Incorporating Type 1 Diabetes Prevention Into Clinical Practice

Justin M. Gregory, MD, Jessica S. Lilley, MD, Amanda A. Misfeldt, PhD, Daniela L. Buscariollo, BS, William E. Russell, MD, and Daniel J. Moore, MD, PhD

Type 1 diabetes is estimated to affect between 1.2 and 2.4 million individuals in America. For most patients, the disease will present in childhood. Although the rising epidemic of type 2 diabetes in children has garnered significant attention in recent years, type 1 diabetes remains the predominant diagnosis seen by pediatricians and pediatric endocrinologists. Although the incidence of type 1 diabetes is also increasing. Two large, multinational studies analyzing incidence trends of type 1 diabetes during nearly four decades found 2.8 and 3.0% annual increases globally.

Surprisingly, the incidence of type 1 diabetes is also increasing. Two large, multinational studies analyzing incidence trends of type 1 diabetes during nearly four decades found 2.8 and 3.0% annual increases globally. Although the reasons for this increased incidence are unknown, it highlights the need for efforts to prevent and cure type 1 diabetes. Currently, numerous research efforts worldwide are engaged in this endeavor, including the clinical trials networks Type 1 Diabetes TrialNet (TrialNet; www.diabetesclinical.org) and the Immune Tolerance Network (www.immunetolerance.org). In this article, we will review what is known about the pathogenesis of type 1 diabetes, present a summary of prevention efforts, and examine how primary care providers can participate in and facilitate research to prevent type 1 diabetes.

Pathogenesis of Type 1 Diabetes
To understand the multiple approaches to the prevention of type 1 diabetes, it is valuable to begin with an overview of diabetes pathogenesis. Type 1 diabetes is first and foremost an autoimmune disease. It is frequently found in families with a high prevalence of other autoimmune diseases, and individuals with type 1 diabetes are at higher risk to develop other autoimmune disorders over their lifetime (Table 1). A predisposition for diabetes begins at birth because of the inheritance of genetic risk factors, many of which remain unknown. Although most new-onset patients will have no clear family history of type 1 diabetes, those currently unaffected children with a parent, sibling, or other relative with diabetes are at increased risk compared to the general population (Table 2). The translation of these genetic factors into disease requires additional events, however, a feature best evidenced by the fact that monozygotic twins are not uniformly concordant for disease development.

It has been proposed that environmental factors play a substantial role in the development of type 1 diabetes in those genetically at risk. Although no single trigger of diabetes onset has been identified, a number of candidates have emerged from epidemiological studies. The most well known among these are viral infections such as Coxsackie virus, influenza B, herpes simplex, and human herpes 6 virus and dietary factors such as exposure to cow’s milk. In a study of 28 children aged 3–14 years with recently diagnosed type 1 diabetes, 39% had a Coxsackie B virus–specific IgM response compared to 5.5% of age-matched control children.

These triggers may contribute directly to immune activation by inciting cross-reactivity against islet proteins bearing a similar structure or nonspecifically by inciting the production of pro-inflammatory cytokines that injure islet tissue. Identifying these environmental factors and understanding their effects is part of the ongoing Environmental
Determinants of Diabetes in the Young study (http://teddy.epi.usf.edu).

Although the process that leads to the activation of islet-reactive lymphocytes is not known, T-lymphocytes mediate islet tissue injury. At the earliest stages, islet injury is not readily detectable by any simple clinical monitoring and thus goes undetected by parents and practitioners. As islet destruction progresses, the loss of β-cells is evidenced by a decrease in the insulin response to a meal challenge even before the onset of frank hyperglycemia. This change in insulin secretory dynamics is a strong predictive factor for the future appearance of disease and indicates significant islet injury.

Eventually, the process progresses to a stage where the plasma glucose becomes persistently elevated, and the clinical features of diabetes emerge. Diabetes is defined by a fasting plasma glucose exceeding 126 mg/dl or a postprandial plasma glucose exceeding 200 mg/dl on two separate occasions.

Prediction of Type 1 Diabetes

Thus, diabetes progresses from genetic risk to immune activation to β-cell injury to impaired insulin secretion to glucose intolerance and, finally, to frank disease. Although practitioners are most familiar in the clinical setting with the latter stages of the disease pathogenesis, identifying individuals at risk for type 1 diabetes before substantial islet injury is our best chance for diabetes prevention. At the time of clinical presentation of diabetes, these individuals will usually have diminished islet cell mass in addition to abnormal immune activation. Both of these processes must be addressed to reverse new-onset disease. If diabetes can be predicted earlier, it may be possible to prevent disease progression while an adequate islet mass remains to maintain euglycemia throughout a patient’s lifetime. Studies suggest that individuals must lose 50–90% of their islet mass before onset of hyperglycemia.

Substantial efforts have been directed to develop models that predict when susceptible individuals will develop diabetes. At present, the most highly predictive model results from identifying people with autoantibodies and abnormal insulin secretion and glucose intolerance who do not yet meet the criteria for diabetes diagnosis; these individuals have a > 50% 5-year risk for diabetes progression, and it is likely that nearly 100% of them will eventually develop the disease. Identification at this stage is relatively late, and it is not clear whether preventing diabetes in these patients will be any more achievable than reversing diabetes in patients who have been recently diagnosed.

Although the biochemical criterion of abnormal glucose tolerance is highly predictive, its clinical utility for diabetes prevention is limited because of the substantial islet injury that precedes this finding. Thus, predictive models that measure abnormalities more remote from diabetes diagnosis are sought. The most widely applied model at present involves the detection of β-cell–directed autoantibodies in the blood. These autoantibodies are markers of autoimmunity and are not themselves directly destructive to islets. These markers include antibodies against the insulin molecule, glutamic acid decarboxylase (GAD), zinc-transporter-8, and insulinoma antigen 2 (IA2). In addition, the histochemical islet cell antibody test (ICA) detects any immunoglobulin directed at intact human islets but does not identify the specific antigen(s). Antibodies against whole islets and insulin are specific to pancreatic β-cells, whereas IA2 and GAD are also present in brain, pituitary, and other areas in the pancreas.

<table>
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Table 2: Risk of Progression to Type 1 Diabetes for Family Members of Probands With Type 1 Diabetes in Selected Studies
Prevention Trial-1 (DPT-1) showed that the number of autoantibodies correlates with eventual development of type 1 diabetes. Higher titers of ICA correspond to a higher 5- to 10-year risk of developing type 1 diabetes according to multiple studies. The DiMe Study Group in Finland measured antibodies in a large cohort of children newly diagnosed with type 1 diabetes who were < 15 years of age. Nearly 75% of children were GAD-positive at diagnosis; just over half had anti-insulin antibodies. IA2 was the most common and was found in 85.7% of newly diagnosed children, and most children (72.6%) tested positive for more than one antibody at diagnosis. The authors also observed an inverse relationship between age at onset and number of positive autoantibodies; younger children present with a higher number of positive antibodies than older children.

Another large, ongoing study, Diabetes Autoimmunity Study in the Young (DAISY: www.uchsc.edu/misc/diabetes/Teddy/DAISY/DAISY_home.htm) was an observational study that compared children who have first-degree relatives with type 1 diabetes and children without affected family members but who expressed high-risk HLA haplotypes, with a focus on the implications of known autoantibodies. Of the children in this study who progressed to type 1 diabetes, all were positive for at least one autoantibody, although not all positive progressed to overt diabetes, and some patients were transiently positive. Because some antibody-positive children in the DAISY trial did not develop diabetes, hope remains that the factors responsible for disease progression will be elucidated or protective factors will be identified.

The Finnish Type 1 Diabetes Prediction and Prevention study (DIPP) is evaluating the general population to describe the natural history of preclinical type 1 diabetes while determining the predictive values of risk markers including specific genes and antibodies. Almost half of antibody-positive children in both the DIPP and the DAISY studies have since tested antibody-negative. The German BABYDIAB study examined newborns of patients with type 1 diabetes to better characterize early detectable predictive factors. Although antibodies were found in infancy, determining whether these were acquired via placental transmission is important because they are all of the IgG subclass; one study following serial antibody measurements showed that most maternal antibodies associated with increased risk for diabetes are cleared from the infant’s circulation by 12 months of age.

Considering the risk of maternally acquired positives in the first year of life and in light of the rarity of presentation of clinical disease in infancy, Hämmäläinen et al. proposed targeting general population screens to the 18- to 24-month age-group. Considering that > 90% of individuals testing positive for more than two anti-islet antibodies progressed to type 1 diabetes in one long-term study of first-degree relatives of people with the disease, testing for autoantibody positivity is clearly important in targeting individuals for prevention.

However, anti-islet antibodies are not the sole predictor of type 1 diabetes risk, especially given that some patients are antibody negative at diagnosis. Although some of these antibody-negative patients may have nonautoimmune forms of diabetes, such as defects in pancreatic development or insulin secretion (so-called monogenic diabetes or mature onset of diabetes in youth, some still likely have classic type 1 diabetes as evidenced by the presence of other factors such as characteristic diabetes risk genes.

Understanding the genetic risk for diabetes ultimately may be even more valuable than antibody screening because at-risk genes could be identified long before the production of even the first autoantibody. The most significant genetic linkage to type 1 diabetes is the human leukocyte antigen (HLA) group, the family of genes that controls antigen presentation within the immune system. Antigen presentation is a critical aspect of T-lymphocyte activation. At-risk HLA genes may allow abnormal presentation of islet proteins and survival and expansion of islet-reactive T-cells and thus compromise regulatory lymphocyte function. In fact, half of the heritable risk can be traced to HLA haplotypes, with HLA-DR and -DQ carrying the highest risk for autoimmune changes leading to type 1 diabetes.

Combining knowledge of high-risk HLA haplotypes with antibody testing allows practitioners to more specifically classify patients at highest risk of diabetes. The HLA-DR3/4-DQ8 genotype when combined with positive autoantibodies has been highly successful in predicting progression to clinical diabetes. In the BABYDIAB study, certain HLA genes were highly predictive of autoantibody positivity and thus anti-islet autoimmunity. In addition, many polymorphisms of these genes exist, and some have been shown to protect against the disease.

Nonetheless, not all individuals who have anti-islet autoimmunity or who eventually develop diabetes have the at-risk haplotype. Thus, the risk conferred by these genes may be modified by other loci, and a number of other important genetic regions have been identified.
important non-HLA genes include insulin, polymorphic cytotoxic T-lymphocyte–associated antigen, and protein tyrosine phosphatase nonreceptor type 22. By altering insulin transcription and T-cell activation, these genes contribute to persistent islet autoimmunity as well as affect deterioration to clinical diabetes.

**Interventions to Prevent Type 1 Diabetes**

To date, no intervention has been developed that can unequivocally prevent the development of type 1 diabetes or arrest the progression of immune system destruction of β-cells after diagnosis, although some promising studies have given the field much encouragement. The potential benefits of such interventions are clear: preservation of islet mass, even when it is insufficient to maintain normal glucose homeostasis, results in a clinical scenario in which diabetes is much easier to regulate in terms of glucose excursions and is accompanied by fewer episodes of potentially dangerous hypoglycemia. Obviously, earlier intervention, before the autoimmune process has begun or early enough to prevent significant islet loss, holds the promise of true diabetes prevention.

Although prediction of type 1 diabetes remains complex and actively investigated, models using antibody screening are currently used to drive diabetes prevention trials. In addition, several trials have reported modest utility in diabetes reversal. Although strategies that prevent diabetes may not be potent enough to reverse disease, it is likely that therapies that achieve diabetes reversal may be useful in diabetes prevention. As mentioned above, the goals for diabetes prevention depend in part on when during the pathogenesis of disease the intervention is applied. In the late stages of diabetes progression (or with reversal), several goals must be achieved including deactivation of islet-reactive lymphocytes, correction of the inflammatory milieu that injures islets and promotes lymphocyte activation, and restoration of an adequate islet mass. In earlier stages of diabetes prevention, it remains possible that these interventions may be effective even if applied singly. The following sections consider the current state of each of these strategies based on completed and ongoing trials and proposals.

**Antigen-specific interventions**

In efforts to prevent type 1 diabetes, it is highly desirable to either correct the abnormal function of or eliminate those lymphocytes that have targeted the β-cells. It is well established that insulin itself is a primary target of the immune response, and modulation of anti-insulin reactivity may be beneficial. In animal models, both parenteral and oral insulin delayed or prevented disease onset, by acting either metabolically by allowing the β-cells to rest, or immunologically by inducing tolerance or reducing T-cell infiltration into the pancreatic islets.

DPT-1 examined the effects of antigen-based therapy with insulin in first-degree relatives at risk of type 1 diabetes. Two studies sought to determine whether exposure to insulin in ways thought to induce tolerance (oral administration or very-low-dose injection) could delay or prevent the onset of type 1 diabetes in these individuals. In the first study, relatives projected to have a 5-year risk of > 50% for progression to type 1 diabetes were given low-dose parenteral insulin, and in the second study, relatives with a 25–50% risk were given oral insulin therapy. The oral insulin is metabolically inactive because of degradation in the stomach, but these degraded peptide products were hypothesized to possess immune-regulating potential.

Unfortunately, neither intervention groups showed a significant delay in type 1 diabetes progression compared to placebo. However, oral insulin was retrospectively observed to delay progression to type 1 diabetes in the subgroup of participants with the highest anti-insulin antibody levels. These findings inspired the Type 1 Diabetes TrialNet Oral Insulin Study, analyzing the preventive or delaying effect of oral insulin in individuals with similar characteristics. This trial is presently enrolling subjects. Other antigen-specific interventions currently in development include the use of a GAD vaccine and the isolation and expansion of regulatory T-cells that are able to suppress islet-reactive lymphocytes in an antigen-specific manner.

**Antigen nonspecific interventions**

While some studies have looked at modulating the autoimmune response specific to the β-cells, others seek to alter the body’s immune response in general. Although antigen-specific therapies are desirable because they should affect only those immune cells that have targeted the β-cells, we do not presently know the full range of β-cell autoantigens. Thus, more globally directed, nonspecific therapies may have a better chance to reach all islet-injurious lymphocytes.

Many components of the immune system have been implicated in autoimmunity leading to type 1 diabetes, including cytotoxic and helper T-cells, B-cells, macrophages, and dendritic cells. In fact, global defects have been characterized in all these cell types in both type 1 diabetes–prone mice and people with diabetes. To date, nonspecific interventions directed against the T-lymphocyte have been the most widely used
because T-cells are the known end-stage effectors of islet destruction. T-cells express CD3 along with CD4 or CD8, so targeting either receptor could in theory modulate T-cell response and therefore alter autoimmunity. Targeting of the CD3 receptor with monoclonal antibodies has been tested on newly diagnosed patients with type 1 diabetes and showed improved insulin production 2 years after diagnosis but did not successfully lead to remission of the disease.

Other constituents of the immune system are also emerging as foci for intervention. Although T-lymphocytes are most closely linked with the immunopathogenesis of type 1 diabetes, B-lymphocytes also play a central role in type 1 diabetes and other autoimmune diseases and depleting B-cells can prevent and reverse diabetes in mouse models. Rituximab, an anti-CD20 chimeric antibody that depletes B-lymphocytes, has shown encouraging initial clinical results. A recent TrialNet-funded study demonstrated that a four-dose course of rituximab could preserve β-cell function over a 1-year period in patients with newly diagnosed type 1 diabetes. In addition, systemic anti-inflammatory agents such as IL-1 receptor antagonists and agents that stimulate β-cell proliferation are being studied as potential components of a multidrug prevention of β-cell destruction.

**β-cell preservation and regeneration**

Although it is crucial to prevent or halt β-cell destruction, diabetes prevention and therapy also necessitates ensuring adequate β-cell number and function. Ideally, immunomodulation will protect against β-cell decline, but this strategy will require both early detection of at-risk individuals and highly effective interventions. Successful preventive and therapeutic regimens will ultimately depend on β-cell replacement, which is currently provided by a limited number of allogeneic islet transplants.

To make this therapy feasible for more patients, additional supplies of β-cells will be required. Potential sources include existing β-cells, progenitor cells, and stem cells. Potential sources include existing β-cells, progenitor cells, and stem cells. Directed differentiation of embryonic stem (ES) and induced pluripotent stem (iPS) cells offers promise as an alternative supply of β-cells. Evidence of continued production of new β-cells in patients with type 1 diabetes is encouraging, but further work is needed to confirm its clinical efficacy.

Although high rates of β-cell differentiation and proliferation occur during embryogenesis and early development, proliferation slows later in life, and little, if any, differentiation occurs. Accordingly, the β-cell population does not readily replete itself when under immunological attack, although there is evidence of continued production of new β-cells in patients with type 1 diabetes. Furthermore, β-cell proliferation can be stimulated in vivo and in vitro. However, because β-cells are highly differentiated, their proliferative potential is inherently limited. Thus, there is much interest in identifying and isolating progenitor cells that can be stimulated to proliferate and subsequently differentiate into β-cells.

Additionally, because stem cells can proliferate indefinitely and differentiate into any cell type, much work is being performed to direct their differentiation down the normal β-cell developmental pathways. However, stem cells have yet to be used in clinical trials, so their efficacy and potential risks, particularly of tumorigenicity, are...
unknown. It is also unclear whether exogenously derived \( \beta \)-cells will be more or less susceptible to immunological attack and whether this susceptibility can be manipulated genetically or during the differentiation protocol. Nonetheless, developing an adequate and clinically potent \( \beta \)-cell resource is likely to be a key component of any strategy to prevent or cure type 1 diabetes.

**Role of Primary Providers in Diabetes Prevention**

Although there are exciting opportunities in diabetes prevention and reversal, most of these efforts are unfolding at large academic or research-focused medical centers. Nonetheless, there is a vital role for practitioners who work with families at risk for developing type 1 diabetes.

In families with established type 1 diabetes, all first-degree relatives, including the parents of the proband (if they are < 45 years of age) are at increased risk for type 1 diabetes and should be counseled regarding this risk. Identical twins are the greatest risk. Second- and third-degree relatives of a proband with type 1 diabetes are also at heightened risk if they are < 21 years of age.

Once apprised of their diabetes risk, these individuals should be made aware of type 1 diabetes screening and intervention studies such as Type 1 Diabetes TrialNet. The advantages of screening for type 1 diabetes risk through such research-oriented programs include state-of-the-art antibody determinations in specialized research laboratories, a superb follow-up and support network of type 1 diabetes specialists, protection of laboratory data from insurance carriers, and the opportunity to participate in further clinical research studies aimed at diabetes prevention. Participating in a research study incurs no cost to patients or their insurance companies.

Far better than tertiary diabetes centers, primary care provider offices are able to reach the unaffected relatives of index patients with type 1 diabetes. Unaffected individuals may visit their family practitioner for routine health maintenance and express that they are aware of a new diagnosis in their family; these same individuals are unlikely to ever encounter a subspecialty provider unless they are diagnosed with type 1 diabetes. Thus, there is great opportunity for primary care physicians to engage in conversations about such patients’ potential risk for developing type 1 diabetes and the possibility of enrolling in monitoring or prevention trials. If the primary care community outside of the research setting is aware of such opportunities to promote awareness about diabetes trials, we will have the chance to move ever more quickly toward preventing and reversing type 1 diabetes.

Although we have been successful in recruitment for diabetes prevention trials at the Monroe Carell, Jr. Children’s Hospital at Vanderbilt, we anticipate that there are many patients whom we are unable to reach or who are unwilling to participate. To address this concern, we recently undertook a survey to better understand parental attitudes toward clinical trials for type 1 diabetes. As part of this study, we determined that parents’ willingness to enroll their child in a study was most strongly influenced by whether they had received clear information about trials from their primary pediatric endocrine provider (D. Buscariollo, W. Russell, D. Moore, unpublished observations). By extension, it is likely that there is a very important role for all practitioners in promoting awareness and confidence in families that will ensure the success of these ongoing efforts.

In addition to informing families about the opportunities for diabetes prevention trials, it is reasonable to wonder whether primary care providers can make recommendations that may limit future diabetes risk. Although many current trials are developing pharmacological approaches to type 1 diabetes prevention, some trials are investigating approaches that can be utilized routinely and safely in practice.

For example, there has been growing interest in the potential role of early feeding patterns in the development of diabetes. This interest is founded on a body of evidence suggesting a protective effect of breastfeeding for children at risk for type 1 diabetes. In 1984, Borch-Johnson et al.\(^{63}\) first reported an inverse correlation between the duration of breastfeeding and diabetes risk in humans. Since then, there has been a long debate in the literature about the possible beneficial effects of breastfeeding for children at risk for type 1 diabetes.

Part of the challenge has been isolating the effects of breastfeeding from other potentially contributing factors (e.g., delayed exposure to exogenous stimuli such as cow’s milk proteins). Nevertheless, both prolonged breastfeeding and delayed exposure to cow’s milk proteins have been associated with protection against the development of type 1 diabetes.\(^{64,65}\) Putative mechanisms of protection include passive immunity provided by secreted immunoglobulin A antibodies against infectious agents that may contribute to the autoimmunity trigger\(^{66}\) and delayed exposure to diabetogenic agents such as cow’s milk proteins, which may be involved in the pathogenesis of...
type 1 diabetes among those with a dysfunctional gut immune system.67

The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) is the first primary prevention effort to explore whether avoidance of exposure to cow’s milk can prevent type 1 diabetes in infants with a genetic predisposition.68 Although this ongoing trial is limited to genetically high-risk infants, it is reasonable to recommend breastfeeding to families in which there is risk for type 1 diabetes. Current recommendations include exclusive breastfeeding for the first 6 months of life for those without contraindications.69 Whether specific alternate formulas would be of benefit is the subject of ongoing trials. As their tolerability is low and expense high, we would not recommend these at the present time.

Another protective intervention of ongoing interest is early vitamin D supplementation. The exact mechanism by which vitamin D may protect against type 1 diabetes remains unclear, but this effect is likely to be through the prevention of vitamin D deficiency.70 Vitamin D is a potent modulator of the immune system and is involved in regulating cell proliferation and differentiation.71 A meta-analysis of data from five observational studies recently indicated that children supplemented with vitamin D had a 29% reduction in type 1 diabetes risk compared to their unsupplemented peers.72 Nevertheless, firm conclusions that can be drawn from these data in terms of appropriate recommendations are limited by the lack of specification of dosage, duration, and particular vitamin D preparations. Thus, data from adequately powered, randomized, controlled trials are still needed.

Although current trials are generally considering pharmacological dosing of vitamin D, it is reasonable to ensure that individuals at risk for autoimmune disease maintain their vitamin D stores in the normal range if they are not able to participate directly in these trials. It is currently recommended that all infants should receive 400 IU of vitamin D supplementation until the infant is ingesting at least 400 IU of vitamin D daily through formula, milk, or other food sources. In addition, it is recommended that an intake of 400 IU of vitamin D per day be continued throughout childhood and adolescence for those who do not ingest that amount per day or for those who do not receive adequate sunlight exposure.73,74

Conclusion

Type 1 diabetes is a clearly heritable disease with multiple genetic and environmental risk factors. No treatment has been devised to date that will successfully prevent the development of type 1 diabetes. However, sentinel laboratory abnormalities have been identified that provide multiple targets for preventive interventions. Nonetheless, successful intervention efforts demand a thorough understanding of disease pathogenesis and a refined approach to disease prediction so that risks and benefits can be well balanced.

The inception of global-scale networks for diabetes trials such as the Type 1 Diabetes TrialNet has presented unprecedented opportunity to alter the course of type 1 diabetes. These trials simultaneously aim toward several clinical endpoints including better identification of at-risk individuals, better prediction of disease progression, and successful implementation of protocols for diabetes prevention and reversal. The success of these efforts is strongly dependent on enrollment, and many eligible patients are not aware that they are at risk for type 1 diabetes or may benefit from these opportunities.

Our discussions with patients suggest that physicians remain the most trusted and important source of this information. Given that, there is a vital role for practitioners in all settings in current efforts to prevent and reverse type 1 diabetes.

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Justin M. Gregory, MD, is a resident physician in the Department of Pediatrics at the University of Tennessee School of Medicine in Memphis. Jessica S. Lilley, MD, is a resident physician at Children’s Hospital of Philadelphia in Pennsylvania. Amanda A. Misfeldt, PhD, is a student in the medical scientist training program, and Daniela L. Buscariollo, BS, is a medical student at Vanderbilt University School of Medicine in Nashville, Tenn. William E. Russell, MD, is a professor in the Departments of Pediatrics and Cell and Developmental Biology and a member of the Vanderbilt Diabetes Center at Vanderbilt University School of Medicine. Daniel J. Moore, MD, PhD, is the senior fellow in endocrinology and diabetes in the Departments of Pediatrics and Microbiology and Immunology at Vanderbilt University School of Medicine.