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Infant Formula, Autoimmune Triggers, and Type 1 Diabetes

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Families are devastated when a child receives a diagnosis of type 1 diabetes. Although tremendous strides in insulin-based treatments — made feasible by technical advances such as continuous glucose monitors, modern “designer” insulin formulations, and novel insulin-delivery devices — have contributed to remarkable improvements in the prognosis of the disease, the proper management of type 1 diabetes is expensive and time-consuming. In addition, not all families and patients marshal the diligence and skills required to control glycemia with sufficient rigor to prevent complications. Moreover, the benefits of tight control of diabetes must be balanced with the detrimental consequences of hypoglycemia, particularly in young children. Thus, one of modern medicine’s “holy grails” since insulin was first used as a therapy in 1922 has been that an understanding of the pathogenic mechanisms underlying type 1 diabetes would lead to a cure or prevention.

For more than 30 years, the center stage of the story of the pathogenesis of type 1 diabetes has been occupied by compelling data on T-cell-mediated autoimmunity. For instance, recent genomewide association studies have identified unambiguous genetic linkages associated with an increased risk for type 1 diabetes, and nearly all identified genes have known roles in cellular immunity.¹⁻³ In addition, clinical trials have

shown that interventions aimed at modifying the cellular immune response (e.g., cyclosporine, antithymocyte globulin, and anti-CD3) can delay the inexorable decline in beta-cell function that follows the onset of the disease. Although anti-beta-cell-specific autoantibodies are predictive of an increased risk for type 1 diabetes, those antibodies themselves are not considered to be pathogenic. Currently, there is no consensus regarding the factors that initiate the autoimmune response.

Although genetics is a strong determinant of risk, concordance for type 1 diabetes is only about 50% among identical twins.⁴ The increasing incidence of type 1 diabetes, particularly among younger persons and persons not traditionally considered to be at the highest risk, fuels efforts to identify environmental autoimmune triggers. Leading most lists are diet and microorganisms (in particular, viruses). Indeed, diet and microbiota may be intimately intertwined. For instance, transmission of maternal antibodies to the newborn through breast-feeding has long been known to decrease the infant’s susceptibility to certain infections, and early introduction of enteral feedings in premature infants is known to alter their susceptibility to disease.

In this issue of the *Journal*, Knip and colleagues report the results of a study⁵ that may shed some light on dietary triggers and type 1

diabetes. They conducted the study in Finland, where the prevalence of type 1 diabetes is among the highest in the world and continues to increase. In 2005, there were 64.2 cases of newly diagnosed type 1 diabetes per 100,000 Finnish children younger than 15 years of age.⁶ Moreover, the Finnish national health care system efficiently tracks each resident, facilitating the ascertainment of long-range clinical outcomes. In their study, Knip et al. investigated whether the composition of formula given to infants in early childhood was associated with seroconversion to beta-cell-specific autoantibodies, which, in turn, might predict the risk of subsequent type 1 diabetes. Knip et al. enrolled 230 breast-fed newborns born at term (≥ 36 weeks of gestation) who had a first-degree relative with type 1 diabetes (the mother in the case of 37% of the children, the father in 43%, a sibling in 15%, and more than one relative in 4%) and an HLA genotype associated with the risk of type 1 diabetes. The infants were randomly assigned to receive either cow's-milk-based formula with 20% hydrolyzed milk protein (control) or an extensively hydrolyzed casein-based formula (hereafter referred to as the casein hydrolysate formula) whenever supplemental feeding was given. Families were encouraged to bring the infants for blood sampling every 3 months during their first year of life, and then at 1.5, 2, 3, 5, 7, and 10 years; serum samples were appropriately stored for assays that were performed later to detect autoantibodies to insulin, glutamic acid decarboxylase, zinc-transporter 8 (a beta-cell-specific zinc transporter), and tyrosine phosphatase-related insulinoma-associated-2 molecule, as well as islet-cell antibodies. Of the 230 infants randomly assigned to a study formula, the authors report data from the 208 infants with at least one follow-up serum sample. Although seroconversion to positivity for autoantibodies was the primary study end point, the investigators also tracked incident type 1 diabetes.

The study's principal finding was that at least one autoantibody developed in 17% of the babies fed the casein hydrolysate formula, as compared with 30% of the children fed the control formula ($P=0.02$). Diabetes ultimately developed in similar numbers of children in each group — 7 of the 113 assigned to the casein hydrolysate formula (6%) and 9 of the 117 assigned to the

cow's-milk-based formula (8%) (a nonsignificant difference). Although the group assignment was randomized, the infants assigned to receive the cow's-milk-based formula were introduced to that formula at a median age of 1.1 months, whereas the children receiving the casein hydrolysate formula were first given the formula at a significantly later median age of 2.6 months ($P=0.03$), raising the question of whether the results could be attributed to the timing of the introduction of the formula rather than to the content of the formula. Although statistical tools used to account for such differences suggest that the control formula resulted in more autoantibody seroconversions, the possibility that there were unmeasured confounders, such as the quantity of formula ingested, cannot be excluded. Confidence in the observation might be increased if the timing of the appearance of autoantibodies, the ultimate autoantibody titer, or the secondary outcome of diagnosis of type 1 diabetes had differed significantly between the groups, but they did not. The authors note that three of the seven participants assigned to the casein hydrolysate group in whom type 1 diabetes later developed had dropped out of the intervention group before receiving any study formula. In the intention-to-treat analysis, these children would be considered not to have undergone seroconversion, since they dropped out before 3 months of age. The fact that they subsequently received a diagnosis of type 1 diabetes, however, suggests that if serum samples from these children had been available, they would probably have been positive for autoantibodies, making the seroconversion rate similar between the two groups. Thus, the intention-to-treat analysis and the vagaries of the design of randomized trials may have influenced the results. One must be circumspect about such post hoc analyses, however.

How should these results be interpreted, given other recent findings relating to the pathogenesis of type 1 diabetes? Increased attention has been focused on the roles of gut-associated microbiome and gut mucosal permeability on the host immune system.⁷ Still other research has suggested that oral administration of low-dose interferon- α preserves pancreatic insulin production in persons with recent-onset type 1 diabetes, despite the fact that such treatment did not alter circulating concentrations of interferon- α .⁸ Although

it seems likely that dietary constituents, not too surprisingly, can influence the immune system and intermediary metabolism, our knowledge of the mechanisms at play are, at present, rudimentary. Data from the ongoing multicenter Trial to Reduce IDDM in the Genetically at Risk (TRIGR; ClinicalTrials.gov number, NCT00179777)⁹ should help clarify whether hydrolyzed casein formula exerts a protective effect against the risk of type 1 diabetes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Strategies for Improving Surgical Quality — Checklists and Beyond

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Long standard in the safety-conscious aviation industry, checklists are now being promoted aggressively in the medical literature and popular press.¹⁻³ Almost all U.S. hospitals mandate simple preoperative “time-outs” to minimize the risk of egregious mistakes, such as operating on the wrong site or the wrong patient. Recently, however, many hospitals have started implementing more comprehensive checklist procedures for the operating room, aimed at increasing compliance with practices known to reduce complications and enhancing teamwork. Last year, a large international study supported by the World Health Organization (WHO) reported that such checklists cut surgical morbidity and mortality almost in half.⁴

Nonetheless, findings from the WHO study left some unconvinced about the true effectiveness of surgical checklists.⁵ First, the preintervention–postintervention study failed to control for confounding factors, including the concurrent implementation of outcomes measurement and feedback. The “surgical Hawthorne effect” — which has it that outcomes tend to improve rapidly when surgeons know they are being evaluated — is widely recognized. Second, the

study’s operating room checklist consisted primarily of common-sense items and processes of care that seemed unrelated to the most common serious complications of surgery. It was implausible to some people that improved compliance with these practices could lead to such drastic reductions in morbidity and mortality. Finally, compliance of the eight study hospitals with the checklists had no bearing on the extent of improvement in outcomes. Overall compliance with processes of care on the checklists improved negligibly even in the two hospitals with the greatest reductions in morbidity and mortality. Conversely, the two hospitals with the greatest increase in compliance showed no change in outcomes.

The study in this issue of the *Journal* by de Vries and colleagues should quiet the skeptics. The authors evaluated the effects of a comprehensive surgical checklist intervention in six regional and tertiary care centers in the Netherlands.⁶ In contrast with the more narrow operating room checklist evaluated in the WHO study, this intervention involved 11 distinct checklists applied during different phases of preoperative, intraoperative, and postoperative care, completed by