Lessening the Burden of Diabetes

Intervention strategies

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OBJECTIVE — To evaluate the impact of primary and secondary interventions on the development of complications from diabetes, we modeled the effects of primary and secondary interventions for diabetes on a single well-studied complication, diabetic retinopathy.

RESEARCH DESIGN AND METHODS — A model was developed to predict cumulative incidence of retinopathy in IDDM and NIDDM. Risk functions are based on duration of diabetes. The effects of intervention strategies were simulated by altering the retinopathy risk. The effects of the simulations were assessed using cumulative incidence.

RESULTS — Simulations of delaying the onset of IDDM from 2 to 8 yr and decreasing the retinopathy rates by 20–80% were performed for each type of retinopathy. Simulating primary prevention shifted the cumulative incidence curves to the right, and simulating secondary intervention shifted the curves downward. Primary prevention was less effective than secondary prevention. This difference was more apparent for IDDM than for NIDDM, where disease duration and exposure to retinopathy risk were shorter. All interventions shifted the development of retinopathy to later in life.

CONCLUSIONS — The greatest effect on cumulative incidence of all forms of retinopathy occurs when primary and secondary interventions are combined.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BDR, BACKGROUND RETINOPATHY; ME, MACULAR EDEMA; PDR, PROLIFERATIVE RETINOPATHY; WESDR, WISCONSIN EPIDEMIOLOGIC STUDY OF DIABETIC RETINOPATHY; DCCT, DIABETES CONTROL AND COMPLICATIONS TRIAL; UKPDS, UNITED KINGDOM PROSPECTIVE DIABETES STUDY; IGT, IMPAIRED GLUCOSE TOLERANCE; NHANES, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY; OGTT, ORAL GLUCOSE TOLERANCE TEST.

Diabetes mellitus affects ~7% of the U.S. adult population (1,2); is the cause of significant morbidity and mortality and is the most common cause of new cases of blindness (3), end-stage renal disease (4), and lower-extremity amputation (5). Diabetes is also a major risk factor for myocardial infarction (6) and stroke (7). How can the burden of diabetes be lessened? Primary prevention of the disease by treating individuals at high risk of developing diabetes is one approach. Secondary intervention by treating glycemia and other risk factors for micro- and macrovascular disease is another. Tertiary intervention, i.e., treatment of the established complications of diabetes, is yet another.

The greatest progress in lessening the burden of diabetes has been made in the area of tertiary interventions. We know that it is cost-effective to screen for diabetic retinopathy (8) and that photocoagulation and vitrectomy can reduce the risk of severe visual impairment by >90% (9–12). We also know that frequent foot examinations and patient education regarding diabetic foot disease can reduce the rate of amputation by 50% (13–15).

The greatest benefit to those with diabetes and to those who will develop diabetes may be a three-pronged attack: primary intervention to delay or prevent diabetes, secondary intervention once the disease is manifest, and tertiary intervention once complications develop. This approach may reduce the overall burden of diabetes by the greatest amount. To evaluate the impact of these approaches on the development of complications, we have modeled the effects of primary and secondary interventions for diabetes on a single well-studied complication, diabetic retinopathy.

RESEARCH DESIGN AND METHODS

— A model was developed to predict cumulative incidence of retinopathy in IDDM and NIDDM. The model is spreadsheet-based (Lotus 123,

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Lotus, Cambridge, MA) and allocates patients to possible outcomes in a manner similar to Weinstein's forecast model for coronary heart disease (16). Risk functions for progression to BDR, ME, and PDR are based on duration of diabetes (8,17). Progression in the model is from no retinopathy to BDR, BDR to ME or PDR, and ME to PDR. Development of ME in those with PDR is also allowed. Annual adjustments for mortality are made using age-specific mortality rates adjusted for retinopathy status as described by Javitt et al. (8) before applying the risk functions for retinopathy progression. For subjects with more than one sight threatening complication of retinopathy (i.e., PDR progressing to ME), the highest retinopathy-specific mortality rate is used. For example, subjects progressing to ME from PDR are subject to the PDR-specific mortality risk. Simulations were performed on a cohort of hypothetical subjects developing IDDM at 12.5 yr of age, the mean age of onset of IDDM in the U.S. population (8).

The model for patients with NIDDM used age-specific mortality rates adjusted for retinopathy status based on previously reported cross-sectional and longitudinal studies (18–23). The model simulations used age at onset of diabetes of 40 yr, and age at diagnosis of 44 yr, when 20–25% of patients have retinopathy (24,25).

The effects of intervention strategies were assessed by altering the retinopathy risk functions. For example, the effect of a secondary intervention such as intensive control of glycemia was simulated by applying a constant percentage reduction (20–80%) to the annual incidence rates for retinopathy progression (8). The effect of primary prevention was simulated by moving the risk functions for retinopathy progression 2, 4, 6 and 8 yr to the right. These two effects were combined to simulate delay in onset of disease and reduction of incidence through secondary intervention. Risk functions for progression to BDR and ME were adjusted in a similar fashion.

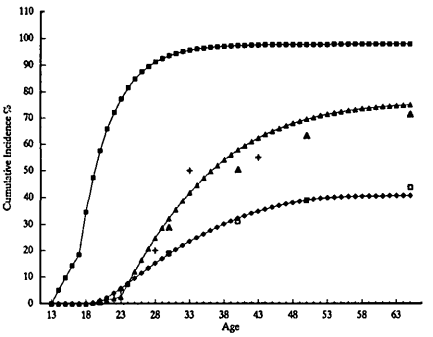

Figure 1—*Model predictions of cumulative incidence of BDR (■), PDR (▲), and ME (◆) in IDDM. Also shown are predictions from Javitt model (□ and △; 8) and from WESDR study (+; 26).*

RESULTS — Model predictions for retinopathy in IDDM are shown in Fig. 1. This model yielded reasonable predictions of retinopathy rates when compared with prior modeling projections using microsimulation (8) and with epidemiological data from the WESDR study (26).

Simulations of delaying the onset of IDDM from 2 to 8 yr and decreasing the retinopathy rates by 20–80% were performed for each type of retinopathy (Fig. 2). Simulating primary prevention shifted the cumulative incidence curve to the right (Fig. 2*A*), and simulating secondary intervention shifted the curve downward (Fig. 2*B*). In the example shown, delaying onset of IDDM had only a small effect on the cumulative incidence of PDR, whereas the effect of secondary intervention was much more pronounced. Both interventions reduced cumulative incidence but had different effects when viewed over the life span of the cohort through 65 yr of age. The cumulative incidence at 33 and 65 yr of age were plotted against the percentage of reduction in incidence and the number of years onset was delayed (Fig. 3). At 33 yr of age, secondary prevention

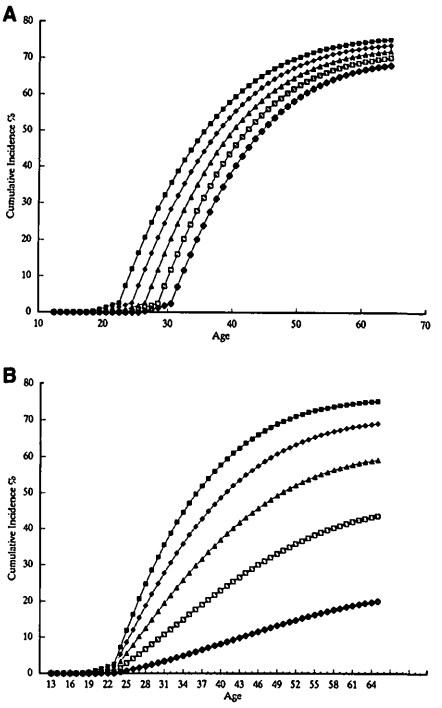

Figure 2—A: *Model simulations of effect of primary prevention on PDR in IDDM. Shown are incidence curves derived using the unadjusted retinopathy incidence functions (■) and when incidence functions are shifted to the right 2 (◆), 4 (▲), 6 (□), and 8 (◇) yr to simulate primary prevention of IDDM.* B: *Model simulations of effect of secondary prevention on PDR in IDDM. Shown are cumulative incidence curves from model when incidence is decreased to simulate secondary prevention: unadjusted risk function (■), 20% reduction (◆), 40% reduction (▲), 60% reduction (□), and 80% reduction (△).*

had a slightly greater effect than primary prevention, whereas at 65 yr of age secondary intervention was substantially more effective than primary prevention.

To compare the effects of primary, secondary, and combined interventions, simulations were performed for a 6-yr delay in onset of IDDM, a 60% reduction in the retinopathy incidence functions, and the combined effect for each type of retinopathy. The effects on BDR, ME, and PDR in IDDM are shown in Fig. 4. Note that over the lifetime of the cohort, little reduction occurred in

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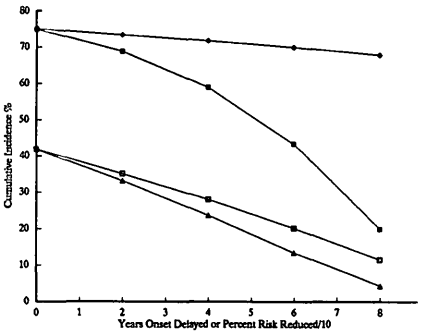

Figure 3—*Comparison of primary and secondary intervention strategies on PDR in IDDM. The y axis represents cumulative incidence of PDR at ages 33 or 65 yr resulting from primary prevention of 0–8 yr or secondary intervention resulting in 0–80% reductions in retinopathy incidence (x axis). Four curves represent primary prevention effects at ages 33 (□) and 65 (◆) yr and secondary prevention effects at ages 33 (▲) and 65 (■) yr.*

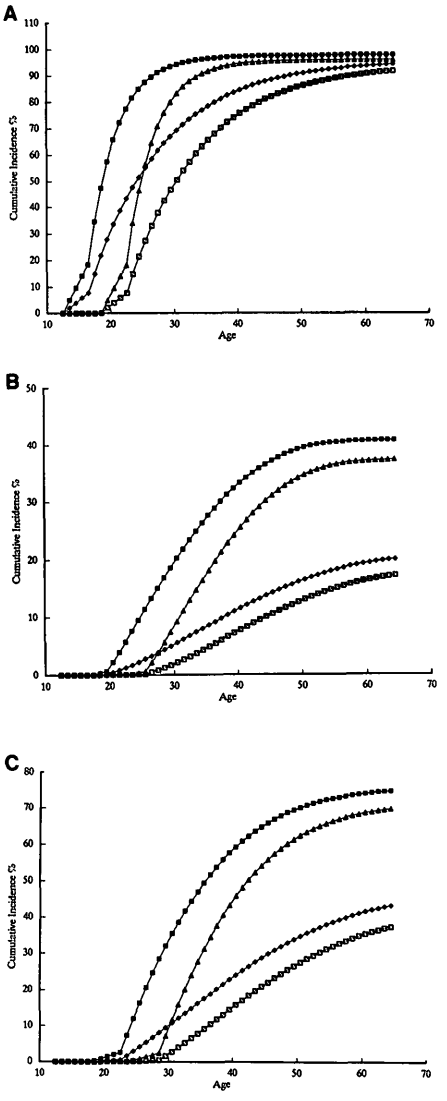

Figure 4—*Model predictions for BDR (A), ME (B), and PDR (C) for IDDM. Shown for each type of retinopathy are model simulations using unadjusted retinopathy incidence functions (■) and simulations of a 60% decrease in retinopathy risk through secondary intervention (◆), 6-yr delay in onset of diabetes through primary prevention (▲), and combined 6-yr delay and 60% risk reduction (□).*

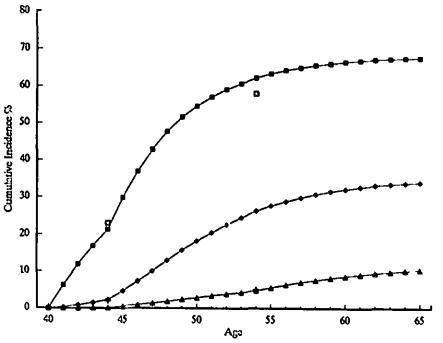

Figure 5—*Model predictions for cumulative incidence of BDR (■), ME (◆), and PDR (▲) in a cohort of patients with onset of NIDDM at age 40 yr and diagnosis at age 44 yr. Data points for prevalence of any retinopathy (□) and PDR (+) at diagnosis and 10 yr after diagnosis in WESDR study are shown. Adapted from Klein and Klein (24).*

the cumulative incidence of BDR, whereas ME and PDR were reduced by ≥50%. The greatest effect was seen when both onset was delayed and incidence of retinopathy was reduced. All interventions shifted the development of retinopathy to later in life, and the incidence curves when IDDM was delayed by 6 yr crossed and then exceeded the curves when retinopathy incidence was reduced by 60%.

Simulations of the cumulative incidence of BDR, ME, and PDR are shown for patients with NIDDM with onset of disease at 40 yr of age (Fig. 5). The model is consistent with clinical diagnosis of NIDDM 4 yr after onset, because 20% of patients with NIDDM have retinopathy at the time of clinical diagnosis (24,25). Simulations of primary, secondary, and combined interventions identical to those performed for IDDM are shown in Fig. 6. As with IDDM, secondary intervention had a greater effect on cumulative incidence than primary prevention. For NIDDM, however, primary prevention was much more effective than primary prevention of IDDM, because of the shorter duration of disease at 65 yr of age in the group with NIDDM. The greatest effect on cumulative incidence of all forms of retinopathy was when primary and secondary interventions were combined.

CONCLUSIONS— In this analysis, retinopathy is used as an example to illustrate the effects of various intervention strategies on the development of complications of diabetes. Retinopathy was chosen because of the availability and reliability of clinical and epidemiological data. Primary and secondary interventions had variable effects depending on the type of retinopathy and the type of diabetes, reflecting in part the longer period at risk of the IDDM cohort. The long-term effects of intervention were lowest when the unadjusted incidence rate was high, as for BDR in IDDM. Once the primary prevention fails, the benefit is quickly lost unless a secondary intervention at the time of onset (after the delay) reduces the incidence of retinopathy. Delaying onset of NIDDM 6 yr reduced the cumulative incidence of PDR by ~50% at 65 yr of age, whereas delaying onset of IDDM had only a small effect. Delaying onset of disease and reducing the incidence of complications at the time of onset had the greatest effect.

Severe vision loss caused by retinopathy is largely preventable by screening and tertiary interventions such as laser photocoagulation and vitrectomy.

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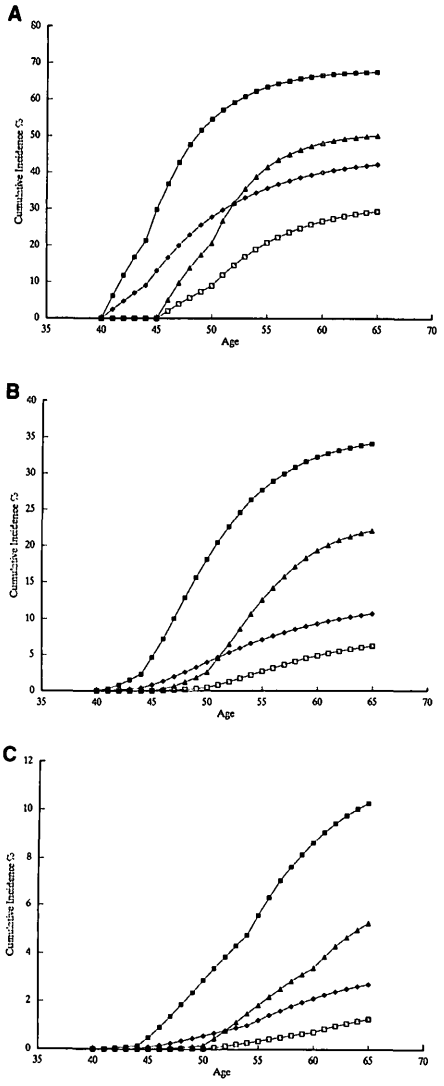

Figure 6—*Model predictions for BDR (A), ME (B), and PDR (C) for insulin-treated patients with NIDDM. Shown for each type of retinopathy are model simulations using unadjusted retinopathy incidence functions (■) and simulations of a 60% decrease in retinopathy risk through secondary intervention (◆), 6-yr delay in onset of diabetes through primary prevention (▲), and combined 6-yr delay and 60% risk reduction (□).*

These approaches have been shown to be cost-effective when retinopathy alone is considered (8). Whether tertiary intervention for retinopathy is more cost-effective than primary and secondary intervention is undetermined. Furthermore, effective primary and secondary interventions may be better for complications for which there are unsatisfactory tertiary interventions, such as nephropathy. For example, end-stage renal disease cannot be prevented once macroproteinuria develops, and dialysis and renal transplantation for end-stage disease entail significant morbidity and cost. Thus, primary and secondary intervention strategies may be more attractive for prevention of this complication. The present model could be used to project the effects of intervention strategies on other complications by changing the incidence functions.

A reasonable assumption is that delaying onset of diabetes will delay microvascular complications that occur only in those with diabetes, such as retinopathy and nephropathy, regardless of the natural history of the particular complication. The model predictions for primary prevention are likely to be accurate unless age of onset of diabetes has an effect on the retinopathy incidence functions. The effects of secondary intervention are less predictable, however. It has not been rigorously proven that secondary intervention to control glycemia will reduce the incidence or prevent vascular complications of diabetes. The DCCT and the UKPDS, both scheduled to end in 1994, should provide significant results regarding this question (27,28). Furthermore, the model assumes a uniform effect of any degree of control on all retinopathy incidence functions. This may not be valid for retinopathy or for other complications, such as nephropathy. Long-term epidemiological data on the effects of secondary interventions on the incidence of different microvascular complications will be needed to validate the model. For example, a given level of control might reduce PDR incidence but have a lesser or greater effect on ME or nephropathy.

The effects of primary and secondary interventions on macrovascular disease are even more difficult to predict. Macrovascular disease occurs in nondiabetic individuals, yet diabetic individuals have a two- to fourfold greater risk even after accounting for other risk factors such as dyslipidemia, smoking, hypertension, obesity, age, sex, and family history (29). The degree of glycemia is an important predictor of macrovascular disease; individuals with IGT have intermediate risk for macrovascular disease that lies between those with normal glucose tolerance and those with NIDDM (30–33). This also suggests that the effect of hyperglycemia occurs at modest levels of glycemia, as occur in IGT. Other evidence suggests that hyperinsulinemia is an independent risk factor for macrovascular disease (34,35), although little evidence implicates use of exogenous insulin as a risk factor (36). It remains to be proven that reducing glycemia or insulin levels or both will have significant effects on macrovascular disease risk. Targeting risk factors other than glycemia, such as smoking, hypertension, and dyslipidemia, may be more effective (37).

Primary and secondary interventions for diabetes have different public health implications. Secondary interventions, if shown to be effective, could be instituted at the time of clinical diagnosis of IDDM. In contrast, because clinical diagnosis of NIDDM is delayed 4–7 yr after onset, as suggested by the NIDDM model and observed prevalence of retinopathy at the time of diagnosis (24,26), early secondary intervention for NIDDM will necessitate screening for undiagnosed diabetes. Primary prevention of either type of diabetes will require screening to identify individuals at risk for subsequent development of the disease. The more stringent the criteria used to select individuals for intervention, the greater will be the loss of specificity. Treatment of these otherwise healthy individuals would require interventions that are low risk, well tolerated, and cost-effective. Interventions would have to be safe and effective and easily done, because acceptance of prolonged treatment by individuals who would never develop

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Table 1—*Prevalence of IGT and undiagnosed diabetes in the NHANES II survey population*

Population screened	People 20–74 of age (%)	People with IGT (%)	People with undiagnosed NIDDM (%)	Percentage of all IGT	Percentage of all undiagnosed NIDDM
20–74 yr of age	100	11	3	100	100
40–74 yr of age	52	16	6	75	87
>120% of desirable body wt	21	21	9	41	49
>120% of desirable body wt plus family history of diabetes	7	24	12	16	29

Family history refers to a family history of diabetes in parents or siblings. Second column from left gives percentage of population screened with age, weight, and family history shown in left column. Data from NHANES II survey were used to estimate prevalence of IGT and undiagnosed diabetes in at-risk populations. NHANES II contained a representative probability sample of U.S. population 20–74 yr of age. Subjects were administered a 75-g, 2-h OGTT after a 10 to 16-h overnight fast. Criteria for IGT and diabetes were applied to results of these OGTTs to estimate prevalence of these conditions (1). Right two columns give percentage of all individuals in population with IGT or undiagnosed diabetes in group specified in left column.

the disease would be necessary. More rigorous interventions might be acceptable for prevention of IDDM as a result of the early age at onset and the greater severity.

Studies in diverse populations have shown that age, family history of diabetes, insulin resistance, gestational diabetes, and IGT are risk factors for subsequent development of NIDDM (38–40). IGT may be a transient phenomenon; 28–76% of those found to have IGT on a single OGTT have post-challenge glucose <140 mg/dl on repeat testing after a short time interval (41,42). Nevertheless, in some populations, even transient IGT carries a significant risk of subsequent diabetes (43,44). The risk of subsequent development of diabetes is related to the severity and duration of IGT. For example, in the Pima Indians, the 5-yr cumulative incidence of NIDDM in those with 2-h postprandial glucose in the upper tertile of IGT is 50% and in the lower tertile 19% (45). Both rates are significantly greater than in those with normal glucose tolerance. Selecting individuals for intervention in this manner would detect only ~50% of those who would ever develop diabetes in the population. If less stringent criteria were used to select individuals to treat, then more people would be treated who would never develop diabetes.

If the U.S. population 20–74 yr of age were screened by glucose tolerance testing, 3.3% of the population would be found to have undiagnosed diabetes and 11% would have IGT (Table 1; 1). The efficiency of screening could be increased by selecting those at increased risk, such as older obese individuals with a family history of diabetes, but the more stringent the criteria for selecting individuals to screen the greater the loss of specificity. Thus, screening individuals 40–74 yr of age who are >120% of desirable weight and have a family history of diabetes would increase yield 12% with previously undiagnosed diabetes and 24% with IGT, yet would detect only 16 and 29% of all of those affected in the population (Table 1).

Screening would not only identify individuals at risk for diabetes but also those with undiagnosed diabetes and would offer the opportunity for earlier secondary intervention. Higher yields would be obtained by screening minority populations, because those individuals are disproportionally affected by the disease (46). Thus screening for IGT can detect substantial numbers of people with diabetes and many who are at risk for developing diabetes. Other approaches that have been used to predict development of NIDDM such as measuring insulin sensitivity using the minimal model of Bergman might also be used (47). Studies are needed to compare different approaches to predicting diabetes in diverse populations. The optimum age for initial screening and the frequency of subsequent screening would need to be determined.

Identification of individuals at high risk for IDDM poses a somewhat different problem than screening for NIDDM (48,49). Risk for IDDM increases progressively if a first-degree relative has diabetes, if islet cell antibodies and anti-insulin antibodies or both are present, and if a diminished insulin response to intravenous glucose administration exists (48,49). These tests make it feasible to screen family members of patients with IDDM and test intervention strategies in controlled trials. However, only 5–10% of patients with IDDM have a first-degree relative with the disease, only 2–3% of these are islet cell antibody positive. The use of autoantibodies to screen for diabetes in the general population is discouraging (50). Clinical trials based on the prediction of IDDM in the general population using this approach would require extremely large numbers of subjects and would be extremely costly. Better techniques for identifying individuals in the general population at risk for IDDM are needed.

What are the prospects of primary prevention of diabetes through treatment of high-risk individuals? Three large epidemiological studies show that

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risk of NIDDM is inversely related to exercise (51–53). Several additional studies have looked at whether NIDDM can be prevented by diet and exercise, sulfonylurea, and biguanide treatment (54–58). No definite conclusion can be reached from these data. Although maintaining desirable body weight through diet and exercise probably will prevent NIDDM or at least delay onset, long-term adherence by individuals to diet and exercise programs has not been demonstrated. Controlled clinical trials examining the effectiveness of life-style modifications and pharmacological agents for delaying onset of NIDDM are needed and are feasible.

Current strategies for primary prevention of IDDM target the autoimmune process. The risks of immunosuppression with available agents may outweigh the benefits. Several alternative strategies have been suggested, including immunomodulation with agents like nicotinamide (59), maintenance of tolerance to specific β-cell autoantigens, development of therapeutic agents that interfere with cellular immunity directed at the β-cell, and stimulation of β-cell regeneration (48,49,60). Studies in animals support the concept that maintenance of tolerance to antigens by oral administration of putative autoantigens is feasible in humans. Use of insulin administered by injection currently is being explored and preliminary results are exciting (49). Too few patients have been treated to date to allow definitive conclusions.

A foreseeable outcome of primary prevention is to delay the complications of diabetes into later life. The older population would not experience an increase in the burden of diabetes, however, and they would be free of complications during earlier, more productive years. Comprehensive modeling of the economic effects of primary, secondary, and tertiary prevention strategies should be done using standard approaches (16; Table 2). Detailed discussion of cost-effectiveness analysis is beyond the scope of this discussion and is problematic because the efficacy of prevention has not been demonstrated. As the DCCT and UKPDS draw to a close, we are poised to learn whether secondary prevention through treatment of glycemia can prevent or slow development of vascular complications. More research is needed to determine if primary prevention is possible.

Table 2—*Elements of cost-effectiveness analysis*

Costs
Research
Screening
Intervention
Side effects of intervention
Treatment off other diseases developing as a result of increased longevity
Cost savings
Health care for diabetes
Screening for complications
Treatment of complications
Rehabilitation services
Custodial care
Effectiveness
Increase in life years
Improvement in quality of life

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