Insulin release, insulin sensitivity, and glucose intolerance
(early diabetes/pathogenesis)

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ABSTRACT Groups of subjects with different degrees of glucose intolerance were examined in order to determine, first, the capacity of the beta cells to release insulin upon glucose stimulation and, second, sensitivity to insulin. The groups were selected on the basis of fasting blood glucose values and tolerances to oral and intravenous glucose administration. The body weights, ages, and sexes of the subjects were well matched with those of control subjects with normal tolerances to oral and intravenous glucose administration. Computer analysis of the glucose and insulin curves during a standardized glucose infusion test made possible the measurement of the initiatory (parameters $K_I$ and $I_P$) and potentiation (parameter $K_P$) effects of glucose on insulin release and of the sensitivity to endogenous insulin (parameter $K_C$). In subjects with impaired oral but normal intravenous glucose tolerance tests, $K_C$ was decreased, $K_P$ was increased, and $K_I$ and $I_P$ were normal. However, in these subjects, $K_I$ and $I_P$ were considerably lower than in a matched group of control subjects with the same decrease in $K_C$, but with normal oral and intravenous glucose tolerance tests. In subjects in which both oral and intravenous glucose tolerance tests were impaired and in subjects with mild manifest diabetes, $K_I$, $I_P$, and $K_C$ were decreased whereas $K_P$ was normal. These observations suggest that all stages of glucose intolerance are accompanied by a decreased ability of glucose to initiate insulin release and by decreased sensitivity to insulin. These derangements seem to be partially compensated for by enhancement of the capacity of glucose to potentiate insulin release in subjects with decreased oral but normal intravenous glucose tolerance tests.

By far the most common type of diabetes is the one for which the patient, at least in the beginning, does not require insulin and is not prone to ketosis. Most often it is diagnosed in adults and elderly subjects and is therefore called maturity-onset diabetes (1). There is ample evidence that two major abnormalities are present in the manifest form of this type of diabetes: impaired insulin response to glucose and resistance to insulin (2–6). However, it is not clear to what extent these derangements participate in the precipitation of glucose intolerance in subjects with normal fasting blood glucose values and decreased oral (OGTT) or intravenous glucose tolerance tests (IVGTT) or both. In the present work, we have tried to shed some light on this question by characterizing the insulin responses to oral and intravenous glucose administration as well as insulin sensitivity in groups of subjects with minor impairment of glucose tolerance or with mild maturity-onset diabetes.

SUBJECTS

One group was composed of 226 subjects (98 women and 128 men) with normal fasting blood glucose (<5.2 mmol/liter) and normal IVGTT ($K$ value <1.0). They were mainly blood donors, hospital staff, and other volunteers. Their body weight was 93% ± 0.6% (± SEM) of the ideal (7). Before they were accepted for the study, detailed case histories were obtained and physical examinations performed. In addition, a series of laboratory tests were done. On the basis of the information obtained, at least the following diseases could be excluded: anemia, heart failure, hypertension, liver or kidney disease, and malabsorption and endocrine disorders. No consideration was given to diabetes in the family history. A dietary history of each subject was obtained; all subjects were consuming a normal mixed Swedish diet with around 45% of the total caloric intake corresponding to carbohydrates. No subjects consuming more than an average amount of alcohol were accepted.

Another group was composed of 10 subjects (7 men and 3 women) with a normal fasting blood glucose (<5.2 mmol/liter) and decreased IVGTT ($K$ value <1.0). Their body weight was less than 115% of the ideal.

A further group consisted of 13 mild diabetics (8 men and 5 women) with a fasting blood glucose of >5.8 mmol/liter (range 5.9–11.1 mmol/liter) and a $K$ value of <1.0.

Among the 226 subjects with normal IVGTT, OGTT revealed that some had borderline or decreased oral glucose tolerance. The criteria used for the evaluation of the OGTT are given in Table 1. Thus, the subjects used in the present study were divided into the following groups:

- **Group A.** Normal fasting blood glucose, normal IVGTT and OGTT; $n =$ 164.
- **Group B.** Normal fasting blood glucose, normal IVGTT, slight impairment of OGTT (borderline-1); $n =$ 23.
- **Group C.** Normal fasting blood glucose, normal IVGTT, moderate impairment of OGTT (borderline-2); $n =$ 29.
- **Group D.** Normal fasting blood glucose, normal IVGTT, decreased OGTT; $n =$ 10.
- **Group E.** Normal fasting blood glucose, decreased IVGTT, borderline or decreased OGTT; $n =$ 10.
- **Group F.** Mild manifest diabetes; $n =$ 13.

Some data concerning groups B–F are given in Table 2, which also includes the matched control groups selected from group A.

METHODS

All tests were performed early in the morning with the subjects resting on a couch after 10–12 hr of fasting.

Glucose Infusion Test (GIT). The test was performed as described (3): 500 mg of glucose per kg of body weight was injected rapidly, and a glucose infusion at a rate of 20 mg/kg per min was initiated immediately thereafter and continued for 60 min. Venous blood samples were drawn through a catheter in a brachial vein of the opposite arm at 5- to 20-min intervals for 120 min. Insulin response to GIT was analyzed by parameter identification in a mathematical model (8). This

Abbreviations: OGTT, oral glucose tolerance test; IVGTT, intravenous glucose tolerance test; GIT, glucose infusion test.

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assumes that glucose initiates insulin release, first, by an immediate action (parameter $K_I$) and, second, by a time-dependent potentiating mechanism (parameter $K_P$) which amplifies the former action. The computer analysis of GIT allows the identification of a further parameter, $K_G$, determining the sensitivity of the tissues for insulin. From the hypothetical insulin release curve given by the mathematical model, an insulin value at 10 min was calculated, called $I_P$, which reflected the response to a standard stimulation by glucose.

**IVGTT.** Twenty-five grams of glucose was injected rapidly intravenously. Capillary blood samples were drawn before the injection and at 5-min intervals between 10 and 70 min after the injection. The disappearance rate of blood glucose (K value) was determined by the visual best fit of the values on semilogarithmic paper (9). Glucose tolerance was considered abnormal if the K value was <1.0.

**OGTT.** Glucose was ingested in a dose of 1.75 g per kg of body weight in 150–200 ml of water flavored with lemon. Venous blood samples were collected through an indwelling catheter before and 15, 30, 45, 60, 90, and 120 min after glucose ingestion.

**Analyses.** Blood was collected in heparin-containing tubes and centrifuged, and the plasma was kept at $-20^\circ$C for later analysis of its insulin content. Plasma insulin was determined by a double-antibody radioimmunoassay (10). Glucose was measured in whole blood with glucose oxidase (11).

**Statistical Methods.** Results are expressed as mean ± SEM, and the Mann–Whitney test was used for comparison of groups.

### RESULTS

As already mentioned, 10 out of the 226 subjects with normal fasting blood glucose and normal IVGTT had decreased OGTT, whereas 23 had slightly (borderline-1) and 29 had moderately (borderline-2) impaired OGTT (Table 2). The insulin responses to GIT and OGTT in these three groups (B, C, and D) were compared with those of control groups matched for age, sex, and weight (Figs. 1 and 2; Table 2).

In groups B–D with impaired OGTT and normal IVGTT, basal plasma insulin and early insulin response to GIT ($K_I$ and $I_P$) were not different from those of the controls (Fig. 1 and Table 2). On the other hand, insulin sensitivity ($K_G$) and IVGTT ($K_P$) were lower than in the controls. Plasma insulin during the late phase of OGTT and GIT was higher in groups B–D, but blood glucose was also higher during this period. The potentiatory mechanism ($K_P$) was elevated in groups C and D but significantly so only in group D (Table 2). This would suggest that the elevation in plasma insulin in groups C and D was not sufficient to compensate for the decreased insulin sensitivity, in spite of the exaggerated potentiation.

In order to test this assumption, the GIT of groups C and D were matched with groups of control subjects with the same degree of insulin sensitivity ($K_G$) but with totally normal OGTT and IVGTT (Fig. 3 and Table 3). In these control groups, plasma insulin was considerably higher during both the early and late phases of the GIT in spite of lower blood glucose levels.

### Table 2. IVGTT, basal glucose and insulin, insulin response to GIT, and insulin sensitivity in subjects with glucose intolerance and matched controls

<table>
<thead>
<tr>
<th>Groups of subjects</th>
<th>Sex ratio</th>
<th>Age, yr</th>
<th>Body weight, % of ideal</th>
<th>IVGTT, K value</th>
<th>Glucose, mmol/liter</th>
<th>Insulin, microunits/ml</th>
<th>$K_I$</th>
<th>$I_P$</th>
<th>$K_G$</th>
<th>$K_P$</th>
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<tbody>
<tr>
<td><strong>Group B: Normal IVGTT, borderline-1 OGTT</strong></td>
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<tr>
<td>Subjects</td>
<td>23</td>
<td>8/15</td>
<td>42.1 ± 2.5</td>
<td>94.9 ± 1.5</td>
<td>1.80 ± 0.13</td>
<td>4.3 ± 0.1</td>
<td>21 ± 1</td>
<td>0.71 ± 0.12</td>
<td>58 ± 8</td>
<td>46.6 ± 4.6</td>
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<tr>
<td>Controls</td>
<td>23</td>
<td></td>
<td>43.0 ± 2.4</td>
<td>94.9 ± 1.4</td>
<td>2.26 ± 0.20</td>
<td>4.2 ± 0.1</td>
<td>21 ± 1</td>
<td>1.01 ± 0.21</td>
<td>61 ± 6</td>
<td>63.1 ± 5.7</td>
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<td><strong>Group C: Normal IVGTT, borderline-2 OGTT</strong></td>
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<tr>
<td>Subjects</td>
<td>29</td>
<td>14/15</td>
<td>40.1 ± 2.3</td>
<td>94.5 ± 1.8</td>
<td>1.56 ± 0.09</td>
<td>4.4 ± 0.1</td>
<td>22 ± 1</td>
<td>0.53 ± 0.10</td>
<td>44 ± 8</td>
<td>41.3 ± 4.8</td>
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<tr>
<td>Controls</td>
<td>29</td>
<td></td>
<td>39.8 ± 2.3</td>
<td>94.9 ± 1.6</td>
<td>2.29 ± 0.21</td>
<td>4.0 ± 0.1</td>
<td>20 ± 1</td>
<td>0.76 ± 0.12</td>
<td>60 ± 8</td>
<td>72.0 ± 7.6</td>
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<td>$P^1$</td>
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<td>&lt;0.001</td>
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<td><strong>Group D: Normal OGTT, decreased OGTT</strong></td>
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<tr>
<td>Subjects</td>
<td>10</td>
<td>3/7</td>
<td>44.1 ± 3.7</td>
<td>100.3 ± 3.1</td>
<td>1.54 ± 0.22</td>
<td>4.5 ± 0.1</td>
<td>23 ± 2</td>
<td>0.64 ± 0.25</td>
<td>41 ± 9</td>
<td>30.9 ± 6.0</td>
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<tr>
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<td>44.4 ± 3.4</td>
<td>98.9 ± 2.3</td>
<td>2.13 ± 0.24</td>
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<td><strong>Group E: Decreased IVGTT, Impaired OGTT</strong></td>
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<tr>
<td>Subjects</td>
<td>10</td>
<td>3/7</td>
<td>45.5 ± 4.9</td>
<td>91.8 ± 3.2</td>
<td>0.93 ± 0.04</td>
<td>4.5 ± 0.1</td>
<td>19 ± 2</td>
<td>0.12 ± 0.03</td>
<td>12 ± 3</td>
<td>23.8 ± 3.6</td>
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<tr>
<td>Controls</td>
<td>20</td>
<td>6/14</td>
<td>44.4 ± 3.4</td>
<td>92.2 ± 1.6</td>
<td>2.18 ± 0.23</td>
<td>4.2 ± 0.1</td>
<td>21 ± 1</td>
<td>1.09 ± 0.18</td>
<td>71 ± 10</td>
<td>56.4 ± 8.4</td>
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<td>$P^1$</td>
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<td><strong>Group F: Mild manifest diabetes</strong></td>
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<tr>
<td>Subjects</td>
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<td>5/8</td>
<td>44.0 ± 4.2</td>
<td>96.8 ± 2.6</td>
<td>0.67 ± 0.04</td>
<td>7.3 ± 0.5</td>
<td>19 ± 1</td>
<td>0.10 ± 0.05</td>
<td>7 ± 2</td>
<td>24.3 ± 4.9</td>
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<tr>
<td>Controls</td>
<td>26</td>
<td>10/16</td>
<td>45.0 ± 3.1</td>
<td>94.5 ± 1.6</td>
<td>1.89 ± 0.12</td>
<td>4.2 ± 0.1</td>
<td>20 ± 1</td>
<td>0.91 ± 0.7</td>
<td>63 ± 10</td>
<td>57.2 ± 8.3</td>
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<td>$P^1$</td>
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* Results are expressed as mean ± SEM.

† Control subjects were selected from a group of 164 subjects (group A) with normal fasting blood glucose, OGTT, and IVGTT.

‡ Significance was calculated according to the Mann–Whitney test.
FIG. 1. — Insulin and glucose responses to GIT in subjects with impaired OGTT and normal IVGTT (groups B, C, and D), in subjects with decreased IVGTT (group E), and in subjects with mild maturity-onset diabetes (group F). - - - , Findings in sex-, weight-, and age-matched control subjects.

The latter finding is also documented by higher $I_P$ and $K_I$ in the controls. In groups E and F, insulin response to both intravenous and oral glucose challenges was decreased in spite of marked hyperglycemia (Figs. 1 and 2). This is further documented by substantial decreases in $K_I$ and $I_P$ (Table 2). Insulin sensitivity ($K_C$) was clearly decreased, whereas the ability to potentiate ($K_P$) was the same as in the control group. However, in some subjects of group E, $K_P$ was elevated, which is reflected by a high SEM (4.3 ± 1.2).

DISCUSSION

In the present study, groups of subjects with different degrees of glucose intolerance have been examined regarding two factors of major impact on blood glucose homeostasis: the capacity of the beta cells to release insulin upon glucose stimulation and the sensitivity of the body to insulin. The groups were selected on the basis of fasting blood glucose and tolerance to oral (OGTT) and intravenous (IVGTT) glucose administration and were well matched as to body weight, age, and sex with control subjects with normal glucose tolerance.

FIG. 2. — Insulin and glucose response to oral glucose administration in subjects with impaired OGTT and normal IVGTT (groups B, C, and D), in subjects with decreased IVGTT (group E), and in subjects with mild maturity-onset diabetes (group F). - - - , Findings in sex-, weight-, and age-matched control subjects.
The beta cell responsiveness to glucose was established by both oral and intravenous glucose challenges. The intravenous procedure makes possible the analysis of both the early and late insulin responses, whereas the oral procedure gives insight mainly into the later response (3, 6). Furthermore, the computer model used for analysis of GIT makes it possible to evaluate two aspects of the effect of glucose on insulin release: the initiation and the potentiation, characterized by parameters $K_I$ and $I_P$, on the one hand, and $K_P$, on the other (6, 8). A measurement of insulin sensitivity is provided by the computer parameter $K_G$, which reflects the ability of endogenous insulin to stimulate glucose uptake.

The mild manifest diabetics in the present series demonstrated markedly impaired insulin response to oral and intravenous glucose administration, comprising the early and late responses. Insulin sensitivity was also markedly decreased. These findings confirm earlier observations (3, 5, 6). Comparable alterations in insulin release and sensitivity had been noted already in the subjects with normal fasting blood glucose but decreased IVGTT. The impaired insulin release in the latter group was recognized previously and was considered the major reason for the development of glucose intolerance (3). Because we always used IVGTT to define glucose intolerance, the finding of grossly impaired insulin release upon intravenous glucose administration was one of the cornerstones in our hypothesis that the failure of the beta cells to respond adequately to glucose was a genetic marker of the type of diabetes for which the patient did not require insulin (12, 13).

In contrast to these two groups of diabetics, our subjects with normal IVGTT but decreased OGTT exhibited normal insulin levels during the early phase of glucose administration and, moreover, markedly elevated plasma insulin during the late phase of GIT and OGTT. Insulin sensitivity was again decreased. The increased insulin levels (in absolute terms) in such subjects during the late phase of an oral glucose challenge, together with decreased insulin sensitivity, have been recognized by other authors (5, 14). Accordingly, they suggested decreased insulin sensitivity as a primary derangement in the development of the disease.

The above reasoning suggests that the differences in opinion regarding the impairment responsible for glucose intolerance most likely originated in the use of intravenous glucose challenges by some authors and oral administration of glucose by others. However, it may be questioned whether a deficient beta cell responsiveness is not also present in the subjects with decreased OGTT and normal IVGTT. Their hyperinsulinemia would reflect the endeavor of the beta cells to overcome the decreased insulin sensitivity—but in vain because OGTT remains decreased. This opinion is strongly supported by the present finding that, in a matched group of subjects with the same decrease in insulin sensitivity but normal OGTT, the

### Table 3. Comparison of groups C and D with controls matched for $K_G$*

<table>
<thead>
<tr>
<th>Groups of subjects</th>
<th>Sex ratio, n</th>
<th>Fasting values</th>
<th>Computer parameters</th>
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<tbody>
<tr>
<td></td>
<td>F/M</td>
<td>Glucose, mmol/liter</td>
<td>Insulin, microunits/ml</td>
</tr>
<tr>
<td>Subjects</td>
<td>29</td>
<td>40.1 ± 2.3</td>
<td>94.5 ± 1.8</td>
</tr>
<tr>
<td>Controls†</td>
<td>29</td>
<td>40.0 ± 2.4</td>
<td>94.9 ± 1.6</td>
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<tr>
<td>$P$†</td>
<td></td>
<td>$&lt;0.01$</td>
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</table>

* Results are expressed as mean ± SEM.
† Control subjects were selected from a group of 164 subjects (group A) with normal fasting blood glucose, OGTT, and IVGTT.
‡ Significance was calculated according to the Mann-Whitney test.
sulinemia reached during GIT, especially during its early phase, was considerably higher. This would imply that all stages of glucose intolerance are accompanied by both impairment of beta cell responsiveness and insulin sensitivity.

In this connection it is pertinent that, even in subjects with diabetes, a further decrease in insulin sensitivity due to, e.g., obesity or acromegaly may lead to increased insulin levels during glucose administration (15, 16). However, the hyperinsulinemia is much more pronounced in obese and acromegalic subjects with normal glucose tolerance (15, 16).

It appears from the present study that there is a substantial difference between subjects with impaired OGGT only and subjects with manifest diabetes regarding the ability of glucose to potentiate insulin release. The former group demonstrated an increase in such capacity (parameter $K_p$ in the computer model). This process, therefore, may be considered an important mechanism for overcoming insulin resistance. Diabetes that does not require administration of insulin is an inherited disease which probably develops from a prediabetic state via a state of glucose intolerance to manifest diabetes (1). This process might be slow or fast. Our groups of subjects, selected on the basis of arbitrary criteria and representing different degrees of glucose intolerance, might reflect the natural history of this type of diabetes. However, it is still possible that there are types of diabetes that do not require administration of insulin with different pathogenesis—e.g., one primarily characterized by major impairment of insulin release and another with marked decrease in insulin sensitivity as a principal derangement.

In conclusion, all stages of glucose intolerance are accompanied by impairment of the beta cell response to glucose and by decreased insulin sensitivity. It remains to be clarified whether one or both of these derangements characterize the prediabetic states.

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