Why Can't We Prevent Type 1 Diabetes?

Maybe it's time to try a different combination

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Type 1 diabetes is potentially preventable

Both the name and that notion emerged in the mid-1970s, when it became clear that this form of diabetes has an autoimmune basis. Studies in identical twins showed that two of three initially unaffected cotwins would remain nondiabetic, an experiment of nature implying that type 1 diabetes was a disease involving a dose of happenstance, not solely of genetic predestination. Knowledge that the immune system was involved raised therapeutic possibilities because immunity had been successfully manipulated to our own advantage (e.g., vaccines). Proof of principle for disease prevention emerged from rodent models of type 1 diabetes, and trials of immunosuppression with cyclosporin at disease onset showed that this could prolong β-cell function in humans, if only transiently. Join this to the discovery that islet autoantibodies appeared in the circulation many years before clinical onset and could be used to predict disease development and one has a condition for which screening and intervention are justified, if such an intervention could be identified (1,2).

The emerging therapeutic possibility has been matched to a growing need. The incidence of childhood diabetes continues to rise steadily, and the ever-increasing push toward more intensive management is limited by rising costs and the unremitting demand this form of therapy places on its recipients. It has been clearly demonstrated that improved clinical management can make an enormous difference, but there is at present little evidence to suggest that its impact extends much beyond well-motivated patients attending specialized centers. Meanwhile, the burden of long-term complications continues to rise, and it has been estimated that this increase will continue for at least 20 years after an effective means of prevention becomes available (3).

This combination of need, scientific rationale, and strong backing by public and private sources prompted the launch of three major diabetes prevention trials in the early to mid-1990s. All set out to determine whether progression to type 1 diabetes could be modified in high-risk individuals, in this case, islet autoantibody–positive relatives of an affected proband. Three different agents (nicotinamide, subcutaneous insulin, and oral insulin) and two huge study groups (the European Nicotinamide Diabetes Intervention Trial and the Diabetes Prevention Trial–Type 1), led to but one common result—failure to prevent type 1 diabetes (4,5).

What went wrong?

Success evaded us, it seems, because of both unrealistic expectations and failed assumptions. Failure can, however, be highly educational. The experience gained from these trials, when joined to other recent advances in knowledge (6), provides useful clues and recommendations for the future (Table 1).

The paradox that has emerged is that individuals at very high risk of progression, convenient though they are for trial design and power calculations, may not be the best people in whom to intervene, precisely because their risk is so high. The immune system is a formidable adversary, with an extensive range of weaponry at its disposal (7,8), and it is not easily diverted from its purpose once fully mobilized against any particular set of antigens. The markers that we use to identify risk do so because they represent collateral damage from an assault on the target tissue that is already entering its final stages. Prevention studies with nonobese diabetic mice confirm that it is much easier to intervene early in the disease process than at the stage of overt hyperglycemia (9,10). The literary analogy that springs to mind is that of the little Dutch boy who prevented a flood by putting his finger in a hole in the dyke and thus prevented it from enlarging (11). We may have been waving one finger ineffectually at a much larger breach in the defenses.

Other lines of argument support this inference. Clinical onset of type 1 diabetes is the outcome of a smoldering disease process typically ignited many years earlier, probably soon after birth. Therefore, early disease onset most likely reflects a particularly aggressive and already well-advanced variant of the condition. Clinical trials are largely based around recruitment of children, however, and these have a disproportionate effect on the outcome because most progressors fall into this category. Young though they are, they represent end-stage prediabetes. This line of reasoning suggests that we should shift our focus toward intervention much earlier in life. The problem here is that recruitment should logically be based on susceptibility (high-risk HLA combinations, family history, or both) rather than the far more potent markers of disease activation (islet autoantibodies) or progression (early signs of β-cell failure) that have been used so effectively later in the disease process. Trials in early infancy—when intervention is likely to prove most effective—will run into the practical limitations of low-

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Lessons learned from human trials and studies of animal models aimed at the prevention of type 1 diabetes*

Obstacle	Potential solution
Suboptimal effects of late treatment	Treat earlier in natural history of pre-diabetes
Treatment of children	Agents must have exceptional safety margin
Transient benefits for disease prevention	Compare pilot trials to define optimal agents; identify long-term effects of reducing complications
Treating kids who won't develop diabetes	Better and more accurate methods of prediction
Costs of subject identification (screening)	Improve case for benefits of disease prevention
Potential disease heterogeneity	Better definitions of type 1 disease that include genetic, immunologic, and metabolic markers
Poor understanding of immune mechanisms	Set priority on a better understanding of type 1 disease in humans; improve disease markers, especially those involving T-cells
NOD mice too easy to treat (prevention)	Establish higher standards and realistic applications; utilize additional animal models
Single agents not effective in disease prevention	Attempt combination therapy
Redundant immune cascades	Utilize combination therapy attacking multiple facets of immune response

screening efficiency, massive size with corresponding cost, safety considerations, and the longevity of investigators. At a more fundamental level, we need to inquire whether we truly understand enough about the interplay of genes, environment, and the developing immune system to be able to intervene intelligently and effectively in healthy infants. The honest answer to this has to be "no." In the absence of such understanding, it makes sense to limit our efforts to interventions that are unquestionably safe.

Proposal for the road ahead

Are we truly impaled upon the horns of a dilemma? Is there no middle road between the alternatives of intervening too early or too late? One practical option has been to sidestep this whole issue and focus intervention on the newly diagnosed patient. The rationale here is relatively simple: all newly diagnosed subjects have the disease, so there are no false positives. They are all on a path leading to near-total β-cell failure, so any preservation of β-cell function, even transient, could be beneficial. The knowledge that study entrants are already condemned to lose most of their residual β-cells adds a useful "comfort factor" to the equation when the theoretical possibility that some interventions might inadvertently accelerate β-cell destruction is under consideration. This approach, using endogenous insulin secretion as its end point, allows a number of interventions to be screened in parallel and within a relatively short time frame. The disease process may be too advanced for there to be much prospect of lasting clinical benefit, let alone a cure, but any hint of efficacy could provide a basis for future endeavors. What form should these take?

As we lack insight into the precise immune effector mechanisms, we believe it may be time to learn a lesson from successful therapeutic approaches used in other complex diseases (e.g., cancer, AIDS, and systemic lupus erythematosus). Combination or "cocktail" therapy for these disorders shows that multiple agents in combination are often markedly superior to the use of a single drug. Why should type 1 diabetes be any different? Combined immunosuppression has certainly demonstrated its value in the treatment of islet grafts, and it stands to reason that the reversal of autoimmunity requires a similar approach. Indeed, the experience of Bosi et al. (12) suggests that reactivation of autoimmunity following islet transplantation may be harder to treat than the alloimmune rejection process. Should potential therapeutic agents that are potentially efficacious and acceptably safe be used in combination to limit inflammation and β-cell destruction? These might include, but would not be limited to, nutritional interventions, antigen-based therapies, monoclonal antibodies, and other immunoregulatory and immunosuppressive agents. Single agents that show any promise of efficacy after disease onset—a "flick on the dial" may suffice—could be tested in successive cohorts of newly diagnosed patients in combination with other measures, and in this way, it may prove possible to painfully inch our way forward. This at least is how success was achieved in the examples of effective combination therapy cited above.

Need for optimistic realism

There is a Romanian joke that defines a pessimist as a well-informed optimist. The easy optimism of the early days of attempted diabetes prevention may have evaporated, but pessimism is not yet warranted (13,14). For one thing, and despite their negative outcomes, the large-scale prevention trials mentioned have shown beyond doubt that diabetes can be predicted and that interventions can be tested in the context of controlled trials. This in itself, to our thinking, represents one of the major success stories of diabetes research over the last decades. In addition, the trials have instilled a new sense of discipline and purpose into the diabetes research community, backed by proposed guidelines for further intervention trials (15), including outcome measurements, standardization, safety, efficacy, mechanistic studies, and statistics. Rumors of the death of diabetes prevention may have been exaggerated, but there are no easy victories in sight.

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