reasonable chance that definitive conclusions can be drawn. Such an approach should ensure that we gain the maximum benefit with minimum risk.

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Authors' Response

The editorial by Dr. Allan Drash has raised very important issues on immune intervention trials. We wish to comment on the time and type of interventions and the design of such studies.

We fully agree that interventions—whatever the agents used—have until now been started very late, after the patient has become dependent on insulin. However, studies in the NOD mouse model have clearly shown that even when started at the stage of overt diabetes, some types of immune intervention can restore normoglycemia and even induce immune tolerance (1,2). These results raise the question of whether β-cell destruction is actually as far advanced at the onset of clinical diabetes as it is usually considered to be. They also suggest that provided efficient and well-tolerated agents are available, intervention at the stage of recent-onset diabetes may still deserve consideration. The question is not simply one of the time of intervention but also of the type and mechanism of action of the agent used.

It must be pointed out that at the time when our study was initiated, cyclosporin A was the only agent with a consistent efficacy in randomized placebo-controlled trials. In patients with insulin dependency, cyclosporin A did preserve partial insulin secretion for up to 4 years. The long-term benefit of this effect remains to be determined (3). Nephrotoxicity is one concern raised by the use of cyclosporin A, but its occurrence can be minimized by careful monitoring (4). Long-term follow-up (10 years) has shown that no clinical toxicity was detected in the treated patients (5; R.A., unpublished observation).

Another important issue is the design of intervention/prevention studies. We certainly agree that only carefully designed randomized studies involving sufficient numbers of subjects will draw reliable information. At best, these studies should also be placebo-controlled. However, it seems very reasonable to assess the feasibility and the potential efficacy of new interventions in pilot studies before engaging hundreds of subjects in demanding trials that will last several years. This is exactly what has been done with the two agents, nicotinamide and insulin, that are currently tested in prediabetes (6,7). In the same respect, documenting efficacy, even partial, in patients with overt diabetes can be a preliminary step before intervening in prediabetic subjects.

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