Can We Prevent IDDM?

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"If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties" (Francis Bacon)

Diabetes always has been a defensive specialty for the physician. The treatment of insulin-dependent diabetes mellitus (IDDM) aims to mimic normal physiology, minimize hazards, palliate late complications, and offer guidance and support. It is essentially an exercise in damage limitation. Much can be achieved with current therapy, and microvascular complications can be prevented—or at least delayed—by improved glycemic control. Even so, current means of achieving safe near normoglycemia remain limited at best. Many of us hope and believe that, as the next millenium approaches, it will for the first time prove possible to assume the offensive, whether by restoring insulin secretion or halting the incipient disease process before clinical onset of IDDM. New and safer means of restoring normoglycemia are high on the research agenda for the established diabetic patient, but progress remains frustratingly slow. In contrast, work into the pathogenesis of IDDM continues to gather momentum 20 years after its human leukocyte antigen associations (1,2) and islet cell antibodies (ICAs) (3) were discovered.

The pathogenesis, prediction, and ultimate prevention of childhood IDDM constitute one of the great intellectual and human challenges of modern medicine. Certain broad inferences already can be drawn. Susceptibility to the disease is conferred by several genes acting independently or in concert, and immune-response genes are prominent among these. The latter stages of the process leading to β-cell loss are mediated by the immune system, and immune intervention after clinical diagnosis can delay the rate of β-cell destruction (4), providing a rationale for treatment of subclinical disease in high-risk individuals (5). It is increasingly practicable to identify first-degree relatives at risk of progression to diabetes and to quantify their level of risk, thus producing estimates that can be used to design intervention trials in prediabetes.

Estimating diabetes risk

Estimates used in diabetes prediction can be set out in the form of a decision tree, a stepwise selection procedure offering progressively increasing probability that a given outcome will or will not occur. One consequence of this procedure is that increasing specificity is gained at the expense of diminished sensitivity. The more certain we become that individuals in a certain category will develop diabetes, the greater the proportion of future cases we are likely to miss. Reasonably sound risk estimates may now be provided for ICA^+ first-degree relatives, but not for the background population. Intervention trials should therefore be targeted at relatives (6).

The decision-tree approach allows interventions appropriate to differing levels of risk to be proposed (Fig. 1). One such controlled trial aims to test the effect of exclusion of cow's milk proteins from the diet of newborn children whose parents or siblings have IDDM (7). We are involved with an intervention trial using nicotinamide in all relatives with ICA ≥20 Juvenile Diabetes Foundation units (JDF U), a population with an estimated overall 35% risk of progression to insulin requirement within 5 years. A trial of parenteral insulin will be conducted in a higher risk subgroup of the ICA^+ population with loss of the first-phase insulin response (FPIR) to the intravenous glucose tolerance test (IVGTT), in whom risk has been estimated at ~95% within 4 years (8).

The clinical implications of these three levels of intervention differ considerably. The cow's milk intervention is the most far-reaching of the three proposals. Although the initial intervention is targeted at newborn children with a family history of IDDM, the means proposed are so safe and simple that a successful outcome could lead to dietary changes that might lower the overall risk of IDDM in the population as a whole. In contrast, insulin treatment will be offered to high-titer ICA^+ individuals with an advanced metabolic abnormality; a group that might be characterized as having end-stage prediabetes. This is a logical group in which to pilot interventions because the great majority of those offered treatment will progress to diabetes within a few years. On the other hand, these individuals represent only about one third of high-titer ICA^+ individuals and will contribute perhaps only 20% of familial cases

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IDDM, insulin-dependent diabetes mellitus; ICA, islet cell antibody; JDF U, Juvenile Diabetes Foundation unit; IVGTT, intravenous glucose tolerance test; FPIR, first-phase insulin response; ENDIT, European-Canadian Nicotinamide Diabetes Intervention Trial; NIH, National Institutes of Health; ICARUS, Islet Cell Antibody Register User's Study.

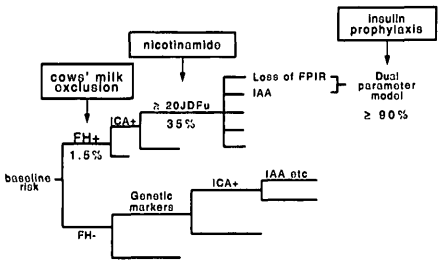

Figure 1—*The Decision tree representation of prediction of IDDM with intervention trials planned in 1994.*

of IDDM during the next 10 years (6). Therefore, interventions are needed that may safely be given to those at lesser degrees of risk, which inevitably entails treatment of many who might not, in any case, have developed diabetes during the study period. The nicotinamide trial design targets a larger group at a lower level of risk, but contains within it about twice the number of future cases of IDDM. An acceptable low-risk intervention targeted at this level could potentially prevent more cases of diabetes than a less acceptable or more hazardous intervention at a later stage in the disease course, even if it also proved rather less efficacious.

This commentary focuses on possibilities of intervention in first-degree relatives who already show signs of immune activation directed against pancreatic β-cells. We consider some of the problems involved in choosing and piloting an intervention, in designing a trial to test it, and in getting it under way.

Choosing an intervention

We are fortunate that a form of spontaneous autoimmune diabetes occurs in two inbred rodent strains. There are important similarities between diabetes in the NOD mouse, the most commonly favored model, and humans. Both show lymphocytic infiltration of the islets (9), circulating autoantibodies, and genetic susceptibility, and the genome of the NOD mouse has been explored in an attempt to identify candidate regions conferring genetic susceptibility to human IDDM (10). These models are invaluable as a means of generating and testing hypotheses concerning the pathogenesis of human IDDM, but the comparison should not be pushed too far. Humans are an outbred strain. Our genetic material parted company with that of the rodents many millions of years ago, our lifestyle is very different, and our diabetes differs in a number of crucial respects. In other words, experience gained with animal models provides useful analogies rather than a blueprint for prevention of human diabetes.

What can we learn from these analogies? In the NOD mouse, as in humans, inherited susceptibility is polygenic. A humoral and cellular immune response is mounted against multiple epitopes. Many attempts have been made to explain the immune processes that initiate and sustain autoimmune destruction of the islet β-cells, but the immune processes involved are so complex, and can be arranged in so many ways, that the number of potential models is almost infinite. The hope must be either to abort the disease process at the earliest possible stage (for example, by avoidance of dietary antigens) or to identify key common points in the subsequent pathogenesis at which intervention might be possible.

Although the key events in initiation and promulgation of the immune response are currently matters for speculation, a staggering number of interventions appear to prevent diabetes in the NOD mouse (11). However, these observations should be taken with some caution because most studies have tested interventions started in the neonatal period, before or around the time of immune activation, rather than at a relatively advanced stage of β-cell damage as in human prediabetes. Further, most studies terminate when the mice have reached 30–32 weeks of age, and it is therefore not always possible to say whether the agents tested have provided lasting protection against the onset of diabetes or simply delayed it. Finally, diabetes is so easy to delay or prevent in the NOD mouse that its value as an analogy is diminished. We simply do not have the resources to test all the hypotheses the mouse model can generate.

From mouse to man

Although the NOD mouse might appear as a signpost pointing in too many directions at once, the clinician will have little difficulty in eliminating a number of possibilities, either because they are known to be too toxic for human use, or because their safety has yet to be fully evaluated in humans. The main issue with safety evaluation is that small trials can show that an agent works, but much larger numbers are needed to show that it is safe (12). All toxic agents, and most novel ones, may therefore be excluded from the list for immediate consideration. Of the remainder, it is of note that two intervention trials have been proposed that would not entail small pilot trials of efficacy in humans. One of these, exclusion of cow's milk proteins, has already been mentioned, and the other is a proposed trial of oral insulin based on promising studies in the NOD mouse (13). The decision to proceed directly to large-scale controlled trials was presumably based on the perceived strength of the scientific rationale and minimal risk. Time is another consideration because it takes almost as long to carry out a small pilot study as a definitive clinical trial.

These interventions apart, assessment of potential agents in humans must rest on assumptions concerning safety and likely efficacy. Because estimates of safety must be derived from relatively wide experience with a therapy, agents that have been used for other clinical purposes must stand high on the list for consideration. Insulin does well from this point of view, and high-dose nicotinamide treatment, which has been used for various indications in thousands of patients during the past 30 years, also appears to have an acceptable margin of safety (14). The risks of immunosuppression are also familiar (12) and have deterred the majority of investigators from

using such agents for trials in prediabetes. The likely efficacy of therapies in human prediabetes is either completely untested in humans, has been inferred from trials in recently diagnosed patients with IDDM, or has been tested in small pilot studies in high-risk subgroups of ICA^+ relatives.

Studies in newly diagnosed patients with IDDM

Although the great majority of β-cells are assumed to have been destroyed before onset of clinical symptoms, controlled trials have shown that cyclosporin prolongs the functional life of the residual β-cell mass (4,15). The combination of azathioprine and prednisolone looked promising in a smaller controlled trial (16), whereas azathioprine alone was ineffective in another (17). No other agent as yet has shown convincing benefits in this situation. Insulin is taken by all newly diagnosed patients and is, therefore, impossible to evaluate; one study reported that a brief period of insulin infusion and glucose normalization resulted in better β-cell function at one year (18), a result that has yet to be confirmed. Nicotinamide has been tried after diagnosis with conflicting results, but no clear benefit has been established (19–22). Evidence for the efficacy of insulin and nicotinamide therefore rests almost entirely on small pilot studies in human prediabetes.

Pilot interventions in prediabetes

Pilot studies, i.e., exploratory investigations of a potential therapy, should be treated with caution. To begin with, they are inevitably somewhat ad hoc in their approach, often with less stringent entry criteria and follow-up procedures than one would expect from prospective controlled trials. Further, both the investigators and the patient volunteers involved are highly motivated individuals who know that an active compound is being used; acceptability, compliance, and outcome are therefore optimized. Pilot studies tend to overestimate treatment effect because only strongly positive results are followed up. Further, and more critically, they cannot prove a negative, and there is a high risk that useful therapies will be discarded. The resulting data are available in full only to a few individuals who may already be convinced of the value of the new therapy, whereas results are published mainly to attract support for clinical trials. Conversely, negative results often are not published at all. There are obvious grounds for caution in all this.

Elliott and Chase (23) described a pilot study of nicotinamide in children who were first-degree relatives of patients with IDDM with ICA ≥80 JDF U, low FPIR, and normal HbA_1. The first 8 cases identified in Denver served as control subjects, and treatment was given to the next 4 eligible children in Denver and 10 from Auckland, Australia. At the time the report was published, 8 of 8 in the untreated group had developed diabetes (mean time to diabetes 17 months) as against 1 of 14 in the treated group after 25 months, with a mean follow-up of 24 months for the remainder. The difference in outcome was analyzed by Fisher's exact test after 1 and 2 years of follow-up, and significant differences between treated and untreated groups were shown. Log-rank testing was used to compare the survival experience at the time of reporting, and significant differences between the two groups were found ($P < 0.001$). Keller et al. (24) have reported a pilot study of parenteral insulin prophylaxis in high-risk relatives. Five children considered to have >90% risk of developing diabetes within 4 years were compared with seven similar family members (children and adults) who declined the treatment option of a 5-day hospital admission every 9 months for continuous insulin infusion and twice daily subcutaneous insulin between admissions. All of those who declined treatment developed diabetes within 2.5 years compared with 1 of 5 in the treated group and ~70% of historical controls. The mean follow-up in the non-diabetic individuals in the treated group is 3.15 years. There was a significant difference in survival between treated and untreated groups ($P = 0.002$). At the time of writing this editorial, it is our understanding that 7 of 14 subjects studied by Chase and Elliott (50%) have developed diabetes within a maximum follow-up period of 4 years (8), compared with 1 of 5 (20%) in the insulin study. It would seem difficult to maintain that either pilot intervention was effective or ineffective or clearly superior to the other, based on such limited data. A further negative pilot trial of nicotinamide, however, has been reported in three high-risk individuals who progressed to insulin treatment within a maximum of 21 months (25). All were evidently very close to clinical diagnosis when treatment started, and the chances of missing a useful treatment effect in this tiny sample are obviously large.

Trial design

The science of prediabetes is novel and exciting, and as a result, it is sometimes forgotten that there is nothing innovative about the process of clinical evaluation of a new marker or potential therapy. The same statistical considerations apply when designing studies for which the entry criteria might be a given level of cholesterol, or blood pressure, or ICA. Conventional sample size calculations depend on the risk in the untreated group, the treatment effect considered clinically relevant, as well as the required level of statistical significance and power to detect a difference (26). The size of a study also is determined by the prevalence of the risk marker and the rate of participation among eligible individuals. This is best illustrated by an example: a recent review opens by contrasting the European-Canadian Nicotinamide Diabetes Intervention Trial (ENDIT), which aims to screen 22,000 relatives and randomize 422 to treatment or placebo arms, with a trial of parenteral insulin that would involve screening no more than 8,000 relatives and that would allow four treatment arms to be examined (6). Who would doubt that the latter trial design was superior? In

fact, the statistical methods used to design the two trials are probably very similar. Sample size calculations lend an air of scientific respectability, but their limitations and vulnerability to minor changes in the starting assumptions often are not appreciated. The difference in estimated sample sizes in the two trial designs derives directly from the degree of optimism shown by the investigators in their assumptions. Any fair comparison should therefore examine these with some care.

Assumption 1. The entry criterion for the insulin trial is loss of FPIR in family members with high-titer ICA. Because these individuals represent a minority of those with ICA, the risk estimate is necessarily based on a small number of subjects, and the confidence intervals are correspondingly wide, with a range of 0–30% at 2.8 years (6). Further, there is some doubt concerning the biological significance of low FPIR in young children because prepubertal ICA^- first-degree relatives have been shown to have unexpectedly low insulin responses (27). In the ENDIT, study entry is based only on ICA ≥20 JDF U, a robust entry point that has been associated with very similar levels of risk of developing diabetes (~35% in 5 years) in large groups of individuals in several family studies (28,29). The 95% confidence intervals are therefore < ± 10%. Its predictive significance is enhanced rather than reduced in young children (29). Because all these estimates of risk are based on relatively small numbers, it seems prudent to base any large study on the most robust, best validated entry points available.

Assumption 2. The treatment effect sought in the nicotinamide trial as a whole is 40%. Sample size calculations show that 422 subjects will be needed to undertake this study. Many, but not all, who progress to diabetes in the early stages of the trial will have lost their FPIR, and these will constitute about one third of those recruited. The trial has the power to detect a 20–25% treatment effect within this subgroup, assuming a 90% risk of diabetes within 5 years. In contrast, the insulin trial is based on less conservative assumptions. Forty-eight subjects will give 90% power to detect a 35% treatment effect if the risk of diabetes in the placebo group is 95%. If the risk in the placebo group differs only slightly from that in the group on which the calculations were based, the power of this study would fall precipitously.

Assumption 3. The population to be screened for the ENDIT study is 22,000. A relatively high level of participation (80%) for this simple treatment has been assumed. The frequency of ICA ≥20 JDF U in family members has been almost identical in many family studies (~2.4%). Screening 8,000 family members for an insulin trial, as described in the review, should yield ~160 individuals with ICA ≥40 JDF U (the threshold of detection of the assay on which their previous studies have been based) (30). If one third of these have loss of FPIR, 53 potential study subjects will be identified; the study designers expect that 48 (91%) of these will participate—perhaps somewhat optimistic in light of the 5 of 12 (42%) participation rate in their pilot study. If the rate of recruitment were to reflect the rate in the initial pilot study, >17,000 family members would have to be screened.

The same issues are raised by the hypothetical study into the effect of nicotinamide in individuals with loss of FPIR proposed by Eisenbarth et al. (8). Table 1 contrasts this design with the subanalysis in relatives with loss of FPIR possible within ENDIT. Here again, it is readily apparent that the more efficient trial design is based on more optimistic assumptions—a 95% risk of developing diabetes and 100% uptake among eligible individuals—and therefore has a much greater risk of missing a clinically useful effect. Small changes in the starting assumptions make a huge difference to the final estimated sample size, and comparisons are meaningless unless these assumptions are clearly stated.

In practice, and as a statistician ruefully remarked at a recent meeting, the predominant consideration in calculation of sample size for trials in prediabetes often has been the number of subjects the investigator felt able to recruit. Even the smallest samples proposed for such trials depend on screening very large numbers of first-degree relatives, and it is clear that large well-coordinated clinical studies will be needed before recent and future advances in our understanding of the events leading up to a diagnosis of diabetes can be evaluated and brought into clinical practice. We note that the intervention trials currently under consideration by the National Institutes of Health (NIH) currently envisage screening populations even larger than that proposed by ENDIT. Clinical groups throughout

Table 1—*Alternative designs for a study of the effect of nicotinamide in ICA^+ family members with loss of FPIR*

	Hypothetical trial design (8)	ENDIT subanalysis in those with loss of FPIR
Assumptions		
The risk associated with loss of FPIR (%)	95	90
The treatment effect considered clinically relevant (%)	33	20–25
The sample size required in each group (n)	28	70
The participation rate (%)	100	80
The number of individuals to be screened to undertake the study	8,400	22,000

the world will need to collaborate effectively if such studies are to be accomplished.

The need for standardized procedures and registries

The need for clinical groups throughout the world to collaborate effectively implies the need for well-standardized clinical measures and procedures. ICAs, despite their leading role in current predictive models, are difficult to measure and standardize. The Immunology of Diabetes Workshop (9) group conferred an immeasurable benefit on the research community when ICAs and other markers were for the first time brought into the disciplined environment of a workshop group. A further step toward standardization was the introduction of ICARUS (Islet Cell Antibody Register User's Study), a registry of individuals judged on various grounds to be at increased risk of progression to IDDM. Sera are distributed to international reference laboratories and checked for ICAs and insulin autoantibodies; other markers will in time be added to the list. A standard protocol has been decided for performance of the IVGTT (31), data collection, and follow-up. A recent meeting of the group established that the registry contained sera and data on 838 ICA^+ nondiabetic individuals, 109 of whom developed IDDM in the course of follow-up. Reports on the predictive value of current markers in first-degree relatives and in children with no family history of IDDM will be submitted, superseding much current debate on these issues. The registry also will provide a validated and accessible source of data for all those planning future intervention studies.

Where do we go from here?

It is sometimes difficult to recollect that the first trials of immune intervention in newly diagnosed patients were planned only some 10 years ago, at a time when only a few lonely visionaries conceived of intervention before the onset of diabetes. Now, as the NIH moves toward support for trials of early intervention, prediabetes promises to enter the mainstream of clinical practice. Inevitably, there is a rush to test the therapies that seem most promising, and those convinced that a given therapy will work undoubtedly see this as the main priority. They may feel with equal fervor that therapies of which they disapprove should not be accorded equal status. Strong opinions flourish on inadequate data. Researchers in the U.S., for the most part, favor injected insulin as an intervention, whereas their counterparts in Europe and Canada, by and large favor nicotinamide. We must accept that neither of these therapies may work, or if so, that they may produce no lasting benefit. We may hope for a "penicillin of prediabetes," but we have no right to expect it.

Clinical researchers inevitably tend to segregate into hawks and doves. The hawks are impatient to get in there and test new therapies, and the doves worry about the consequences of doing just that. This tension is necessary. Enthusiasts are needed to get things done, and skeptics are needed to make sure they are done right. The main problem is that it is easier to generate emotion about the need to try out a new therapy than about the need to do so with circumspection. Controlled clinical trials are our only means of overcoming the power of preconception and have shown again and again that the enthusiasts can be wrong. Less commonly, they also have shamed the skeptics.

Although the overall challenge of prevention of IDDM is daunting in its scale, there are grounds for optimism that it can be done. This is because it is increasingly possible to break the overall problem down into component parts, which individually, are capable of solution. Thus, it should prove possible to define both the basis of genetic susceptibility and the antigen-receptor interaction at a molecular level. These laboratory studies should, however, be complemented by clinical and epidemiological studies designed to identify the disease in its earliest stages and pinpoint environmental influences on its genesis. The process requires an interdisciplinary collaborative approach in which the work of the bench scientist can be provoked, tested, and validated by rigorous sampling from clearly defined populations. The science is new, but standard methods of clinical evaluation still apply. New means of intervention should and must be pioneered by enthusiasts, but skeptics should play a leading role in their evaluation and, where appropriate, introduction into clinical practice.

Even if we have the good fortune to discover that one of the interventions currently under evaluation does delay the onset of diabetes, further studies will be needed to define its role in clinical practice. To take one example, many trials with many different combinations of agents were needed to develop the most effective therapy for childhood leukemia. Equally, international registries have proved invaluable in the continued evaluation of new forms of cancer therapy. As we move forward into what may prove a new era of diabetes treatment, we should not forget the old axiom that "those who fail to learn the lessons of history are condemned to repeat them."

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