himsworth²) and in respect to the unhampered degree of fall in blood glucose. It is essential, therefore, that for a good test of responsiveness these latter two factors be registered before any extensive fall in glucose has had an opportunity to excite the body's counter-effort at homeostatic readjustment. Such time would fall well within the first few minutes after injection of insulin.

The valid criticisms of tests now in vogue for sensitivity to insulin can be obviated by careful timing, using an insulin which is free of the hyperglycemic-glycogenolytic factor (HGF or glucagon). The suggested responsiveness test with glucagon-free insulin records blood glucose readings in a time period before marked reactive compensatory phenomena have come into play, namely within the first six minutes after administration of the insulin. Under such conditions, only factors already residing in the individual and actively functioning at the very time of the injection of insulin could prevent the

initiation of a fall in blood glucose. These are anti-insulin factors peculiarly inherent in the individual and possibly actually creating the diabetic state in the obese adult.³

PROCEDURE

As controls, each of forty nondiabetic individuals (medical students and nurses) with no family history of diabetes was given three units of glucagon-free insulin by vein after a sixteen-hour fast. Determinations of the glucose content of venous blood were made with stop-clock timing precisely at 2, 4, 6, 12, 24 and 30-minute intervals after the glucagon-free insulin was administered. The Somogyi-Nelson macromethod for true blood glucose was used.

To obviate repeated venipuncture, a 20-gauge needle was inserted into an antecubital vein and a slow infusion of physiologic saline solution was instituted, thereby keeping the needle patent between blood withdrawals. The volume of saline solution infused during the six-minute period was rarely more than 60 cc. A tourniquet was used only at the time of insertion of the needle, the blood withdrawn at this time being discarded, as were the subsequent two or three samples over an eight-minute period before the sample designated as "fasting" was arrived at.

With regard to adrenal activity incidental to the procedure, every effort was made to place the subject at ease. Blood pressure readings were made before the test as well as frequently during it to detect any unusual play of adrenal response. Simultaneous pyruvate determinations were, however, not made. Glucose determinations on the first two or three discarded blood samples suggested that within eight minutes after the venipuncture the blood glucose had established itself at a fixed basic fasting level, whereupon in subsequent cases the insulin for testing was administered after an eight-minute period. A single team of two persons carried through all procedures, including the blood sugar determinations. Spot

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duplicate determinations were made, especially in event of bizarre readings.

FINDINGS

The dominant trend of change in blood glucose was well indicated within the first six minutes after the insulin administration, the line of depression thereafter often being interrupted by marked counterregulatory responses. The downward glucose trend then became more gradual and straightened out toward a nadir which usually occurred within the last twenty-four-minute period of the testing. Since in both nondiabetic and subsequently in diabetic individuals the nadir of the glucose curve ultimately arrived at could usually be roughly predicted by the behavior of the blood glucose pattern within the first six minutes of the test, and since, in a significant number of persons, varying amounts of insulin seemed to bear no consistent stoichiometric relationship to the results obtained, the study was ultimately confined to blood glucose patterns made over a six-minute period after a fixed dose of three units of glucagon-free insulin by vein.

The nondiabetic control subjects usually showed a drop of 19 per cent \pm 7 per cent from the fasting blood glucose level within the six-minute period.* Exceptions to this occurred in two types of cases: (1) in the obese but otherwise "normal" adult with normal blood glucose readings and glucose tolerance tests, who frequently exhibited poor responsiveness to glucagon-free insulin within the first six minutes of the test, as in the curves of diabetics presented in figure 2; and (2) in the normal individual whose fasting blood glucose happened to be exceptionally low, in which event further depression usually did not occur (probably a homeostatic defense against excessively low blood glucose).

The six-minute test was subsequently carried out in one hundred cases of diabetes unselected save for reliability of the diabetic history. In many of these the test was performed serially before and after effective treatment. In diabetic subjects customarily receiving insulin, a quick preliminary blood glucose level with the Wilkerson-Heftmann⁴ technic was recorded before the

test dose of insulin was administered in order rapidly to preclude the existence of any marked initial hypoglycemia before the test was started.

The responses in diabetic subjects conformed with three major distinctive patterns within six minutes after the insulin administration:

(1) The juvenile type of diabetic (at any age) unless markedly out of control usually showed a rapid precipitous drop in blood glucose (figure 1). This decline was with rare exception well on its way to consummation within four to six minutes. The attainment of excessive body weight in the juvenile type of diabetic or even the process of rapid gain in weight was often associated with the development of poor responsiveness to insulin, as in some nondiabetic obese individuals (figure 2). This lack of responsiveness was frequently reversible by weight reduction.

(2) The untreated obese-adult type of diabetic without "brittleness" commonly showed sluggishness of response apparent only after a latent period, a lack of fall in blood glucose, or even a rise to above the fasting level within six minutes after the insulin administration (figure 2). With adequate clinical treatment of the diabetes, including weight reduction, these poorly responsive persons (figure 2), usually showed curves tending to approach the responsiveness shown in figure 1 or anticipated in nondiabetic, nonobese subjects. When the uncontrolled obese diabetic ultimately develops an absolute beta-cell deficiency, his sensitivity (responsiveness) becomes extreme—far beyond the normal (cell paucity proved by postmortem examination).

(3) In the labile or so-called "brittle" diabetic, not only of the juvenile but also of the obese-adult type, there was an extremely precipitous and deep decline within the first two to four minutes of the test, followed by an equally sharp ascent, often to well above the initial fasting level—all within six minutes after the insulin administration (figure 3).

CONCLUSIONS

1. A practical, speedy clinical test for responsiveness to insulin is presented.
2. Glucagon-free insulin is utilized to avoid extraneous factors which in preparations of crystalline insulin ordinarily available in the United States and Canada counteract and mask the initial and earliest action of injected insulin.
3. Blood glucose values obtained within a six-minute period by this method yielded distinctive curves which permitted classification into three types: (a) the obese-

* Jørgen Pedersen of Copenhagen has pointed to the fact that even in the fasting state blood glucose fluctuates considerably. The average reading of three tests over the six minutes immediately before the insulin can be compared with the low points after injection of insulin. The sizable drop in responsive individuals ($19\% \pm 7\%$) precludes the practical need for this.

A SIX-MINUTE TEST WITH GLUCAGON-FREE INSULIN IN THE CLASSIFICATION OF DIABETES AND PREDIABETES

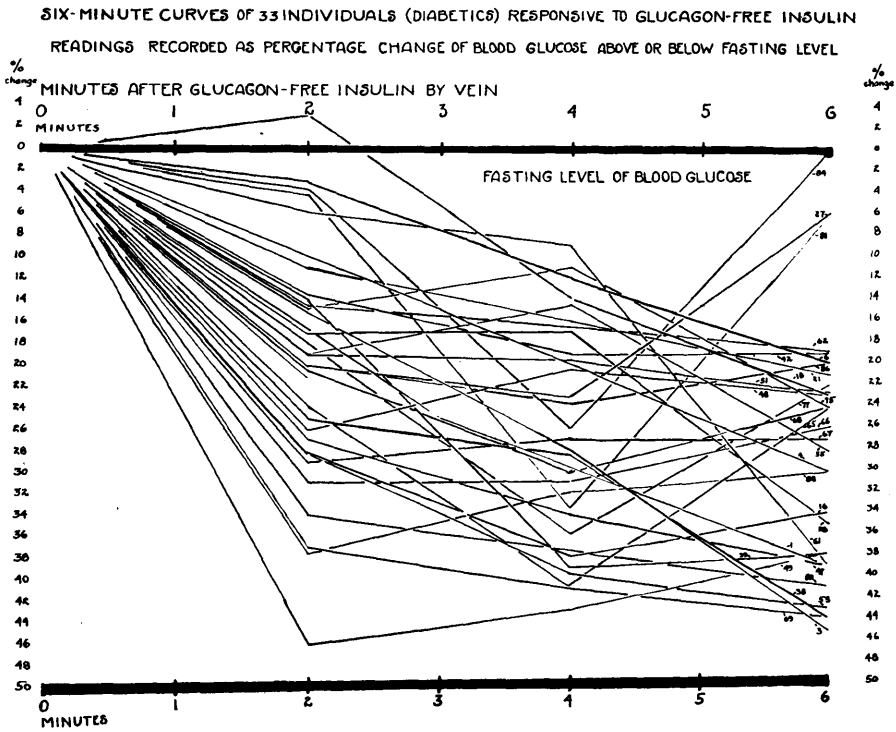


FIGURE 1

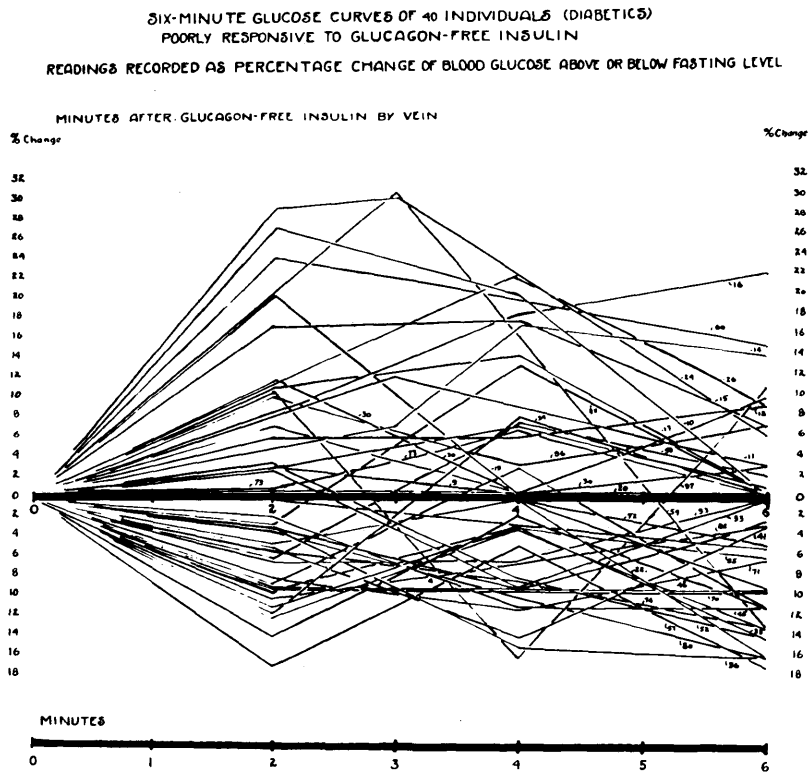


FIGURE 2

SIX-MINUTE GLUCOSE CURVES OF LABILE ("BRITTLE") DIABETICS
SHARPLY RESPONSIVE TO INSULIN WITH MARKED REBOUND

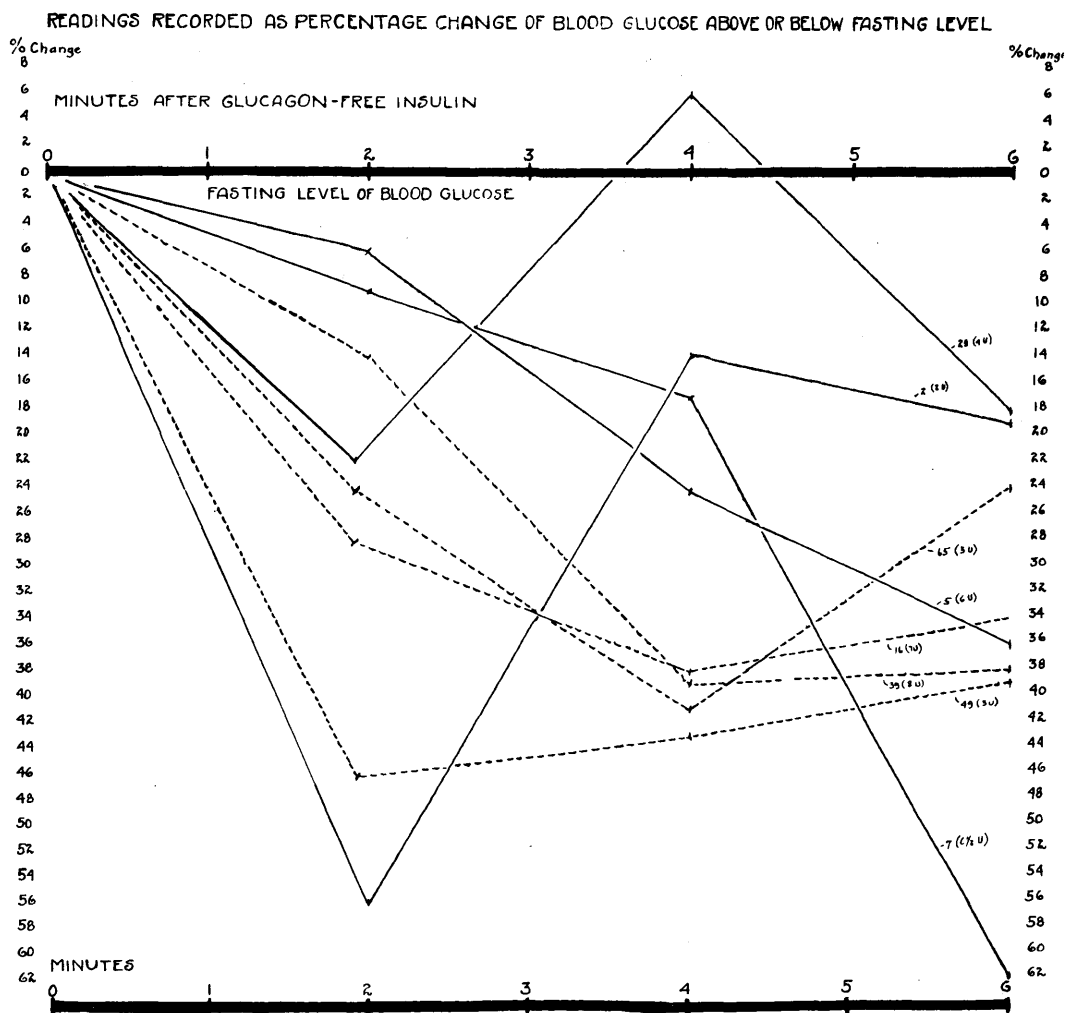


FIGURE 3

adult type of diabetic, before adequate treatment; (b) the juvenile type of diabetic, at any age, unless markedly out of glucose control, when the curve may approach that of (a); and (c) the labile or "brittle" type of diabetic.

4. The impaired responsiveness to-insulin in the non-diabetic obese but otherwise "normal" individual, who has normal blood glucose values and glucose tolerance test, raises the question whether faulty responsiveness to insulin as indicated by the six-minute test may not be a more delicate index of potential future clinical diabetes than are these conventional tests now in use.

5. Whatever may be the mechanism involved in the production of the phenomena presented, for example,

varying liver glycogenation, labile glycogenolysis, or other explanation, the information obtainable by this procedure is sufficiently definitive and reproducible to serve as one means of classifying diabetics.

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