Magic bullets, reportable disease, and prevention of childhood diabetes

RONALD E. LAPORTE, PHD, SHIGEAKI BABA, MD

During the past few years major strides have been made in our ability to predict asymptomatic children who will develop insulin-dependent diabetes mellitus (IDDM). Also, rapid advances in our understanding of the immune system have led to specific immune intervention "magic bullets" that appear to reduce or halt β-cell destruction. This has provoked the question of whether we are at the point whereby specific immunotherapies can be tried in clinically healthy people with the goal of preventing childhood diabetes (1). Recently, a position statement by the American Diabetes Association came out in favor of immunomodulation trials of asymptomatic individuals (1). Disappointingly, no other approaches for prevention were advocated, nor even discussed. Herein, we present an alternative path to the "magic bullet" direction.

We present the parallels between one HLA-associated autoimmune disease that has been successfully prevented, rheumatic fever/rheumatic heart disease (RF/RHD), with an HLA-associated autoimmune disease that has not been prevented, childhood diabetes. We argue that successful preventive approaches used with RF/RHD could equally be applied to IDDM, the first step being that of making IDDM a reportable disease.

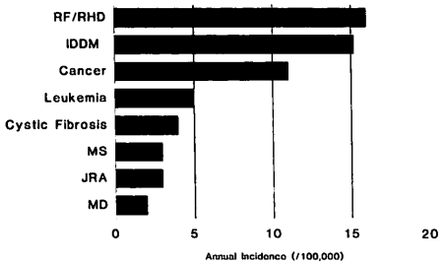

Figure 1—*Chronic diseases of children. RF/RHD, rheumatic fever/rheumatic heart disease; IDDM, insulin-dependent diabetes mellitus.*

EPIDEMIOLOGY

There are striking similarities between the epidemiology of (RF/RHD) and IDDM in children (2). For both RF/RHD and IDDM, the onset mortality is high (2,3). RF/RHD and IDDM have had a similar incidence and were two of the leading chronic diseases of children (4–6; Fig. 1). The ages at onset are almost identical, with few cases diagnosed at <2 yr of age, a rising incidence until puberty, and a steady decline there after (4–6; Fig. 2). There is an enormous geographic variation for both diseases with the incidence being higher further from the equator (4,6; Fig. 3). The seasonal patterns are almost identical with a reduction of cases in warm summer months (7,8; Fig. 4).

GENETICS

RF/RHD clusters within certain families as does childhood diabetes. There is a markedly increased risk for identical twins (9,10) and siblings (11–13) for both diseases. In addition, the risk to siblings for both RF/RHD and IDDM appears to be primarily determined by age, rather than when the proband developed the disease (12,14). As with IDDM, a specific Mendelian mode of inheritance has not been found for RF/RHD (7,8).

EVIDENCE FOR AUTOIMMUNE NATURE

Both RF/RHD and IDDM are characterized by HLA associations and tissue-specific autoantibodies, as are typically found in autoimmune diseases. The prevalence of tissue autoantibodies is as high if not higher for RF/RHD than childhood diabetes (15–17). Moreover, the tissue antibodies have been directly related to target tissue damage (16) with rheumatic heart disease and has been presented as a model of molecular mimicry unlike IDDM. HLA-DR4 associations are seen with both diseases (18). In addition, for both diseases, affected siblings exhibit segregation distortion with >65% of affected siblings being HLA-haplotype identical when

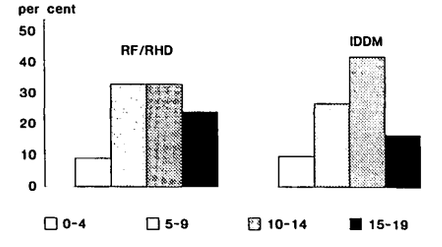

Figure 2—*Age at onset. RF/RHD, rheumatic fever/rheumatic heart disease; IDDM, insulin-dependent diabetes mellitus.*

FROM THE DEPARTMENT OF EPIDEMIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PENNSYLVANIA; AND THE HYOGO INSTITUTE FOR RESEARCH IN ADULT DISEASES, AKASHI, JAPAN.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO RONALD E. LAPORTE, PHD, DEPARTMENT OF EPIDEMIOLOGY, DIABETES RESEARCH CENTER, RANGOS RESEARCH CENTER, 3460 FIFTH AVENUE, PITTSBURGH, PA 15213.

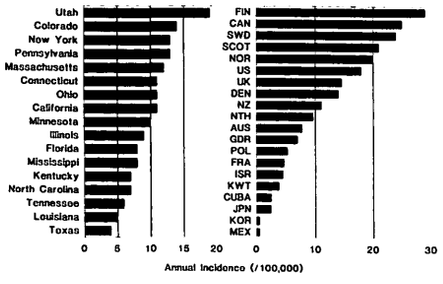

Figure 3—*Geographic variation for rheumatic fever/rheumatic heart disease (RF/RD) and insulin-dependent diabetes mellitus (IDDM).*

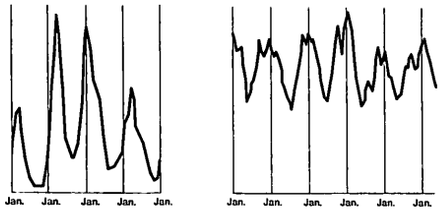

Figure 4—*Seasonal patterns of rheumatic fever/rheumatic heart disease (RF/RHD) and insulin-dependent diabetes mellitus (IDDM).*

only 25% would be expected, indicating strong HLA linkage (19,20; Fig. 5).

The similarities between the two HLA-associated diseases are striking but there is a major dissimilarity (Fig. 6). During a 30-yr period, RF/RHD has been virtually eradicated, in contrast there appears to be a global rise in the incidence of IDDM, in some cases of epidemic proportion (21,22).

Why is it that RF/RHD has almost disappeared and IDDM continues to rise, despite the fact that we know as much if not more about the immunology and immunogenetics of IDDM than we know about the immunology and immunogenetics of RF/RHD? The obvious reason is that for RHD we know the environmental factors causing the disease, i.e., group A streptococci, and how to break the chain of causation (7). For IDDM we do not know the specific agents. With the knowledge of the environmental factors, surveillance, changing life-styles, and control measures, the incidence of RF/RHD has precipitously declined. We believe the same would occur with childhood diabetes.

Classic epidemiological studies of RF/RHD directly linked streptococcal infection to the disease (7). Similar types of studies are needed with IDDM to identify the agents causing disease. RF/RHD studies investigated "outbreaks" of disease in populations (7). Many "outbreaks" of IDDM have been found (22,23) but systematic, active, and rapid pursuit of these epidemics has not taken place.

We propose that the route to eradication of IDDM is that of epidemiology and public health. The prevention task is probably easier than with RF in that there are few problems of diagnosis with IDDM as with RF. Moreover, specific DNA markers have been identified that are highly associated with the disease (24). Thus, investigations can be limited to the small, genetic subset of the population who can develop IDDM, comparing those genetically susceptible people who develop the disease with those who do not, to make it easier to identify the agents responsible for the death of the pancreas.

Perhaps, at this juncture, we need to be wary of blindly continuing down the exciting and glamorous magic bullet route. Despite what we were told in the 1970s, 1980s, and now, the prevention of diabetes with magic immunologic bullets is not just around the corner. We must be concerned that in the rush to find the bullet that no harm be done to asymptomatic children (21). Despite the bright promise of immunotherapy, gene therapy, and pancreatic transplant, is there any HLA-associated disease that has been prevented/cured in asymptomatic people with a magic bullet? We cannot think of any. In contrast, epidemiology and public health have a strong track record in identification of agents causing HLA-associated diseases and prevention. In addition to RF, other HLA-associated diseases that have or are being prevented include toxic oil syndrome in Spain (25) and tryptophan-associated eosinophilia myalgia (26). Lyme arthritis is another apparent autoimmune HLA-associated disease where the agent has been found through epidemiology and public health measures have been devised for prevention (27). In each case, removal of the agent eradicated or would eradicate the disease.

Hopefully, we will be as successful with IDDM as with RF. The incidence of RF declined in Denmark from >300/100,000 per yr in the late 1800s to 50/100,000 in the 1950s and

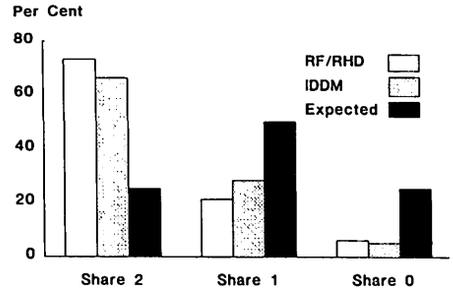

Figure 5—*HLA associations. RF/RHD, rheumatic fever/rheumatic heart disease; IDDM, insulin-dependent diabetes mellitus.*

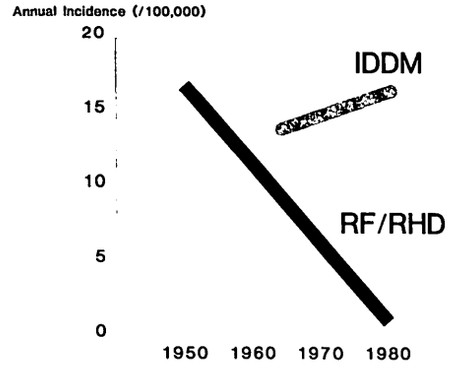

Figure 6—*Temporal trends in the United States. RF/RHD, rheumatic fever/rheumatic heart disease; IDDM, insulin-dependent diabetes mellitus.*

10/100,000 in the 1970s (28). In Baltimore, the incidence of RF precipitously declined from 17/100,000 in 1950 to .23/100,000 in 1980, a 98.6% reduction (29). The hope is that we could be equally as successful with IDDM as with RF and RHD in Baltimore. If we were, then during the next 30 yr in the U.S. instead of 12,000 childhood IDDM cases being diagnosed each year, there would be only 170. In Allegheny County, Pennsylvania, 70 new cases are diagnosed annually. If we are successful in prevention, only 2 would develop. Can the search for the "magic bullet" to prevent IDDM offer such an optimistic projection?

How best to use the RF/RHD model? Surveillance of RF began with small, short-term population-based registries that gave hints about the epidemic nature of the disease. We are at this point with IDDM. However, it was not until RF became a reportable disease in the 1940s and 1950s that our knowledge of the etiology and preventive approaches began as the epidemics were found early and the agent identified. This effort was a marriage between the primary health-care providers (pediatricians, internists, and family practitioners) and the public health officials. The primary health-care providers identified the epidemics by reporting the diseases and also provided hypotheses about what was causing RF/RHD. The public health officials provided the methods for testing and control measures (7). A similar model should be established to prevent IDDM in the U.S., Japan, and the rest of the world. It is time that IDDM became a reportable disease. The Centers for Disease Control in the U.S. and the Ministry of Health in Japan should take on this responsibility.

To quote Dr. Paul "For the epidemiologist it is difficult to imagine any feature about rheumatic fever of greater significance to the physician, the public health worker, or the general public than the discovery of a method of prevention and the demonstration of its successful application" (7). We hope that we can soon say the same about childhood diabetes.

Safe prevention of RF occurred as the result of changing environmental conditions, epidemiology, and public health. We predict that in the next 30 yr the preventive medicine approach will be successful for the eradication of childhood diabetes (31,32). We are not saying that the immunomodulatory route toward prevention is wrong; however, it is an untrodden path. More attention needs to be directed toward a proven well-travelled route of disease prevention; that of epidemiology and public health.

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