of diabetes when comparing children who had received four doses of vaccine at 3, 4, 6, and 14 to 18 months of age with children who received only one dose at 24 months of age (67). A recent study conducted in four large health maintenance organizations (HMOs) in the United States did not observe any association between receipt of routine childhood vaccines and the risk of type 1 diabetes. There was no influence of the timing of HB or Hib vaccination on the diabetes risk (68).

Therefore, at this stage there are no serious indications of any significant influence of current childhood vaccines on the occurrence of type 1 diabetes.

## NEW GENERATION VACCINES AND AUTOIMMUNITY: APPROACHES TOWARD EARLY RISK ASSESSMENT

During the course of vaccine development, only a comprehensive and multidisciplinary strategy may help to reduce the theoretical risk that a new vaccine would induce autoimmune manifestations. First, one should question whether clinical manifestations of an autoimmune nature are known to be associated with the infectious disease that will be the target of the new vaccine. If such events have been reported, for example, for group A streptococcal diseases, attention should be given to avoid reproducing the natural disease pathogenic process. This may include the identification and the exclusion of naturally pathogenic epitopes. Second, potential molecular and immunological mimicry between vaccine antigens and host components should be extensively and critically analyzed through an intelligent combination of bioinformatics and immunological studies. One should keep in mind that, by itself, an identified mimicry is of little pathogenic significance. Information should be gathered on the relative ability of such epitopes to bind to human MHC molecules, to be processed by human antigen-presenting cells and to be recognized by autoreactive T cells. Molecular mimicry in itself is not sufficient to trigger autoimmune pathology and other factors intrinsic to infections such as tissue damage, and long-lasting inflammatory reaction might be required as well. For example, a recently developed Lyme disease vaccine was shown to contain an immunodominant epitope of the outer surface protein A of *Borrelia burgdorferi* (Osp A) displaying significant homology with human LFA-1, an adhesion molecule of the β2 integrin family. Although this raised concern about the safety of this vaccine, there was no evidence for an increased incidence of arthritis in individuals having received the Lyme vaccine (42). Third, indicative information can be obtained through the use of ad hoc experimental models of autoimmune diseases. Different vaccine formulations and adjuvants can be compared regarding their potential capacity to induce or enhance the expression of pathology in relevant models. For example, there are models of experimental allergic encephalitis, which are sensitive to the administration of IL-12 inducing microbial products and can help to compare the nonspecific effects of different adjuvants or vaccine formulations (32). Fourth, appropriate immunological investigations (e.g., autoimmune serology) may be systematically included in phase I-II-III clinical trials. On an ad hoc basis, clinical surveillance of potential autoimmune adverse effects may have to be included in the monitoring protocol. Such surveillance will have to be extended through the post-marketing stage if specific rare events have to be ruled out.

## CONCLUSION

Isolated case reports and increased attention in the media to possible side effects of vaccines have dramatically modified the perception by the medical community and the public of the risk of autoimmunity elicited by vaccination, despite the lack of epidemiological support for such a concern. Although available data are reassuring, vigilance is still required as the risk of autoimmunity associated with some of the new generation vaccines might be increased as compared to current vaccines. A number of new adjuvants that are developed aim to induce strong Th1-type or Th17-type immune responses against viruses or other intracellular pathogens. Such effects may occasionally favor the expression of underlying autoimmune diseases or induce autoimmune responses in exceptional cases when the vaccine antigens do contain immunodominant epitopes that cross-react with self-antigens. Special attention should be given to adjuvants acting as strong inducers of IL-12 and IL-23 synthesis (30,31). Cancer vaccines based on dendritic cells pulsed with tumor antigens might also induce autoimmunity (69,70). There is an increasing interest in the combination of vaccines with agents targeting regulatory T cells or molecules involved in suppression of T-cell responses such as CTLA4 and PD1 (71,72). Clearly, this type of combined treatment will carry a significant risk of precipitating autoimmune pathology (73).

Finally, it is of paramount importance to keep in mind that the mere occurrence of autoimmune markers (autoreactive antibodies or T cells) is a frequent phenomenon in a normal population and that pathological expression, that is, the development of an autoimmune disease, is by far much less frequent.

## REFERENCES


1. Jacobson DL, Gange SJ, Rose NR, et al. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997; 84:223–243.
2. Onkamo P, Vaananen S, Karvonen M, et al. Worldwide increase in incidence of Type I diabetes—the analysis of the data on published incidence trends. Diabetologia 1999; 42:1395–1403.
3. Wynn DR, Rodriguez M, O'Fallon WM, et al. A reappraisal of the epidemiology of multiple sclerosis in Olmsted County, Minnesota. Neurology 1990; 40:780–786.
4. Salvetti M, Ristori G, Bomprezzi R, et al. Twins: mirrors of the immune system. Immunol Today 2000; 21:342–347.
5. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. N Engl J Med 2000; 343:938–952.
6. Dahlquist G. The aetiology of type 1 diabetes: an epidemiological perspective. Acta Paediatr Suppl 1998; 425:5–10.
7. Cunningham MW, Antone SM, Smart M, et al. Molecular analysis of human cardiac myosin-cross-reactive B- and T-cell epitopes of the group A streptococcal M5 protein. Infect Immun 1997; 65:3913–3923.
8. Rees JH, Soudain SE, Gregson NA, et al. Campylobacter jejuni infection and Guillain-Barre syndrome. N Engl J Med 1995; 333:1374–1379.
9. Levin MC, Lee SM, Kalume F, et al. Autoimmunity due to molecular mimicry as a cause of neurological disease. Nat Med 2002; 8:509–513.
10. Davidson A, Diamond B. Autoimmune diseases. N Engl J Med 2001; 345:340–350.
11. Robles DT, Eisenbarth GS. Type 1A diabetes induced by infection and immunization. J Autoimmun 2001; 16:355–362.
12. Clarke WL, Shaver KA, Bright GM, et al. Autoimmunity in congenital rubella syndrome. J Pediatr 1984; 104:370–373.
13. Ferri C, Zignego AL. Relation between infection and autoimmunity in mixed cryoglobulinemia. Curr Opin Rheumatol 2000; 12:53–60.