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The Genetic Basis of Type 2 Diabetes Mellitus: Impaired Insulin Secretion *versus* Impaired Insulin Sensitivity

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I. Introduction

A. General considerations

TYPE 2 diabetes mellitus accounts for 80–90% of all diabetes in most countries (1). It is, however, an extremely heterogeneous disorder: 5–10% of patients may have maturity-onset diabetes of youth (MODY) (2); another 5–10% may have latent adult-onset autoimmune diabetes (3); and another 5–10% may have diabetes secondary to rare genetic disorders (4–6). The etiology of diabetes in the remaining 70–85% of patients, the typical patient, remains poorly defined and a matter of great controversy. Ethnic and geographic differences in the incidence of this "garden-variety type" type 2 diabetes indicate that it too is heterogeneous (1). Indeed, two diabetes susceptibility genes for type 2 diabetes have recently been identified: the one found in Mexican Americans [NIDDM 1 (7)] is different from the one found in Finnish families (NIDDM 2) (8).

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Although the pathogenesis of "garden-variety type" type 2 diabetes is controversial, it is generally agreed that: 1) the disease has strong genetic and environmental (acquired) components (9–13); 2) its inheritance is polygenic (14–17), meaning that the simultaneous presence of several abnormal genes or polymorphisms is necessary for development of the disease; 3) impairment of insulin sensitivity and insulin secretion, each of which is under genetic control (18–20), are both important elements in its pathogenesis (12, 16, 21–23); 4) most patients are obese; and 5) obesity, especially intra-abdominal obesity (24–27), causes insulin resistance and is under genetic control (11).

What is disputed are: 1) the quantitative contribution of insulin resistance and impaired insulin secretion; 2) their role as genetic factors; 3) the major sites of insulin resistance (liver *vs.* muscle *vs.* adipose tissue *vs.* kidney); and 4) the steps that lead to the development of type 2 diabetes (28–34).

The focus of this debate is whether the primary genetic determinants for type 2 diabetes are abnormal genes or polymorphisms related to insulin resistance or impaired insulin secretion, not whether insulin resistance or impaired insulin secretion is more important in the pathogenesis of type 2 diabetes. Clearly, both are important and whether or not their basis is genetic does not diminish their importance.

The overwhelmingly predominant view at the present time, as reflected in textbooks and review articles (35–37), is that genes affecting insulin sensitivity are the primary genetic factors. Consequently, a substantial effort is underway to determine its molecular basis. As will become apparent, however, there is also a considerable body of evidence suggesting that genes affecting insulin secretion may be the primary genetic factors. Because insulin resistance almost universally is regarded as the primary genetic factor in type 2 diabetes, I have taken pains to point out potential shortcomings in studies supporting this point of view. Clearly, many of the studies supporting a genetic defect in the β-cell have similar shortcomings. Although not pointing these out with equal emphasis may be viewed as a bias on my part, this approach was taken to demonstrate that the evidence supporting insulin resistance as the primary genetic defect is not as strong as is generally perceived. It is not expected that this debate will resolve the question of whether impaired insulin secretion or insulin resistance is the primary genetically determined factor for development of type 2 diabetes, but rather it is hoped that this debate will lead to a reassessment of current dogma and perhaps a more equitable reallocation of efforts to determine the molecular basis for the genetic

components of type 2 diabetes consistent with available evidence.

B. Diabetogenic vs. diabetes-related genes

A major problem limiting our understanding of the genetic basis of type 2 diabetes is that many environmental and genetically based factors influence insulin sensitivity and insulin secretion: these include age, gender, ethnicity, physical fitness, diet, smoking (38), obesity, and fat distribution (12). Although many of these may be under genetic control (11), it is important to emphasize that the genes may not necessarily represent specific diabetes genes. For example, let us suppose that the insulin resistance in type 2 diabetics was mainly due to intraabdominal fat accumulation and that this were mainly under genetic control. One could conclude that the insulin resistance found in type 2 diabetics was genetic, but it would not represent a specific diabetes gene since most insulin-resistant obese people do not develop diabetes (39). On the other hand, a mutation in the insulin receptor gene causing insulin resistance could be considered a diabetes-specific gene since, if severe enough, most people with the genetic defect would develop diabetes and most people without diabetes would not have this gene.

It is important, therefore, to distinguish between diabetogenic genes, with which this article is concerned, and diabetes-related genes (*e.g.*, those regulating appetite, energy expenditure, and intraabdominal fat accumulation) (10). The latter class of genes may be defined as not being specific (*i.e.*, not being mainly limited to people with diabetes), as by themselves not being sufficient to cause diabetes and not necessarily being essential. These genes are best considered as genetically determined risk factors. An example might be a gene or group of genes causing obesity. These genes would not be limited to individuals destined to become diabetic (*e.g.*, not specific), would not be sufficient since most obese individuals do not become diabetic, and would not be essential since, depending on the population, a considerable number of lean individuals develop type 2 diabetes. A diabetogenic gene may be defined as being essential and relatively specific but, given the polygenic nature of type 2 diabetes, may not be sufficient in itself to cause diabetes. For example, a mild alteration in the activity of glucokinase, such as is found in some MODY patients (32), which reduces insulin secretion, is relatively specific, being mainly limited to families with this type of diabetes; it may not be sufficient to cause diabetes in most individuals unless there are increased requirements for insulin such as that due to superimposition of acquired insulin resistance (*e.g.*, obesity, physical inactivity, or pregnancy) but it may be considered to be essential since without this defect, diabetes would not otherwise occur.

Thus, depending on the severity of the expression of the genes in a given individual and on the accompanying environmental (acquired) factors, a combination of several diabetes-related genes and several diabetic genes may be necessary to cause diabetes. Indeed, in the GK rat there appears to be at least six genetic loci involved (40), and in humans two different susceptibility genes have been recently identified, one in Mexican-Americans (NIDDM 1) (7) and one in Finnish families (NIDDM 2) (8).

C. Secondary impairment of insulin secretion and insulin sensitivity

Another confounding factor is that hyperglycemia and hyperinsulinemia in themselves can impair insulin secretion and insulin sensitivity (41–43). Thus, people with impaired glucose tolerance (IGT) and overt type 2 diabetes can be expected to have insulin resistance and impaired insulin secretion independent of genetic causes merely because they are hyperglycemic. Because of this, cross-sectional studies including individuals with IGT and type 2 diabetes have not proven to be particularly informative in delineating between genetic and acquired alterations in insulin secretion and action.

D. Insulin deficiency vs. impaired insulin secretion

Another factor that has led to confusion regarding our understanding of the genetic basis of type 2 diabetes is that the literature has been obfuscated by establishment of a dichotomy of insulin deficiency *vs.* insulin resistance. For example, it has been argued that individuals with type 2 diabetes or IGT are hyperinsulinemic, and therefore the main problem must be insulin resistance rather than insulin deficiency (21, 28, 29). Although this may be true, it is a misleading analysis. It assumes that hyperinsulinemia, even if inappropriate for the prevailing hyperglycemia, indicates normal pancreatic β-cell function. In other words, insulin deficiency, rather than impaired β-cell function, has been contrasted with insulin resistance.

Strictly speaking, absolute insulin deficiency rarely occurs except in patients with insulin-dependent type 1 diabetes of several years duration. Many type 1 diabetic patients in ketoacidosis have been reported to have plasma insulin levels in the normal range (44). These insulin levels are of course grossly inappropriate for the degree of hyperglycemia.

The dichotomy established between insulin deficiency and insulin resistance has led to a general underemphasis of the issue of the appropriateness of β-cell function. According to the dichotomy, a person having a plasma glucose level of 200 mg/dl and a plasma insulin of 20 μU/ml would be hyperinsulinemic compared with a person with a plasma glucose of 100 mg/dl with a plasma insulin of 10 μU/ml. Such a person would be considered not to have impaired β-cell function, but to be insulin resistant because of the hyperinsulinemia. However, a person with normal glucose tolerance whose plasma glucose level is raised 200 mg/dl would secrete 2–4 times more insulin than a type 2 diabetic patient with a plasma glucose of 200 mg/dl (45, 46).

Thus, although hyperinsulinemia may signify the presence of insulin resistance, this may not necessarily be the case, and increased plasma insulin levels do not necessarily indicate normal β-cell function. It is important to recognize that another determinant of insulin secretion, in addition to the ambient plasma glucose levels, is insulin sensitivity. Obese insulin-resistant individuals secrete more insulin than lean insulin-sensitive individuals at comparable plasma glu-

cose levels (45). Few studies have analyzed insulin secretion in relation to insulin sensitivity (47).

As recently pointed out by Reaven (48), because of the feedback between plasma glucose concentration (the major stimulus for insulin release) and β-cell insulin secretion, it is virtually impossible to develop diabetes due to the severity of insulin resistance found in most type 2 diabetic patients unless the capacity to secrete additional amounts of insulin to compensate for the insulin resistance is impaired. Thus, hyperglycemia may be considered prima facia evidence for impaired insulin secretion. The question of course is whether this inability to compensate for insulin resistance is the result of an underlying genetic defect or merely secondary to β-cell exhaustion.

E. Misinterpretation of the Oral Glucose Tolerance Test (OGTT)

The misleading dichotomy between insulin deficiency (*vs.* impaired insulin release) and insulin resistance has been reinforced by questionable interpretation of cross-sectional studies examining plasma insulin responses during OGTTs (21, 49).

Virtually all studies examining the relationship between the 2-h plasma glucose level (a generally recognized index of glucose tolerance) and the 2-h plasma insulin level have found an inverted U relationship (Fig. 1) with plasma insulin levels increasing to a peak around 200 mg/dl followed by a progressive decrease. This pattern has been interpreted to indicate that early on, as glucose tolerance decreases, there is increased insulin secretion and, therefore, that insulin resistance, rather than insulin deficiency, is responsible for the development of IGT; later on, diabetes develops when the β-cell can no longer compensate for this insulin resistance (21, 49, 50).

This interpretation may be questioned. First of all, it is incompatible with the results of numerous studies (32, 47, 51–62) demonstrating that individuals with IGT already have impaired insulin secretion.

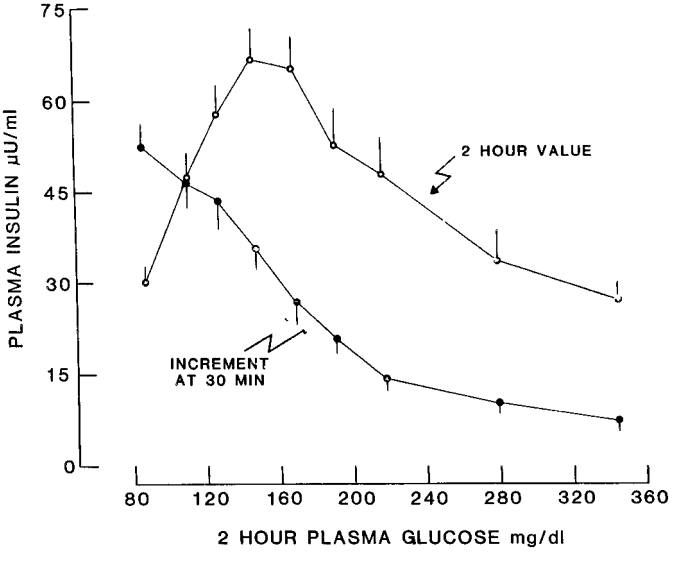

FIG. 1. Relationship between 2 h plasma glucose, 30 min plasma insulin, and 2 h plasma insulin levels during OGTTs.

Second, it does not take into consideration the importance of the kinetics of insulin release and the dependence of insulin secretion upon the prevailing plasma glucose concentration. As shown in Fig. 1, if one examines the early (30 min) plasma insulin response during the OGTT, one finds that there is a progressive decrease in this early plasma insulin response as glucose tolerance deteriorates. This decrease is clearly evident *before* the diagnosis of IGT would be made (*e.g.*, 2 h plasma glucose exceeding 140 mg/dl). Moreover, experimental reduction in early insulin release in normal human volunteers has been shown to produce glucose intolerance *and* late (2 h) hyperinsulinemia (63). These observations provide evidence that there is impaired pancreatic β-cell function before the onset of IGT and that late hyperinsulinemia may actually be the result of an inadequate β-cell response to the hyperglycemia due to impaired early insulin release and *may not* necessarily indicate the presence of insulin resistance.

II. Strategy

Because IGT and type 2 diabetes can be associated secondarily with impaired insulin secretion and insulin resistance due to glucose toxicity, this review will rely primarily on the analysis of data derived from study of individuals with normal glucose tolerance (NGT) who are at high risk to develop type 2 diabetes, presumably on a genetic basis. These individuals include 1) NGT first-degree relatives of people with type 2 diabetes; 2) NGT women with a history of gestational diabetes; and 3) NGT individuals who subsequently developed IGT or type 2 diabetes. In addition, the reversibility of defects in insulin sensitivity and insulin secretion by weight loss will be examined. The rationale for this is that if insulin resistance or impaired insulin secretion were purely genetic in origin, these abnormalities should not be completely reversed by such an intervention. On the other hand, it is possible that genetic factors may cause a given degree of obesity to have exaggerated effects on insulin sensitivity and β-cell function. This possibility will be considered in detail later. Although, as indicated earlier, it is generally agreed that development of type 2 diabetes cannot occur without impaired insulin secretion, evidence will be presented that type 2 diabetes can occur without insulin resistance. Finally, based on this review of the literature, a schema will be proposed for the pathogenesis of type 2 diabetes incorporating the concept of interactions between diabetes-related genes, diabetogenic genes, and environmental factors.

III. Studies in Genetically Predisposed Individuals with NGT

A. First-degree relatives (excluding twins)

1. Insulin secretion. Over the past 30 yr, there have been more than 60 studies of insulin secretion and/or insulin sensitivity in normal glucose-tolerant individuals who were the first-degree relative of someone with type 2 diabetes (30, 31, 39, 47, 53, 56, 60, 61, 64–119) (Tables 1, 2, and 3). Unfortunately, in most of these studies insulin secretion and insulin resistance were not simultaneously assessed. Furthermore, in

TABLE 1. β-Cell function in NGT individuals with a first-degree type 2 diabetic relative

Author (Ref.)	Subjects	β-Cell function	Comments
1. Grodsky *et al.* (64)	8C, 24FM	Normal (OGTT)	*a*
2. Welborn *et al.* (65)	46C, 4FM	Normal (OGTT)	*a*
3. Ricketts *et al.* (156)	24C, 21FM	Normal (OGTT)	*ab*
4. Colwell and Lein (66)	7C, 6FM	Reduced (OGTT)	
5. Siperstein *et al.* (67)	15C, 27FM	Normal (OGTT)	*a*
6. Simpson *et al.* (68)	10C, 10FM	Reduced (IVGTT)	
7. Boden *et al.* (69)	13C, 13FM	Reduced (IVGTT)	
8. Daweke *et al.* (70)	58C, 21FM	Reduced (OGTT)	
9. Paulsen *et al.* (71)	16C, 11FM	Increased (OGTT)	*a*
10. Soeldner *et al.* (72)	11C, 5FM	Reduced (OGTT)	*c*
11. Rojas *et al.* (73)	25C, 14FM	Reduced (IVGTT) Normal (TTT)	 *c*
12. Serrano-Rias *et al.* (74)	34C, 22FM	Reduced (IVGTT) Normal (OGTT, TTT)	 *c*
13. Rull *et al.* (75)	31C, 67FM	Reduced (OGTT)	*c*
14. Lowrie *et al.* (76)	10C, 12FM	Normal (IVGTT)	*c*
15. Jackson *et al.* (77)	17C, 28FM	Increased (OGTT)	*b*
16. Sonksen *et al.* (78)	26C, 24FM	Reduced (OGTT, IVGTT)	*c*
17. Pozefsky *et al.* (79)	7C, 9FM	Reduced (OGTT)	*c*
18. Boberg *et al.* (80)	93C, 116FM	Reduced (IVGTT)	*c*
19. Aronoff *et al.* (81)	26C, 32FM	Normal (OGTT, IVGTT)	
20. Ohlsen *et al.* (82)	33FM	Reduced (GIT)	*a*
21. Bonora *et al.* (83)	55C, 55FM	Reduced (OGTT)	*d*
22. Berntorp and Lindgarde (84)	51C, 22FM	Reduced (OGTT)	*c*
23. O'Rahilly *et al.* (60)	64C, 75FM	Normal (GIT)	*a*
24. Leslie *et al.* (85)	18C, 32FM	Increased (OGTT)	*de*
25. Haffner *et al.* (86)	1013C, 584FM	Increased (OGTT)	*ad*
26. O'Rahilly *et al.* (53)	10C, 10FM	Reduced pulsatility	*e*
27. Laws *et al.* (87)	16C, 19FM	Reduced (OGTT)	
28. Ho *et al.* (88)	25C, 25FM	Normal (OGTT)	*a*
29. Eriksson *et al.* (56)	14C, 13FM	Normal (OGTT, clamp)	*a*
30. Warram *et al.* (39)	186C, 155FM	Normal (IVGT)	*af*
31. Ramachandran *et al.* (89)	15C, 24FM	Increased (OGTT)	*af*
32. Johnston *et al.* (90)	12C, 12FM	Normal (MM, clamp)	
33. Osei *et al.* (91)	10C, 10FM	Increased (IVGTT)	*af*
34. Elbein *et al.* (92)	35C, 171FM	Reduced (OGTT)	*a*
35. Henriksen *et al.* (93)	29C, 20FM	Reduced (OGTT) Normal (MM)	
36. Lemieux *et al.* (94)	28C, 11FM	Normal (OGTT)	*ad*
37. Gulli *et al.* (95)	10C, 11FM	Increased (OGTT, clamp)	*be*
38. Gelding *et al.* (96)	12C, 12FM	Normal (OGTT)	
39. Byrne *et al.* (47)	11C, 10FM	Normal—various tests	
40. Pimenta *et al.* (30)	50C, 50FM	Normal (OGTT) Reduced (clamp)	
41. Armstrong *et al.* (97)	90C, 93FM	Normal (HOMA)	
42. Taylor *et al.* (98)	29C, 19FM	Reduced (OGTT)	*a*
43. Cerasi and Luft (99)	6C, 2FM	Reduced (GIT)	*a*
44. Clark *et al.* (100)	28C, 8FM	Reduced (GIT)	
45. Vaag and Henriksen (101)	20C, 20FM	Increased (OGTT)	
46. Roder *et al.* (102)	14C, 11FM	Normal (clamp)	
47. Birkeland *et al.* (103)	30C, 26FM	Normal (OGTT)	
48. Migdalis *et al.* (106)	31C, 96FM	Normal (OGTT)	
49. Fernandez-Castaner *et al.* (107)	49C, 86FM	Reduced (HOMA)	
50. Schmitz *et al.* (105)	13C, 15FM	Reduced (GIT)	*f*
51. Vauhkonen *et al.* (117)	14C, 38FM	Reduced (IVGTT)	*af*
52. Henriksen *et al.* (118)	20C, 20FM	Reduced (IVGTT)	
53. Van Haeften *et al.* (119)	21C, 21FM	Reduced (clamp)	

OGTT, Oral glucose tolerance test; IVGTT, intravenous glucose tolerance test; TTT, tolbutamide tolerance test; GIT, glucose infusion test; MM, minimal model; Clamp, hyperglycemic clamp; HOMA, homeostasis model; C, control subject; FM, subject with type 2 diabetic relative.

[a] Questionable matching.
[b] Blood glucose levels different.
[c] All nonobese.
[d] Did not evaluate early insulin responses.
[e] Included IGT.
[f] FM more obese.

most of the early studies, the methods used to evaluate insulin secretion or insulin sensitivity would not be considered to be state of the art by present standards. Finally and most importantly, in many studies subjects were usually not well matched for acquired factors such as age, gender, and obesity that are known to influence insulin secretion and insulin sensitivity.

TABLE 2. Insulin sensitivity in normal glucose tolerant individuals with a first degree type 2 diabetic relative

Author (Ref.)	Subjects	Insulin sensitivity	Comments
1. Pozefsky *et al.* (79)	7C, 9FM	Normal (FGU)	
2. O'Rahilly *et al.* (60)	64C, 75FM	Normal (GIT)	*a*
3. Leslie *et al.* (108)	10C, 10FM	Reduced (GIIT)	*a*
4. Laws *et al.* (87)	16C, 19FM	Reduced (GIIT)	
5. Ho *et al.* (88)	25C, 25FM	Reduced (GIIT)	*a*
6. Eriksson *et al.* (56)	14C, 13FM	Reduced (clamp)	*ab*
7. Ramachandran *et al.* (89)	15C, 24FM	Reduced (ITT)	*b*
8. Johnston *et al.* (90)	12C, 12FM	Normal (MM)	
9. Osei *et al.* (91)	10C, 10FM	Reduced (MM)	*b*
10. Henriksen *et al.* (93)	20C, 20FM	Reduced (MM)	
11. Handberg *et al.* (109)	8C, 10FM	Normal (clamp)	
12. Gulli *et al.* (95)	10C, 11FM	Reduced (clamp)	*c*
13. Schalin-Jantti *et al.* (110)	16C, 18FM	Reduced (clamp)	*b*
14. Gelding *et al.* (96)	12C, 22FM	Normal (ITT)	
15. Gelding *et al.* (111)	9C, 8FM	Normal (ITT)	
16. Byrne *et al.* (47)	11C, 10FM	Normal (MM)	
17. Pimenta *et al.* (30)	50C, 50FM	Normal (clamp)	
18. Armstrong *et al.* (97)	90C, 93FM	Normal (ITT, HOMA)	
19. Vaag and Henriksen (101)	20C, 20FM	Reduced (clamp)	
20. Eriksson *et al.* (112)	12C, 10FM	Reduced (clamp)	*ab*
21. Migdalis *et al.* (106)	31C, 96FM	Normal (HOMA)	
22. Nyholm *et al.* (104)	22C, 21FM	Normal (clamp)	
23. Warram *et al.* (39)	188C, 155FM	Reduced (MM)	*ab*
24. Fernandez-Castaner *et al.* (107)	49C, 86FM	Normal (HOMA)	
25. Schmitz *et al.* (105)	13C, 15FM	Reduced (clamp)	*b*
26. Vauhkonen *et al.* (117)	14C, 38FM	Normal	*ab*
27. Henriksen *et al.* (118)	20C, 20FM	Normal (MM)	
28. Van Haeften *et al.* (119)	21C, 21FM	Normal (clamp)	

Clamp, Euglycemic hyperinsulinemic or hyperglycemic clamp; ITT, insulin tolerance test; MM, minimal model; HOMA, homeostasis model; C, control subject; FM, subject with type 2 diabetic relative; FGU, forearm glucose uptake; GIT, glucose infusion test.

[a] Questionable matching.

[b] FM more obese.

[c] Included IGT.

TABLE 3. β-Cell function and insulin sensitivity in monozygotic twins discordant for type 2 diabetes

Author (Ref.)	Subjects	β-Cell function	Insulin sensitivity
1. Cerasi and Luft (113)	85C, 5M	Reduced (GIT)	NS
2. Gottlieb *et al.* (114)[a]	24C, 12M	Normal (OGTT)	NS
3. Pyke and Taylor (116)[b]	24C, 9M	Reduced (OGTT)	NS
4. Barnett *et al.* (115)	5C, 5M	Reduced (OGTT)	NS
5. Vaag *et al.* (61)	13C, 5M	Reduced (H-Clamp)	Normal (E-clamp)

GIT, Glucose infusion test; OGTT, oral glucose tolerance test; H-Clamp, hyperglycemic clamp; E-Clamp, euglycemic hyperinsulinemic clamp; M, monozygotic discordant twin; C, control subject; NS, not studied.

[a] Probably included twins of type 1 diabetic patients.

[b] May have included 3 twins of type 1 diabetic patients.

Table 1 provides the observations of β-cell function of NGT first-degree type 2 diabetic relatives excluding those of monozygotic twins. Of the 53 studies, 26 (49%) indicate impaired β-cell function, 20 (38%) indicate normal β-cell function, and only 7 (~13%) indicate β-cell hypersecretion. Thus, the preponderance of experimental evidence favors impaired, rather than excessive, insulin secretion being present in these individuals before the development of IGT and thus provide support for the concept that the initial (? genetic) lesion in type 2 diabetes may involve impaired insulin secretion rather than insulin resistance.

It is important to point out that the studies using more sophisticated techniques or more rigorous tests to evaluate β-cell function (*e.g.*, hyperglycemic clamps and standardized glucose infusion tests) were more likely to detect abnormalities. For example, Pimenta *et al.* (30) and Van Haeften *et al.* (119) found absolutely normal plasma insulin responses to OGTTs in first-degree relatives with NGT but during hyperglycemic clamp studies found reduced responses. These results suggest that, in some individuals with NGT, the OGTT may not be a sufficient stress to elicit subtle defects in β-cell function.

Certain widely cited reports deserve additional comment. In one of the earliest studies, Rojas *et al.* (73) examined plasma insulin responses to intravenous glucose in control volunteers and NGT offspring of two diabetic parents who were carefully matched for age, gender, and obesity. It was found that glucose-stimulated insulin release was decreased in the NGT offspring. Warram *et al.* (39) subsequently analyzed the data of these and additional offspring of two diabetic parents using the minimal model approach of Bergman *et al.* (120, 121). Initial results of those who subsequently either had or had not developed diabetes were compared. In this population, already demonstrated to have reduced β-cell function,

presumably on a genetic basis, it was found that those who subsequently developed diabetes had been insulin resistant when they were still NGT, whereas those who did not develop diabetes had not been insulin resistant. It was concluded that insulin resistance was a risk factor for development of type 2 diabetes.

This study is often cited in the literature as providing evidence that insulin resistance is the main genetic factor for type 2 diabetes. However, since the group who subsequently developed diabetes were markedly obese compared with the group that did not develop diabetes (*i.e.*, 140 *vs.* 106% ideal body weight), it is possible that the insulin resistance was simply the result of obesity. Indeed, comparison of the minimal model parameters of insulin secretion and insulin sensitivity in this group with those of similarly obese individuals having no family history of diabetes reported by Bergman *et al.* (120, 121) (Table 4) provides evidence that the subjects studied by Warram *et al.* (39) were no more insulin resistant than these individuals but had reduced first-phase insulin release. Thus, the study of Warram *et al.* (39) can be interpreted as showing that people with a genetic predisposition to impaired insulin secretion develop diabetes when acquired insulin resistance (due to obesity) is superimposed and exceeds the ability of the β-cell to compensate for it.

The study of Gulli *et al.* (95), which examined plasma insulin responses during hyperglycemic clamp experiments in nondiabetic offspring of two type 2 diabetic parents with other nondiabetic Mexican-American subjects, is also often cited as finding insulin resistance without impaired insulin secretion. However, the study had two limitations: first, subjects with IGT were included in the group with diabetic parents, and second, subjects were not clamped at identical plasma glucose levels. During the clamps, plasma glucose levels were increased by a certain increment. Since it is likely that the subjects included with IGT had higher fasting plasma glucose levels, they would have been clamped at higher plasma glucose levels, thus providing a greater stimulus for insulin release. Consequently, it is difficult to interpret the results of this study.

The study of Eriksson *et al.* (56) is also cited frequently as demonstrating increased insulin release in offspring of people with type 2 diabetes. However, in this study relatives of type 2 diabetic and control subjects were not well matched for gender and obesity. Furthermore, during the hyperglycemic clamps, plasma glucose levels were increased by a certain increment so that the groups were not necessarily studied at identical plasma glucose levels. These limitations make the results of the study difficult to interpret. Indeed, in a subsequent study (102), which probably included some of the same subjects but with better matching, insulin responses during hyperglycemic clamps were similar in the control group and first-degree NGT relatives of type 2 diabetics.

In summary, contrary to the current prevalent view, the preponderance of the data from studies examining β-cell function of individuals with NGT and a presumed genetic predisposition to develop type 2 diabetes, because they had a first-degree type 2 diabetic relative, provides evidence for an underlying impairment in insulin secretion.

2. Insulin sensitivity. Twenty-eight studies have examined the appropriateness of insulin action in NGT individuals with a first-degree type 2 diabetic relative (Table 2). Of these, 15 (54%) found normal insulin sensitivity while 13 (46%) found reduced insulin sensitivity. If one excludes studies that probably included some people with IGT or where there was obvious poor matching of groups for factors known to affect insulin sensitivity (*e.g.*, age, gender, obesity, VO_2 max), or where it is not clear whether groups were well matched (39, 56, 60, 88, 89, 91, 95, 108, 110, 112, 105, 117), we are left with 16 studies of which 14 (~88%) indicate normal insulin sensitivity and 3 (~12%) indicate reduced insulin sensitivity. Granted that these exclusions may represent a certain bias, it is safe to say, nevertheless, that the preponderance of data do not provide strong support for the concept that NGT first-degree relatives of type 2 diabetic patients are insulin resistant independent of factors such as age, gender, obesity, physical fitness, and body fat distribution. Indeed, Nyholm *et al.* (104) recently reported that apparent differences in insulin sensitivity between NGT subjects with and without a family history of diabetes were no longer statistically significant when data were corrected for differences in VO_2 max, an index of physical fitness.

B. Identical twins discordant for type 2 diabetes

Studies of discordant identical twins (Table 3) have provided a more definitive picture of β-cell function and insulin sensitivity before development of diabetes than those of first-degree relatives of type 2 diabetic patients. Of the five studies, all (61, 113, 115, 116) except that of Gottlieb *et al.* (114) have indicated that the NGT discordant twin had reduced insulin secretion. Gottlieb *et al.* (114) studied children and thus probably included twins discordant for type 1 diabetes. As shown in Table 3, the only study examining both insulin sensitivity and beta cell function (61) found impaired insulin secretion *without* insulin resistance. This latter study deserves more comment.

Although the small number of subjects studied presents the possibility of type 1 and type 2 statistical errors, certain observations are of interest. Discordant twins with NGT and IGT both had impaired insulin release. The degree of impairment was comparable but those with IGT also had reduced insulin sensitivity. This was associated with an increased waist/hip ratio (1.04 ± 0.03 *vs.* 0.93 ± 0.02 in NGT twins and 0.90 ± 0.03 in normal controls), and an increased Hb_{A1C} ($9.1 \pm 0.05\%$ *vs.* $6.8 \pm 0.3\%$ in NGT twins and $5.7 \pm 0.37\%$ in normal controls). Thus, one could postulate from these data that glucose toxicity (41, 42) and excess intraabdominal fat in the IGT twins were responsible for the decreased insulin sensitivity. The twins with type 2 diabetes were more obese than those with IGT [body mass index (BMI) 30.1 ± 1.5 kg/m^2 *vs.* 27.6 ± 2.0 kg/m^2] and had moderately worse insulin sensitivity (M value 5.2 ± 0.7 *vs.* 8.1 ± 0.6 mg/kg/min) and markedly worse first-phase insulin secretion (-67 ± 16 *vs.* 151 ± 22 μU/ml/min). Note that the value for insulin secretion in the type 2 diabetic twin is negative.

The observations of this study suggest that the major factor responsible for transition from NGT to IGT is superimposi-

tion of insulin resistance upon impaired β-cell function and that the major factor responsible for transition from IGT to type 2 diabetes is worsening of the already impaired insulin secretion. The latter could represent progression of a genetic β-cell deficit and/or toxic effects of hyperglycemia. The appearance in insulin resistance could be readily explained by a combination of obesity and glucose toxicity (*i.e.*, not necessarily a diabetogenic gene).

In summary, the data from twin studies are consistent with the consensus of the data from other family studies discussed above indicating that impaired β-cell function precedes insulin resistance in the pathogenesis of type 2 diabetes when confounding factors such as age, gender, and obesity are taken into consideration.

IV. Prospective Studies of Individuals Before Development of Type 2 Diabetes

There have been numerous studies reporting baseline data on NGT individuals who subsequently developed type 2 diabetes (Table 5). Many of these have been epidemiological in that they compared, within a certain population, the baseline characteristics of individuals who did or did not subsequently become diabetic. These studies have provided evidence that both impaired insulin secretion and insulin resistance are risk factors for development of type 2 diabetes (22, 23, 122–124). However, they do not directly address the issue of which of these factors precedes the other and which is genetic because often those who subsequently developed diabetes were more obese or less physically active than those who did not develop diabetes (22, 122, 124). Moreover, in many cases insulin sensitivity was not directly measured, and surrogate determinations such as fasting or 2 h OGTT plasma insulin levels were used. Recall that an increased 2 h plasma insulin level may be the result of impaired early insulin release because this leads to greater hyperglycemia and a greater stimulus for insulin release and therefore may not necessarily indicate insulin resistance. Finally, individuals with IGT and potentially secondary changes due to glucose toxicity were often included (122, 125).

TABLE 4. Minimal model analysis and baseline data of matched subjects who developed diabetes with normal controls

	Controls[a] (n = 15)	Future type 2 diabetics[b] (n = 25)
Age (yr)	29 ± 4	33 ± 2
IBW (%)	143 ± 4	146 ± 7
Insulin sensitivity ($min^{-1}/\mu U$ per ml)	2.4 ± 0.6	1.9 ± 0.3
Insulin release (10^3 pmol/min/mmol)	10.5 ± 1.6	3.7 ± 1.0

[a] Data from Bergman *et al.* 1987 (120) and 1981 (121).
[b] Data from Warram *et al.* (39).

Several of these studies deserve comment. There have been two relevant reports from the Pima Indian Study (49, 126). In one report, baseline data of subjects who developed type 2 diabetes were compared with a group of NGT subjects (126). Unfortunately, individuals with IGT were included and no demographic data were given to assure the groups were well matched. OGTT plasma insulin levels at 30 min were not significantly different. However, if increments in plasma insulin responses had been evaluated in relation to increments in plasma glucose, the group that subsequently developed type 2 diabetes might have been seen to have a reduced plasma insulin response (0.39 *vs.* 0.48 μU/mg per dl). Thus, it would be difficult to conclude that pancreatic β-cell function was normal as had been suggested. Insulin sensitivity was not reported.

In the other study of the Pima Indians (49), longitudinal data were given for 24 individuals who developed IGT. Although not analyzed, the baseline acute insulin response of these individuals (IVGTT) was less (~190 *vs.* 220) than that of a control group while their glucose infusion rate (~3.3 mg/kg/min) during a hyperinsulinemic clamp was comparable to that of the control group (3.8 mg/kg/min). Since the subjects that became diabetic were more obese (BMI 38 *vs.* 32 Kg/M^2), the small reduction in their glucose infusion rates

TABLE 5. β-Cell function and insulin sensitivity of normal glucose tolerant individuals who subsequently developed type 2 diabetes or IGT

Author (Ref.)	Subjects	β-Cell function	Insulin sensitivity	Comments
1. Danowski *et al.* (157)	0C, 3FDM	Reduced (OGTT)	NS	[a]
2. Strauss and Hales (158)	16C, 12FDM	Reduced (OGTT)	NS	
3. Cerasi and Luft (159)	134C, 16FDM	Reduced (GIT)	NS	
4. Savage *et al.* (126)	13C, 13FDM	Normal (OGTT)	NS	[b]
5. Charles *et al.* (123)	4079, 23FDM	Normal (OGTT)	NS	[cd]
6. Lillioja *et al.* (49)	0C, 24FIGT	NS	NS	[a]
7. Saad *et al.* (160)	12C, 11FDM	Increased (OGTT)	NS	
8. Lundgren *et al.* (161)	221C, 8FDM	Reduced (IVGTT)	NS	[a]
9. Skarfors *et al.* (153)	1262C, 46FDM	Reduced (IVGTT)	NS	[a]
10. Martin *et al.* (127)	126C, 25FDM	Normal (IVGTT)	Reduced (MM)	[c]
11. Lillioja *et al.* (22)	151C, 17FDM	Reduced (OGTT)	Reduced (Clamp)	[c]
12. Haffner *et al.* (23)	545C, 44FDM	Reduced (OGTT)	NS	
13. Eriksson and Lindgarde (122)	4521C, 116FDM	Reduced (OGTT)	NS	[b]
14. Chen *et al.* (125)	114C, 23FDM	Reduced (OGTT)	NS	[b]
15. Sicree *et al.* (124)	215C, 14FDM	Increased (OGTT)	NS	[cd]

OGTT, Oral glucose tolerance test; GIT, glucose infusion test; IVGTT, intravenous glucose tolerance test; MM, minimal model; C, control subjects; FDM, future diabetic; FIGT, future impaired glucose tolerance; NS, not studied.
[a] No controls.
[b] Included IGT.
[c] FDM more obese.
[d] Did not evaluate early insulin responses.
[e] Questionable matching.

could be attributable to their greater obesity. Moreover the fact that their acute insulin responses were not greater than that of the control group, despite their greater obesity, suggests that their β-cell function may have been impaired. These two studies (49, 126) are widely cited as supporting genetically determined insulin resistance as the initial factor predisposing to type 2 diabetes but the evidence is equivocal.

The report of Martin *et al.* (127) represents the same data reported by Warram *et al.* (39), which has already been commented on in detail. As explained earlier, the observations of this study actually are consistent with the concept that superimposition of the insulin resistance of obesity upon a genetically impaired capacity to secretion insulin is a common sequence leading to type 2 diabetes.

Chen *et al.* (125) reported baseline data on 23 individuals who developed type 2 diabetes and compared them to 144 individuals who remained nondiabetic. Those who developed type 2 diabetes initially had impaired early insulin release during an OGTT. Unfortunately, about half of each group had IGT at baseline. Thus, it is difficult to use these data to distinguish between a genetic cause and one due to glucose toxicity in explaining the reduced insulin secretion.

Taken together, these prospective studies indicate that both impaired insulin release and insulin resistance are risk factors for development of type 2 diabetes and that each can, and usually does, precede type 2 diabetes. However, they do not provide unassailable evidence that either the impaired insulin secretion or the insulin resistance necessarily has a genetic basis.

V. Studies of Normal Glucose-Tolerant Women with a History of Gestational Diabetes

Women who have experienced transient diabetes during a pregnancy (gestational diabetes) are at high risk to subsequently develop type 2 diabetes (128), and it has been suggested that gestational diabetes and type 2 diabetes are the same disorder (129). Current evidence suggests that gestational diabetes occurs in women who cannot secrete sufficient insulin to compensate adequately for the reduction in insulin sensitivity that normally occurs during the third trimester of pregnancy (128, 130). This would be analogous to the situation wherein a person with a genetically reduced capacity to augment insulin secretion develops type 2 diabetes after becoming obese.

Several studies summarized in Table 6 have examined insulin secretion and insulin sensitivity in women with prior gestational diabetes after their glucose tolerance had returned to normal. Of the eight studies (131–139) examining insulin secretion, all but one (136) found evidence for reduced insulin secretion. On the other hand, of the five studies (132, 135, 137–139) examining insulin sensitivity, only one (135) found it to be reduced, and in that study there was also evidence of reduced insulin secretion. Thus, if gestational diabetes represents the forerunner of type 2 diabetes, the results of these studies support the view that a defect (possibly genetic) in insulin secretion precedes insulin resistance in the pathogenesis of type 2 diabetes. It should be pointed out, however, that gestational diabetes represents a heterogeneous disorder that may include those destined to develop type 2 diabetes as well as those with type 1 diabetes, latent adult-onset autoimmune diabetes, and MODY.

VI. Reversibility of Insulin Resistance and Impaired Insulin Secretion by Therapeutic Interventions

One may examine the extent to which insulin resistance or impaired insulin secretion represents the underlying genetic predisposition for type 2 diabetes by the relative ability of therapeutic interventions to reverse these abnormalities. Genetic defects would not be expected to be completely eliminated simply by weight loss unless, of course, genetic defects predisposed individuals to become more insulin resistant for a given amount of weight gain. This possibility, however, seems unlikely since, as indicated earlier in *Section III.A.2*, the preponderance of studies indicate that obese normal glucose-tolerant individuals with a first-degree type 2 diabetic relative are not more insulin resistant than comparably obese individuals with no first-degree type 2 diabetic relative.

Three studies have unequivocally demonstrated complete reversal of insulin resistance with dietary intervention in type 2 diabetic patients (140–142). Reversal to normal (143) or near normal (144) insulin sensitivity had also been observed after insulin therapy in lean and obese type 2 diabetic patients. In contrast, no study has unequivocally demonstrated restitution of normal islet β-function with therapeutic interventions.

Beck-Nielsen *et al.* (141) studied obese type 2 diabetic subjects before and after a year's treatment on a weight-reducing diet and compared the results to a control group of nondiabetic subjects. Although the type 2 diabetic subjects did not attain a normal weight, insulin sensitivity (assessed by the

TABLE 6. β-Cell function and insulin sensitivity in normal glucose tolerant women with prior gestational diabetes

Author (Ref.)	Subjects	β-Cell function	Insulin sensitivity
1. Dornhorst *et al.* (131)	44C, 44PGD	Reduced (OGTT)	NS
2. Ward *et al.* (132)	19C, 19PGD	Reduced (IVGTT)	Normal (MM)
3. Chan *et al.* (133)	15C, 15PGD	Reduced (OGTT)	NS
4. Damm *et al.* (134)	30C, 23PGD	Reduced (OGTT)	NS
5. Ryan *et al.* (135)	14C, 14PGD	Reduced (OGTT, IVGTT)	Reduced (MM)
6. Persson *et al.* (136)	39C, 108PGD	Normal (OGTT)	NS
7. Efendic *et al.* (137)	10C, 17PGD	Reduced (OGTT, GIT)	Normal (SGIT)
8. Catalano *et al.* (138)	5C, 5PGD	NS	Normal (clamp)
9. Dornhorst *et al.* (139)	7C, 7PGD	Reduced (OGTT)	Normal (ITT)

OGTT, Oral glucose tolerance test; IVGTT, intravenous glucose tolerance test; GIT, glucose infusion test; ITT, insulin tolerance test; MM, minimal model; SGIT, somatostatin, glucose, insulin infusion test; Clamp, euglycemic hyperinsulinemic clamp; C, control subject; PGD, previous gestational diabetes; NS, not studied.

percent decrease in plasma glucose after intravenous insulin) improved to the point where it was indistinguishable from that of the normal controls. In contrast, insulin secretion (evaluated as the acute response to intravenous glucose) remained markedly impaired. Bak *et al.* (140) and Freidenberg *et al.* (142) found similar resolution of insulin resistance using the euglycemic hyperinsulinemic clamp technique.

These studies demonstrating the reversibility of insulin resistance but not impaired insulin release therefore provide evidence that, in type 2 diabetes, insulin resistance may be an acquired defect and that impaired insulin secretion is the genetic factor.

VII. Are All Type 2 Diabetics Insulin Resistant?

Although one would expect that all people with type 2 diabetes should be insulin resistant simply because of glucose toxicity (41, 42), such is actually not the case. Several studies have failed to find people with type 2 diabetes to be insulin resistant (27, 145–151). Arner *et al.* (145), for example, have reported that newly diagnosed lean Swedish type 2 diabetics are not insulin resistant but merely have impaired insulin secretion. Banerji *et al.* (27) have reported that a similar situation exists among nonobese blacks. Byrne *et al.* (47) found normal insulin sensitivity in a mixed population. Furthermore, it appears that insulin resistance, when present in this population (26, 27), may be largely explained on the basis of body fat distribution. Finally, two other studies have found that British and Japanese people with IGT have impaired insulin secretion without being insulin resistant (58, 60). Although there are no population-based studies indicating what percentage of people with type 2 diabetes or IGT are insulin resistant, one can nevertheless conclude that not all people with type 2 diabetes are insulin resistant. Thus, insulin resistance is not a requirement for development of type 2 diabetes.

VIII. Hypothesis for Pathogenesis of Type 2 Diabetes

Based on the reviewed evidence, the following working hypothesis is proposed as an explanation for the interaction between genetic and environmental factors in the pathogenesis of most cases of type 2 diabetes, realizing, of course, that type 2 diabetes is genetically and environmentally heterogeneous (Fig. 2). This hypothesis is based on the premise that a threshold exists which, if exceeded by the cumulative adverse effects of genetic and acquired factors on insulin secretion and insulin sensitivity, will lead to either IGT or type 2 diabetes. Another premise of this hypothesis, supported by the literature reviewed, is that defects in β-cell function are likely to be the most important genetic predisposing factors.

According to this schema, in some individuals, depending on the severity, a combination of several genetic defects or polymorphisms affecting insulin secretion would be sufficient to cause diabetes in conjunction with normal adaptations to aging (*e.g.*, changes in body composition and physical activity). Examples include MODY (2, 32), nonobese blacks (99), and Swedes (145) who develop type 2 diabetes without being insulin resistant.

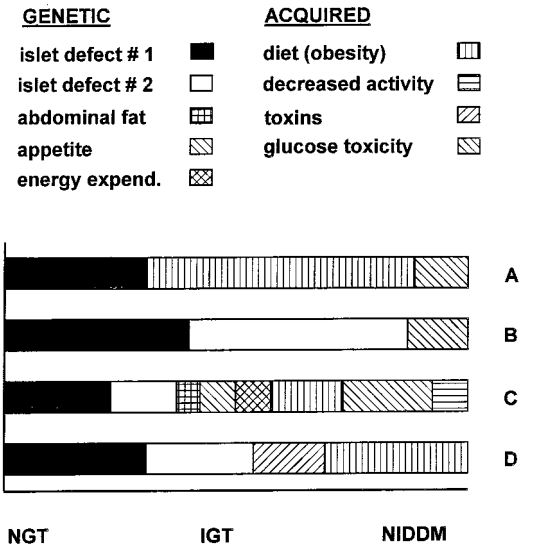

FIG. 2. Hypothesis for interaction of genetic and environmental factors in the pathogenesis of type 2 diabetes. Four possible combinations are depicted. *Length of segments in each bar* reflects severity of the adverse influence of the factor on glucose tolerance.

In most individuals, however, multiple genetic defects in insulin secretion may be necessary but not sufficient to cause diabetes without acquired factors such as superimposition of insulin resistance (*e.g.*, pregnancy, weight gain, glucose toxicity, physical inactivity, etc.) or without the simultaneous presence of diabetes-related or diabetogenic genes causing or predisposing to insulin resistance. An experimental example of such a situation comes from the results of recent knockout studies in mice (152): mice with a homozygous knockout of insulin receptor substrate 1 (IRS 1) had insulin resistance and hyperinsulinemia but maintained NGT with aging. Mice heterozygous for knockout of the β-cell glucokinase (GK) gene developed glucose intolerance with aging due to reduced insulin secretion. Double knockout mice (IRS 1 plus GK) developed overt diabetes with aging.

In different individuals, different combinations of genetic defects of insulin secretion and insulin action and of environmental factors are expected. This could readily provide an explanation of the heterogeneity of type 2 diabetes. For simplicity, if one assumes 1) that two defective β-cell genes are required and four exist; and 2) that, in addition, one environmental factor is needed and four exist (*e.g.*, overeating, reduced physical activity, toxins, glucose toxicity); and 3) that one genetic polymorphism in either appetite or energy expenditure or body fat distribution is needed, the unique combination of these elements leading to diabetes would exceed 4000.

IX. Summary and Conclusion

Despite the fact that it is the prevalent view that insulin resistance is the main genetic factor predisposing to development of type 2 diabetes, review of several lines of evidence in the literature indicates a lack of overwhelming support for this concept. In fact, the literature better supports the case of impaired insulin secretion being the initial and main genetic

factor predisposing to type 2 diabetes, especially 1) the studies in people at high risk to subsequently develop type 2 diabetes (discordant monozygotic twins and women with previous gestational diabetes), 2) the studies demonstrating compete alleviation of insulin resistance with weight loss, and 3) the studies finding that people with type 2 diabetes or IGT can have impaired insulin secretion and no insulin resistance compared with well matched NGT subjects. The fact that insulin resistance may be largely an acquired problem in no way lessens its importance in the pathogenesis of type 2 diabetes. Life style changes (exercise, weight reduction) and pharmacological agents (*e.g.*, biguanides and thiazolidendiones) that reduce insulin resistance or increase insulin sensitivity clearly have major beneficial effects (122, 144–146, 153–155).

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