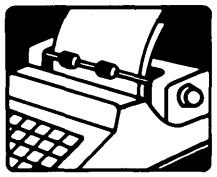
Editorial



Immunotherapy of Type I Diabetes

A recent NIH panel in which I participated unanimously agreed that wide clinical application of immunotherapy for type I diabetes is at present inappropriate. The risks of premature application of such therapy outweigh potential benefits. In this editorial, I will briefly review the current information upon which I and my colleagues have begun small research trials of immunotherapy which I believe are essential for the eventual development of therapy to prevent type I diabetes.

An issue in considerations of immunotherapy in man is whether an *acute* viral-induced diabetes occurs which immunotherapy may worsen. The existence of acute viral-induced diabetes is a controversial area despite years of research. I suspect that if acute virally induced diabetes occurs, it is extremely rare, and even the best documented case of Dr. Notkins and co-workers appears not to have been acute.[1] Dr. Gepts, studying sections of the pancreas of the child from which the virus was isolated, reported finding signs of chronic beta-cell damage (the pancreas contained multiple "pseudoatrophic" islets with no inflammation and only non-beta islet cells remaining).[2] Despite little evidence of an acute viral etiology for diabetes, viruses and perhaps other environmental factors may play a major role in initiating an autoimmune process in a genetically susceptible host. A very high percentage of DR3/DR4 positive children with congenital rubella in later life develop diabetes.[3]

If type I diabetes is not an acute viral illness, is it an autoimmune disease? [By an autoimmune disease I refer to tissue destruction, which is created by lymphocytes (T- or B-cells) reacting with self antigens.] The autoimmune hypothesis has been reviewed many times and though current data are convincing, it should be emphasized that the hypothesis that type I diabetes of humans is an autoimmune disease is not proven. In contrast, the diabetes of the BB rat is a proven genetically determined autoimmune disease with no defined viral or environmental etiologic factors.[4] More than seven forms of immunotherapy can prevent these animals from developing diabetes and one form (anti-lymphocyte serum) can "cure" one-third of these animals.[5,6] Though the BB rat is an important animal model of type I diabetes, these animals are fundamentally different from patients with type I diabetes in that they inherit a profound T-cell immunodeficiency that is necessary but not sufficient for the development of diabetes.[7] These animals are equivalent to a child with severe immunodeficiency (e.g., adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency) plus diabetes. Several of the successful immunotherapies in the BB rat involve transfer of normal lymphocytes (e.g., transfusions) where the transferred lymphocytes can grow in the immunodeficient BB rat creating a chimeric state. Lymphocyte transfer therapies, except in monozygotic twins, are unlikely to have a direct counterpart in the therapy of diabetes of man where there is no overwhelming immunodeficiency.

The hypothesis that type I diabetes is an autoimmune disease in man is changing to a hypothesis that in the great majority of patients it is a slow autoimmune disease with years of chronic beta-cell loss before overt hyperglycemia. Pioneering studies from Great Britain by Dr. Irvine and co-workers[8] and the late Dr. Cudworth and co-workers[9] demonstrated that islet cell antibodies precede insulin dependence or overt diabetes. In addition to islet cell antibodies an abnormal increase in T-cells bearing the Ia antigen also precedes diabetes.[10] Temporally correlated with immunologic abnormalities, there is a slow regular loss of first-phase insulin release stimulated by intravenous glucose.[11,12] This progressive loss of insulin release occurs over years. Several months before overt diabetes there is essentially no insulin release to intravenous glucose, though response to intravenous glucagon is relatively preserved.[13] At the onset of hyperglycemia studies of pancreatic tissue suggest that more than 90% of beta-cells have been destroyed. The chronicity of the development of type I diabetes is also reflected by epidemiologic studies indicating that as many first-degree relatives of patients with type I diabetes become overtly diabetic between the ages of 18 and 40 as in childhood.[14,15] The frequent occurrence of type I diabetes in adults and a long prediabetic period with immunologic abnormalities and progressive beta-

cell dysfunction have obvious implications in considerations of immunotherapy.

Appropriate hesitation concerning immunotherapy of type I diabetes relates less to questions as to whether it is an autoimmune disease as to the serious toxicities of standard drugs used in the therapy of life-threatening autoimmune illness and transplant rejection. In particular, depending on dosage, daily prednisone therapy may create Cushing's syndrome with growth retardation, insulin resistance, opportunistic infections, osteoporosis, etc. Cyclosporine A is associated with hirsutism, gingival hypertrophy, a fall in hemoglobin, hepato- and nephro-toxicity, and lymphoma (depending on dosage and combination with other immunosuppressive drugs). Anti-thymocyte globulin (anti-T-cell antibodies made in animals) is associated with anaphylaxis, fever, rash, and severe transient thrombocytopenia. The specific monoclonal anti-T-cell antibody T12, which we employ in place of antithymocyte globulin, greatly reduces acute reactions but still has the potential for anaphylaxis and is associated with a mild transient rash. Azathioprine and cytoxan are associated with marrow suppression, opportunistic infections, hemorrhagic cystitis, lymphoma, and other malignancies. Plasmapheresis is associated with thrombosis and hepatitis. In my view, none of the above therapies used in pilot trials of recent onset type I diabetes has produced a good enough, long enough benefit to justify clinical application in a non-research setting. Results of several pilot studies suggest that after the onset of overt diabetes, prednisone and plasmapheresis are clinically ineffective, and none of the other agents restores individuals to true normality (completely normal oral glucose tolerance and return of first-phase insulin release after intravenous glucose) though "euglycemia" (? duration) with normal HbA_{1c} is possible. An obvious consideration is to attempt some form of immunotherapy before overt diabetes. This is predicated on the ability to predict the development of diabetes. A combination of immunologic abnormalities and loss of first-phase insulin release may allow such prediction but current measurements of islet cell antibodies are not standardized as a recent exchange of letters in *Lancet* illustrates.

Given our lack of understanding of the immune phenomenon of type I diabetes, should we wait for more information before research trials? I suspect that the immune phenomenon surrounding type I diabetes is "understood" as well as any autoimmune disease. This statement reflects generalized ignorance rather than adequate understanding of the other autoimmune diseases. Despite such ignorance, there exists for many of these autoimmune diseases, pallative therapy, and for a few illnesses truly effective therapy. An important factor in consideration of immunotherapy trials is the seriousness of type I diabetes, which does not appear to have changed dramatically.[16] Published data of Deckert and colleagues as well as the most recent verbal update of the Danish experience by Dr. Nerup indicate a 50% 30-yr mortality. In a socially heterogeneous population studied by Drash and colleagues,[17] there was a 5% acute "metabolic" mortality. In addition to such mortality figures, the morbidity from nephropathy, retinopathy, and renopathy is distressing. It is the frustration of watching complications develop in young adults which has led to consideration of new modes of therapy such as the current NIH trial of intensive insulin therapy with its own complications and ethical questions and to considerations of immunotherapy.

Are clinical trials of immunotherapy at this time ethical? It is my view that some trials will be ethical and others not. All immunotherapy is not the same in terms of toxicity and potential efficacy, nor are all patients the same, ranging from small children who cannot themselves be "informed" to a patient who is a specialist in internal medicine. Perhaps not surprisingly a high percentage of the patients in our own pilot studies are medical professionals. Institutional review boards have been established to weigh such ethical issues and should be biased against approval of trials that are not novel and in which investigators lack immunologic and endocrinologic expertise and familiarity with the therapy proposed. In addition, the central task of such committees is to assess the cost/benefit ratio to the individual participants and the adequacy of informed consent.

In conclusion, it is my opinion that immunotherapy of type I diabetes in the absence of an approved research protocol with institutional review board oversight is not appropriate. Each research protocol needs to be judged on its own merits and at present none of the pilot studies have produced good enough results to warrant large multicenter evaluation. Immunologic and endocrinologic expertise is essential to such trials, as well as a physician investigator keeping the welfare of his patients foremost. As a clincial investigator in this area, I am extremely encouraged by the developments of the past decade and the field is developing rapidly with a number of encouraging pilot studies. I suspect that in a general way we know what must be accomplished to prevent type I diabetes or maintain a "honeymoon" period, but we certainly do not know whether the means are available. There is a dire need for the development of better immunotherapeutic agents, for better understanding of autoimmunity in general and of type I diabetes in particular, and for reliable quantitative assays to replace current crude assays of anti-islet antibodies. We may be fortunate in finding that some current, relatively benign therapy, which alters immune function, will slow "enough" the slow loss of beta-cells. We obviously cannot count on such good fortune, and accumulation of basic knowledge to allow immunoregulation rather than immunosuppression is an important goal.

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