Non-insulin-dependent diabetes mellitus (NIDDM) is a serious and common chronic disease affecting an estimated 6.6% of the U.S. population 20–74 years of age (1) and often leading to disability from vascular complications (including coronary artery disease, renal failure, blindness, and limb amputation), neurological complications, and premature death. Treatment is often unsuccessful in preventing these adverse outcomes. Prevention of NIDDM would, therefore, be preferable and may be possible through modification of risk factors.

WHAT IS THE DISEASE?
NIDDM is defined by the National Diabetes Data Group (NDDG) (2) and the World Health Organization (WHO) (3) as diabetes with resistance to ketoadiposis in the absence of exogenous insulin. Previously, the terms type I and type II diabetes (4,5) were used synonymously with insulin-dependent diabetes and NIDDM (2,3), but this is inappropriate because the former classification is causal and the latter is clinical (6–8). There is considerable phenotypic variation in NIDDM, and the relative importance of genetic and environmental causes of NIDDM differs between people. Nevertheless, in all populations and ethnic groups, most patients with NIDDM have similar characteristics, including both insulin resistance and β-cell dysfunction, which appear to be the basic metabolic abnormalities leading to the disease (9–12). Thus, interventions aimed at reducing insulin resistance and preserving β-cell function could be anticipated to be beneficial in delaying most cases of NIDDM, although such measures might be ineffective in preventing the minority of cases of NIDDM involving an autoimmune process that leads to severe loss of pancreatic β-cells and to insulin deficiency (13). Individuals with genetic defects, such as mutations in the glucokinase gene (14,15), that lead to a relatively mild form of NIDDM may, however, benefit from these interventions.

WHEN AND IN WHOM SHOULD PREVENTION OF NIDDM BE ATTEMPTED?
Goals. A goal of diabetes prevention activities should be to maintain or improve the health of people at high risk of developing NIDDM by preventing or delaying the onset of the disease and associated complications. Mortality (16) and the risk of microvascular complications (2,3) are substantially increased only in those individuals with hyperglycemia above the levels adopted by the NDDG and WHO as diagnostic of diabetes because these criteria were selected, in part, on the basis of risk of microvascular disease (2,3). Although treatment of NIDDM can improve hyperglycemia, especially when treatment is initiated soon after diagnosis, neither nondiabetic glucose tolerance nor normal glycohemoglobin can often be achieved or maintained. Thus, a policy of early detection and treatment, as opposed to prevention, of NIDDM might be less effective in prevention of microvascular complications. Furthermore, macrovascular disease and its risk factors are often already present in subjects at high risk for NIDDM (17), suggesting that an additional benefit of intervention before the diagnosis of diabetes may be prevention of the development or progression of macrovascular disease.

The goals of clinical trials should be 1) to determine whether there is any means of preventing or delaying NIDDM and, if so, 2) to determine the best means. Any decrease in the degree of hyperglycemia or prevention of the age-related increase in hyperglycemia may improve the health of individuals with mild-to-moderate hyperglycemia. Thus, the degree of hyperglycemia (fasting, during an oral glucose tolerance test, or as estimated by glycosylated hemoglobin) could be used as a study outcome. This point is important to consider in the design of clinical trials because the power of a study to detect the effects of treatment on the degree of...
hyperglycemia might be greater than the power to detect an effect on deterioration to NIDDM, a dichotomous outcome.

While the primary end point of a diabetes prevention program or clinical trial would be worsening hyperglycemia or the development of NIDDM itself, important secondary end points could include the complications of NIDDM, such as cardiovascular and renal diseases, and mortality. People with NIDDM often have high levels of other cardiovascular disease risk factors (18). Therefore, one might consider multivariate risk factor scores derived from variables such as blood pressure, serum insulin, total and high-density lipoprotein cholesterol, triglycerides, uric acid and fibrinogen, urinary albumin excretion rate, body mass index, abdominal girth, and smoking, in addition to blood glucose, as outcome variables in prevention trials. These secondary outcome measures may be useful surrogate measures for clinical consequences, such as specific cardiovascular and renal diseases, in clinical trials having insufficient numbers of new cases of these diseases for direct tests of their preventability. Stages in NIDDM. The development and course of NIDDM has been divided into a number of stages (19,20), and NIDDM in individuals may progress through some or all of them.

The first stage is genetic susceptibility. The genetic defects currently known to cause NIDDM, such as mutations in the insulin, insulin receptor (21), glucokinase (14,15), and mitochondrial genes (22), are infrequent, accounting for only a small fraction of cases. Knowledge of these genetic abnormalities has not yet been translated into therapy, either to treat or to prevent diabetes. Except in a minority of cases, the genetic basis of NIDDM is unknown, but in most individuals who develop the disease, the genetic abnormality is apparently manifest as insulin resistance (11,12).

A second stage is impaired glucose tolerance (IGT), arbitrarily defined by hyperglycemia during an oral glucose tolerance test that is not of sufficient degree for the diagnosis of diabetes (2,3). IGT may be secondary to long-standing insulin resistance. It is of particular importance because it can be recognized and defined by a simple clinical test and has been the subject of many follow-up studies and some randomized clinical trials. IGT is accompanied by insulin resistance with compensatory hyperinsulinemia that maintains glycemia in the nondiabetic range (23-25). When insulin secretion is no longer sufficient to compensate for insulin resistance, hyperglycemia worsens to the point of diabetes (9,24,25).

Diabetes without complications can be considered the third stage, characterized by chronic hyperglycemia with or without symptoms. A large proportion of people with NIDDM are asymptomatic or undiagnosed (1) but still at risk for diabetes complications.

The fourth stage is diabetes with vascular or neurological complications. When to start interventions. Intervention at any stage, from genetic susceptibility until the onset of NIDDM, could potentially prevent or delay progression to subsequent stages. Prevention might be most effective when initiated early, which might be possible if those individuals with genes causing susceptibility to NIDDM could be identified. While rapid expansion of knowledge of genetic abnormalities in NIDDM can be anticipated, the implications for prevention and treatment will depend on the nature of the findings. If identification of susceptibility genes ultimately leads to pharmacological or genetic correction of the basic metabolic defects, then the applicability of such treatments will depend on the numbers and frequencies of these genes. On the other hand, environmental factors may play a major role in the development of NIDDM in some individuals. Even in populations such as the Pima Indians with a presumably high degree of genetic susceptibility to NIDDM, the changing incidence rates over time (25) and the strong associations with obesity (25) and physical inactivity (26), both of which are influenced by socioeconomic conditions, suggest that non-genetic factors are very important.

Ultimately, genetically susceptible individuals may be identifiable at or before birth, but it is impractical to undertake clinical trials at this stage to prevent a disease that typically develops in adulthood. At the other extreme, intervention might be targeted to those close to the onset of diabetes. Such individuals can be identified by considering the well-described risk factors for NIDDM, such as obesity (especially central obesity), insulin resistance, and IGT. By considering these factors, it is possible to identify individuals who are at a high enough risk of developing NIDDM to enroll in clinical trials with a duration of several years. It may be, however, that interventions are less effective when the metabolic abnormalities have progressed so far (for example, to IGT) and that intervention at an earlier stage would be preferable. Unfortunately, there are no data to support this hypothesis, and it will be difficult to test because the costs of clinical trials, in terms of size and duration, might be prohibitive. Therefore, studies should first be performed in individuals with high-risk characteristics, such as IGT.

The importance of IGT as a predictor of NIDDM is illustrated in Fig. 1. Age- and sex-adjusted incidence rates of diabetes in Pima Indians ≥15 years old. Incidence (with 95% CIs) of new cases per 1,000 person-years at risk is shown. The plasma glucose concentration was assessed as a predictor of development of diabetes by the next examination within a 5-year period. The plasma glucose concentration of 7.8 mmol/l (vertical dashed line) represents the lower limit of IGT. Adapted from Knowler et al. (25).
able, and body fat and its distribution, are also useful for identifying those at high risk of developing NIDDM (25,28,29). Therefore, a combined strategy might be considered, such as selecting individuals with IGT or other risk factors who also belong to high-risk ethnic groups or selecting individuals with high values of a multivariate risk indicator score.

Other risk factors for NIDDM include obesity, central distribution of body fat, physical inactivity, and high-fat diet (3,30). The evidence for these risk factors is strongest for obesity and least certain for dietary fat: high-fat diet predicted NIDDM in one longitudinal study (30), whereas high consumption of vegetable fats was protective against NIDDM in another (31). These risk factors are associated with and may be partially responsible for insulin resistance and impaired insulin secretion, which are the physiological abnormalities that lead to most cases of NIDDM (9–12,25).

INTERVENTIONS FOR PREVENTION OF NIDDM

Behavioral interventions. The risk factors for NIDDM may be attenuated by modification of obesity, physical activity, and diet. Dietary change is part of most weight-control programs, and caloric restriction decreases hyperglycemia dramatically (32). Lowering the fat content of the diet may aid in weight loss and may have other benefits if high fat intake, per se, causes NIDDM (30). Increasing physical activity improves insulin sensitivity acutely (33) and may also contribute to weight loss. Thus, behavioral interventions, such as restricting caloric intake, reducing dietary fat, and increasing physical activity, may be helpful in diabetes prevention.

Drugs. Two categories of drugs have been tested in clinical trials for prevention of NIDDM, and four others might be considered. Sulfonylurea drugs decrease hyperglycemia and appear to stimulate both insulin secretion and insulin action (34). They are well tolerated but can cause hypoglycemia, which can be symptomatic and even fatal. Therefore, only short-acting sulfonylureas, such as tolbutamide or glipizide, should be considered for a clinical prevention trial because the risk of inducing serious hypoglycemia is lower with these than with the longer-acting sulfonylureas (35).

The biguanides are another category of drugs that have been tested for prevention of NIDDM. There is extensive experience with metformin, the principal biguanide used today. Its mechanism of action is not well established but involves inhibition of intestinal glucose absorption and improvement of insulin action (36,37). It does not cause hypoglycemia, and unlike sulfonylureas, which are associated with weight gain, treatment with metformin is associated with weight maintenance (38) or loss (39,40). Metformin can cause lactic acidosis, but does so much less frequently than other biguanide drugs. It can result in abdominal discomfort and flatulence, but in a double-blind randomized clinical trial in NIDDM patients, metformin and a sulfonylurea were equally well tolerated and effective (39).

Thiazolidinediones are a third category of drugs that improve insulin action (41). Although long-term human experience is limited, they are promising and should be considered in future clinical trials. The glucosidase inhibitors, of which acarbose is most widely used, are a fourth category of drugs to be considered for diabetes prevention. Acarbose delays glucose absorption, decreases hyperglycemia in non-diabetic and diabetic individuals, and improves serum lipid concentrations, but it has gastrointestinal side effects (42–44). The fifth drug to consider is insulin. Although, to our knowledge, insulin has not been seriously considered in clinical trials of prevention of NIDDM, in individuals with newly diagnosed NIDDM, insulin treatment decreases hyperglycemia and increases insulin secretion and action (45), effects that should also be beneficial in preventing NIDDM.

In addition to the drugs discussed above, drugs specifically used for treating obesity should be considered because obesity is such a strong risk factor for NIDDM and is so difficult to treat successfully by behavior modification alone. In one study, the weight-loss effect of diet and exercise was greatly enhanced by treatment with a combination of fenfluramine and phenetermine (46,47). These drugs were associated with no recognizable serious side effects, even when used intermittently for 4 years (46,47). Other drugs have also been effective in weight loss studies (48).

PREVIOUS CLINICAL TRIALS

Interventions that have been proposed and tested for the prevention of NIDDM are weight reduction, exercise, dietary modification, and administration of oral drugs currently used in the treatment of NIDDM. Sulfonylureas or biguanides have been used in three randomized prevention trials, the results of which are summarized in Table 1. In the studies performed in Bedford (49) and Whitehall, U.K. (50), there was no discernible effect of either diet or drugs on the incidence of diabetes in subjects with mild abnormalities of glucose tolerance. In the Bedford study, the rates of decompensation were similar in those subjects randomly assigned to tolbutamide or placebo treatment. Similarly, in the Whitehall study, assignment to treatment with a biguanide, phenformin, had no benefit. Subjects received either phenformin or placebo and were either advised to limit sucrose intake (with no other dietary advice) or given a limited-carbohydrate diet. The incidence of diabetes did not differ significantly by treatment, although little detail was given about compliance in either of these studies.

<p>| Table 1: Summary of drug effects in three randomized clinical trials of prevention of NIDDM |</p>
<table>
<thead>
<tr>
<th>Study and treatment</th>
<th>Number of subjects</th>
<th>Number (%) developing NIDDM</th>
<th>Incidence rate ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedford</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>125</td>
<td>10 (8)</td>
<td>1.1 (0.5–2.5)</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>123</td>
<td>11 (9)</td>
<td></td>
</tr>
<tr>
<td>Whitehall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>80</td>
<td>14 (16)</td>
<td>0.9 (0.4–1.8)</td>
</tr>
<tr>
<td>Phenformin</td>
<td>92</td>
<td>15 (14)</td>
<td></td>
</tr>
<tr>
<td>Malmohus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo or none</td>
<td>98</td>
<td>13 (13)</td>
<td>0.8 (0.3–2.0)</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>49</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Summary Drug/placebo</td>
<td>—</td>
<td>—</td>
<td>0.9 (0.6–1.5)</td>
</tr>
</tbody>
</table>

Follow-up was for 10 years in the Bedford study (49), 5 years in the Whitehall study (50), and 10 years in the Malmohus study (51). The incidence rate ratios are the cumulative incidences in the drug-treated arm divided by those in the placebo-treated arm. At entry, subjects had IGT, using criteria that differed somewhat between studies and from those later recommended by WHO (3). The cumulative incidence rate ratio (95% CI) is shown for each study, along with a summary incidence rate ratio, computed by the method of Mantel and Haenszel (52).

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In the study in Malmöhus, Sweden (51), men with IGT were randomly assigned to one of three groups, each of which received dietary treatment. Subjects in two of the groups also received either tolbutamide or a placebo tablet. In 10 years, the incidence of diabetes was 10% in those assigned to tolbutamide and 13% in the others, a difference that is not statistically significant.

There were differences in entry criteria and treatments in the three studies, and all had small sample sizes, resulting in wide confidence intervals (CIs) around the effect estimates. The summary cumulative incidence rate ratio (52) was 0.9 (active drug/placebo), suggesting little or no effect of the active treatments. The wide 95% CI, 0.6–1.5, is consistent, however, with a clinically important effect (either beneficial or harmful) of the drugs on the incidence of diabetes.

The Malmöhus clinical trial was also analyzed according to estimates of compliance in tablet taking, based on both history and, toward the end of the study, measurement of serum tolbutamide concentrations (51). Twenty-three subjects, less than half of those randomly assigned to tolbutamide, continued to take the drug throughout the entire 10-year study period. None of the 23 (0%) developed diabetes, but this rate was not statistically significantly different from the rate of 15% in all other subjects given dietary treatment, with or without a drug or placebo. Whether there was a true therapeutic effect or those who elected to continue tolbutamide were a self-selected group who had a lower incidence of diabetes for other reasons is unknown. Nevertheless, this small subsample does suggest the possibility that treatment with tolbutamide might be effective in preventing diabetes.

The feasibility of behavioral interventions for the prevention of NIDDM has been demonstrated in Malmö, Sweden, in a study of two groups of middle-aged men with IGT (53). In the intervention group, 161 men were treated with diet and exercise; 56 others, a reference group, were not enrolled in the treatment program for various reasons, including referral to other clinics or physicians because of hypertension, alcohol consumption, or other conditions. The groups were not assigned at random. The reference group was treated for medical conditions according to standard practice but was not given specific treatment for hyperglycemia. Those in the treated group were given physical training and advised to reduce sugar and fat, increase complex carbohydrate and fiber in the diet, and lose weight if they were overweight. They received no drug treatment for hyperglycemia, although some took drugs for other indications such as hypertension. The treated subjects, but not the reference group, had a significant weight loss, most of which was maintained for 5 years. After 5 years, 11% of the treated subjects and 21% of the reference group had developed diabetes according to WHO criteria. Thus, the incidence in the treated group was 0.5 times (95% CI 0.3–1.0) that of the reference group. This study is important primarily in demonstrating the feasibility of conducting a diet-exercise program for 5 years. The effect of treatment, however, remains uncertain because the treatment groups were not assigned at random and differed in their medical conditions at baseline.

Preventive effects of diet and exercise have been reported in an abstract of a randomized clinical trial in Chinese adults with IGT in Da-Qing, China (54). A total of 530 individuals with IGT, as determined by WHO criteria, were randomly assigned to one of four groups: a diet-only intervention group; an exercise-only intervention group; a group receiving diet and exercise treatment; and a control group without intervention. The subjects were followed for 6 years, after which the cumulative incidence rates of diabetes (assessed by oral glucose tolerance testing by WHO criteria) were significantly lower in all three intervention groups (44, 41, and 40%, respectively) than in the control group (65%).

**PROPOSED CLINICAL TRIALS**

Obesity, physical inactivity, and possibly high dietary fat are risk factors for NIDDM and are potentially modifiable. Modifying these factors, however, is very challenging, and in most randomized clinical trials, it has not been established whether their modification reduces the incidence of NIDDM. Insulin resistance and impaired insulin secretion, the metabolic characteristics predicting NIDDM, can be treated pharmacologically. Whether such treatment can prevent diabetes is unknown, but this hypothesis has not been adequately tested.

The major problem in interpreting tests of this hypothesis has been compliance with the interventions. It is generally not possible for subjects in large clinical trials to achieve and maintain large weight losses, and it is difficult to measure changes in fat intake and physical activity. Therefore, it is difficult to test whether changing these risk factors will prevent NIDDM. For example, no effect of dietary modification was reported in the Bedford (49) and Whitehall (50) clinical trials. Because no details on compliance were provided, it is unknown whether subjects ignored the advice or to what extent they followed it, but the advice did not have the desired effect—either because the intervention was of insufficient intensity or because the development of NIDDM cannot be changed by such interventions no matter how well applied. On the other hand, compliance with diet and exercise, as judged by weight loss, was apparently excellent in the Malmö feasibility study (53), but an effect on prevention of diabetes could not be clearly shown because of lack of a randomly assigned control group.

Compliance with drug treatment is just as important and difficult to assess. This issue has been discussed in only one of the clinical trials presented, the one in Malmöhus, Sweden (51). Assessment of compliance in taking tolbutamide was attempted only at the end of that study and by methods, such as measurement of serum drug concentrations, that reflect compliance only shortly before the test. This assessment, however, strongly suggested that poor compliance could have explained the lack of significant drug effect in the intention-to-treat analysis. Other methods of measuring drug-taking behavior, such as electronic recorders on pill bottles (55), should be used in future clinical trials, and more attention must be paid to enhancing medication compliance.

On the other hand, the power of a clinical trial can be reduced if the average compliance of all subjects, including those receiving standard care, is better than expected. This is one potential interpretation of the results of the Multiple Risk Factor Intervention Trial, in which the incidence of coronary heart disease was lower than expected in both the standard care and special intervention groups and the incidence did not differ significantly between these groups (56). This study also illustrates the problem of including a control group in clinical trials involving interventions that may be widely available and accepted by the public and the medical
community—a problem that must be addressed in future clinical trials of prevention of NIDDM.

Randomized clinical trials are needed to test both behavioral and drug treatments, and more emphasis must be placed on measuring and enhancing compliance. An intensive program combining exercise and a diet with reduced total calories and fat should be tested, and testing the effects of diet modification or exercise alone should also be considered. For drug treatment, metformin appears to be advantageous in terms of its low risk of serious adverse effects and its promotion of weight maintenance or loss, but a thiazolidinedione, a short-acting sulfonylurea, acarbose, insulin, anorectic drugs, and combinations of these should also be considered. Subjects could be randomly assigned individually to drug or placebo treatment, but different units of randomization should be considered for behavioral intervention. Because diet and exercise patterns are often shared among families and friends, behavioral interventions might be delivered more effectively in clusters of families or small communities. Factorial designs could be used to address two or more intervention questions simultaneously, such as the effect of a drug compared with placebo and the effects of two different behavioral programs. Combining these interventions in a single study might increase study efficiency. Randomized clinical trials incorporating many of these points are currently being developed in a number of countries, including the U.S. (57).

CONCLUSIONS

Epidemiological studies have identified risk factors for NIDDM. Because there is the potential to modify some of these factors through changes in behavior and because some of the metabolic features predicting NIDDM can be improved pharmacologically, both behavioral and drug interventions for preventing NIDDM must be tested. There is cause for optimism that NIDDM can, at least in some people, be delayed or prevented, but clinical trials are needed to test this possibility and determine the best approaches to prevention.

REFERENCES


