DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20852-1448

JUN 26 2003

J. Barthelow Classen, M.D., M.B.A.
President and Chief Executive Officer
Classen Immunotherapies, Inc.
6517 Montrose Avenue
Baltimore, Maryland 21212

Re: Docket Number 02P-0349/CP1

Dear Dr. Classen:

This responds to your citizen petition (Petition) submitted to the Food and Drug Administration (FDA) on August 5, 2002 (Docket No. 02P-0349/CP1). In your petition, you request that FDA take the following actions:

- Require manufacturers of hemophilus vaccines to amend their package inserts to,

  (1) include a "black box" warning that the vaccine causes diabetes and that for the general public the risk of vaccine-induced diabetes exceeds the benefit of preventing hemophilus; and
  (2) recommend restricting use of the vaccine to those at highest risk for complications from hemophilus, such as users who are immune compromised, and that the risk may still exceed the benefit for these individuals.

- You also request that FDA,

  (1) send letters of warning to physicians and state health departments informing them that for the general public the risk of vaccine-induced diabetes exceeds the benefit of preventing hemophilus, and that letters of warning to state health departments should explicitly state that mandatory immunization of the general public with hemophilus vaccines will cause more children to be harmed than benefit;
  (2) require vaccine manufacturers to perform prospective, randomized, blinded clinical trials to prove that a vaccine causes a benefit in health, not just a reduction in infections or infectious complications;
  (3) restrict manufacturers from promoting vaccine products for general use or lobbying for mandatory immunization until a long-term benefit to health has been demonstrated; and

02P-0349

PDN 1

(4) require manufacturers to alert prescribers that the risk of vaccine-induced diabetes is not limited to the hemophilus vaccine and that the risk of vaccine-induced diabetes may exceed the benefit of other vaccines. Also, that prescribers should be aware that safety testing of vaccines in the past was so severely compromised that the value of the vaccine is in doubt and that prescribers should be told that other autoimmune diseases, beside diabetes, may result from vaccination.

In addition to your citizen petition, you submitted two addenda to the petition (Supplements 1 and 2), which FDA received on September 4 and September 17, 2002, respectively. Supplement 1 provides additional information and requests that hemophilus vaccine package inserts include information on the appearance of a dose response between the number of vaccine doses administered and the development of insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes. Supplement 2 provides additional information regarding the purported mechanism of vaccine-induced diabetes.

For the reasons stated below, we deny your requests.

I. DISCUSSION

A. Response to Statement of Grounds

In support of your requests for FDA action, you provide a statement of grounds citing several published articles. In your statement of grounds, you assert that the hemophilus vaccine has been proven to cause IDDM (Petition at 2). You cite your recently published article, "Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (HiB) Immunization Support Causal Relationship Between Immunization and IDDM",[1] to support this assertion of causality. Customarily, however, the entire body of scientific evidence relating to a hypothesized exposure-disease association is considered when evaluating a proposed causal association. Several general considerations, patterned after those proposed by Hill in 1965 and adapted by others, have been generally accepted in the field of epidemiology for causal inference, i.e., determination of whether a disease is caused by an exposure.[2] The Institute of Medicine (IOM)[3] has used the following criteria for assessing whether evidence indicates the presence of an association between an adverse event and vaccine exposure: Strength of association, dose-response relationship, temporally correct association, consistency of association, specificity of an association, and biological plausibility. Using these criteria, we do not believe that the available evidence demonstrates that Haemophilus influenzae type B polysaccharide protein conjugate (HiB) vaccine causes IDDM.

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[1] Classen JB, Classen DC. Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (HiB) Immunization Support Causal Relationship Between Immunization and IDDM. Autoimmunity. 2002; 35 (4): 247-253.
[2] Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965; 58:295-300.
[3] IOM (Institute of Medicine). Adverse Effects of Pertussis and Rubella Vaccines. Washington, DC: National Academy Press, 1991; 52-55.

The strength of an association refers to the magnitude of the measure of effect of an exposure, usually the relative risk or odds ratio, in a study comparing an exposed and an unexposed group. The larger the magnitude of the effect, the less likely any observed effect is due to chance, bias, or confounding. When evaluating this consideration, three types of studies are generally included: Controlled trials, cohort studies, and case-control studies. These studies have in common the ability to calculate an estimate of the relative risk of an effect from an exposure.

Five studies with a control or a comparison group investigating the link between HiB vaccine and IDDM have been published in peer-reviewed literature.[4, 5, 6, 7, 8] Two of these were case-control studies,[9] one was a prospective cohort study,[10] and two were randomized, controlled, vaccine efficacy trials with linkage to diabetes registries for outcome assessment.[11] In addition, your reanalysis of the Karvonen et al. study has been published.[12] None of the original analyses found a significantly increased risk of IDDM associated with HiB vaccine. Only your reanalysis found a significant increased risk. Furthermore, the relative risk estimates in these studies are not consistent across studies as some estimates are greater than 1.0 and others are less than 1.0.[13] Your single statistically significant relative risk point estimate of 1.2 (95% confidence interval 1.02-1.42) among the 27 comparisons examined in your article is close to 1 (null results).[14] Because you group all vaccinees together (recipients of 1 and 4 doses) and compare them to non-randomized historical controls, this point estimate is subject to confounding by the well-documented trend of rising IDDM incidence in Finland over the last several decades.[15] This trend began in the mid-1960s, well before the introduction of the HiB vaccine, and has continued despite stable immunization rates.[16]

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[4] Karvonen M, Cepaitis Z, Tuomilehto J. Association between Type 1 Diabetes and *Haemophilus Influenzae* Type B Vaccination: Birth Cohort Study. BMJ. 1999 May 1; 318(7192):1169-72.
[5] Black SB, Lewis E, Shinefield HR, Fireman B, Ray P, DeStefano F, Chen R. Lack of Association between Receipt of Conjugate *Haemophilus influenzae* Type b Vaccine (HbOC) in Infancy and Risk of Type 1 (Juvenile Onset) Diabetes: Long Term Follow-Up of the HbOC Efficacy Trial Cohort. Pediatr Infect Dis J. 2002 Jun; 21(6):568-9.
[6] DeStefano F, Mullooly JP, Okoro CA, Chen RT, Marcy SM, Ward JI, Vadheim CM, Black SB, Shinefield HR, Davis RL, Bohlke K. Childhood Vaccinations, Vaccination Timing, and Risk of Type 1 Diabetes Mellitus. Pediatrics. 2001 Dec; 108(6):E112.
[7] Infections and Vaccinations as Risk Factors for Childhood Type I (Insulin-Dependent) Diabetes Mellitus: A Multicentre Case-Control Investigation. EURODIAB Substudy 2 Study Group. Diabetologia. 2000 Jan; 43(1):47-53.
[8] Hummel M, Fuchtenbusch M, Schenker M, Ziegler AG. No Major Association of Breast-Feeding, Vaccinations, and Childhood Viral Diseases with Early Islet Autoimmunity in the German BABYDIAB Study. Diabetes Care. 2000 Jul; 23(7):969-74.
[9] See footnotes 6 and 7.
[10] See footnote 8.
[11] See footnotes 4 and 5.
[12] See footnote 1 on p. 2.
[13] See footnote 1 on p. 2, and footnotes 4, 5, 6, 7, and 8.
[14] See footnote 1 on p. 2.
[15] See footnote 4.
[16] id.

The existence of a dose-response relationship strengthens an inference that an association is causal. A dose-response relationship is defined as an increased strength of association with increased magnitude of exposure. In Supplement 1 (at 1), you state that the package insert of the HiB vaccines should provide information to the prescriber that there appears to be a dose response between the number of doses of vaccine given and the development of IDDM. However, none of the controlled studies identified above examined a dose-response relationship between HiB vaccine and IDDM, and your study does not contain any statistical trend analysis by dose number.

Exposure must precede an event by at least the duration of disease induction. This consideration may be limited by the fact that knowledge of the pathogenesis and natural history of an adverse event may be insufficient. The duration of disease induction is not well established for IDDM and may be variable, although in family pedigree and twin studies these islet cell antibodies have been found to precede clinical disease by months to years.[17, 18] You state (Petition at 2) that most of the cases of diabetes caused by the HiB vaccine occur between three to four years after immunization. In Supplement 1, you present additional data regarding the biological plausibility of a several-year time lag between a provoking agent and IDDM. While this time lag may be biologically plausible based on what is known about this illness, there are no significant differences in IDDM cumulative incidence among any of the treatment groups after that time interval, as you document in Table 1 of your article.[19]

You suggest (Petition Appendix at 2) that you have identified statistically significant diabetes case clusters that support the time lag between HiB vaccine exposure and development of IDDM, but the methods section of your article does not describe a formal cluster analysis. Rather than performing a formal cluster analysis, it appears that you have identified "clusters" by examining areas of increased separation between the cumulative incidence curves and then comparing incidence during this time period selected as appearing "the most different." Given that you selected such time periods post hoc and that an infinite number of such time periods could be selected on any such curve, it is quite likely that by chance some part of the curve would show statistically significant differences when there is in fact no real difference in incidence over the course of the entire period. Therefore, such observations do not provide persuasive evidence of an increase in diabetes risk due to HiB vaccination.

Consistency of association requires that an association be found regularly in a variety of studies, using different study populations and study methods. The purported HiB vaccine-IDDM association does not meet this condition. First, the original investigators of the randomized trial whose data you presented in your recent article did not replicate your results when they examined the same study data.[20, 21] Their published analysis

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[17] Behrman RE. Nelson's Pediatrics. 14th ed. Philadelphia (PA): Saunders Publishers; 1992.
[18] Robles DT, Eisenbarth GS. Type 1A Diabetes Induced by Infection and Immunization. J Autoimmun. 2001 May; 16(3):355-62.
[19] See footnote 1 on p. 2.
[20] See footnote 4 on p. 3.

found no statistically significant association between HiB vaccine and IDDM.[22] An expert panel convened by the Institute for Vaccine Safety of the Johns Hopkins School of Public Health examined both approaches to this randomized trial data and concluded that the analytic methods you used were incorrect.[23]

Second, this proposed association has not been found in any other human population despite your statement (Petition at 2) that your recent study confirmed results from three smaller epidemiological studies. These studies examined the association between HiB and other vaccines with IDDM[24] or islet cell autoantibodies.[25] None of these studies reported a statistically significant association. You confirm this in your article's discussion section, stating that "all [three studies] reported no association between the HiB vaccine and IDDM."[26] Two additional controlled studies also found no significant association between HiB vaccine and IDDM. One small cohort study followed the high-risk offspring of diabetics for anti-islet autoantibodies and diabetes and found no increase in these endpoints associated with any of the vaccines studied, including HiB.[27] Another newly published study examined data from a randomized, controlled, prospective Phase III clinical efficacy trial conducted within a large staff-model health maintenance organization (HMO), in which over 21,000 children were immunized with HiB vaccine.[28] No association between HiB vaccine and IDDM was found after ten years of follow up.

Uniqueness of association between an exposure and an outcome provides a stronger justification for a causal interpretation than when the association is nonspecific. However, perfect specificity between an exposure and an effect cannot be expected in all cases because of the multifactorial etiology of many disorders. Because IDDM clearly existed prior to mass vaccination programs, this association does not meet the criterion of uniqueness of association.

The existence of a possible mechanism of action that fits existing biologic or medical knowledge is thought to increase the likelihood that an association is causal. Antibodies to pancreatic islet cells have been found in 80-90% of newly diagnosed patients with IDDM.[29] In family pedigree and twin studies, these antibodies have been found to precede clinical disease by months to years, suggesting that IDDM is a chronic autoimmune disease.[30] Based on twin studies, an estimated 30-50% of risk for this

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[21] Childhood Immunizations and Type 1 Diabetes: Summary of an Institute for Vaccine Safety Workshop. The Pediatric Infectious Disease Journal. 1999; 18:217-222.
[22] See footnote 4 on p. 3.
[23] See footnote 21.
[24] See footnotes 6 and 7 on p. 3.
[25] Graves PM, Barriga KJ, Norris JM, Hoffman MR, Yu L, Eisenbarth GS, Rewers M. Lack of Association Between Early Childhood Immunizations and beta-Cell Autoimmunity. Diabetes Care. 1999 Oct; 22(10):1694-7.
[26] See footnote 1 on p. 2.
[27] See footnote 8 on p. 3.
[28] See footnote 5 on p. 3.
[29] See footnote 17 on p. 4.
[30] See footnote 18 on p. 4.

disease is inherited.[31] This leaves scientists to search for environmental factors that may play a role in the etiology of this illness, although post-conception somatic mutations may be responsible for some of these differences.[32] It has been hypothesized that many infections, including mumps, rubella, rotavirus, and Coxsackie's virus, may be linked to an increased risk of IDDM.[33] However, wild-type Haemophilus influenzae type b infection has not been associated with increases in IDDM risk,[34] making this vaccine-disease association less likely. Although the second addendum to your petition discusses the hypothesized role of macrophage activation in the development of IDDM, none of the evidence you present links HiB vaccine to such macrophage activation.

In your petition's appendix, you present criticisms of the study design of several published studies evaluating the proposed association between vaccines and IDDM. We confine our response to the studies that examine the specific vaccine-disease association alleged in your petition. Four of the studies addressed in the appendix examine the HiB vaccine-IDDM relationship.[35]

You state (Appendix at 2) that several case control studies found similar or higher odds ratios associated with the HiB vaccine than your analysis of the Finnish data. You contend that these studies were not powered to reach statistical significance and, therefore, their authors inappropriately concluded that their findings do not support an association between the HiB vaccine and IDDM. It is true that neither of the two published studies you cite in support of this statement were powered to identify very small risk increases such as 10-20%. However, the study by Patterson et al.[36] had 80% power to detect a doubling of risk based on statistical calculations from data provided to FDA by the investigators. Also, a recently published large randomized controlled trial by Black et al.[37] was adequately powered to rule out a vaccine effect resulting in a 20% to 90% increase in IDDM incidence, depending on the comparison group selected for the analysis. These analyses were also performed by the study investigator at the request of the FDA as part of our review in responding to your citizen petition.

You argue (Appendix at 2) that Karvonen et al.[38] examined incorrect comparisons in their follow-up analysis of the same Finnish efficacy trial conducted in the late 1980s that you analyzed in your recent publication. You also state that Karvonen et al. made incorrect calculations of incidence and misreported the incidence of IDDM in unvaccinated controls. You report slightly lower denominators for each cohort in your article compared to Karvonen et al., although you do not report any additional exclusion criteria in your methods.[39] However, you confirm the qualitative findings of Karvonen et al. as

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[31] See footnote 25 on p. 5.
[32] See footnote 18 on p. 4.
[33] See footnotes 17 and 18 on p. 4.
[34] See footnote 18 on p. 4.
[35] See footnotes 4, 6, 7, and 8 on p. 3.
[36] See footnote 7 on p. 3.
[37] See footnote 5 on p. 3.
[38] See footnote 4 on p. 3.
[39] See footnote 1 on p. 2.

you report no significant differences after ten years of follow up between either of the treatment arms or the vaccinated versus the unvaccinated subjects using a two-tailed Fisher's exact test (id. at Table 1).

Regarding your analysis of the Finnish trial results, you present no explanation for analyzing 9 time periods resulting in 27 separate comparisons (id.). Since your analysis involves 27 comparisons, one would expect to find at least one comparison to be statistically significant by chance using the conventional cutoff for the p-value (0.05), even though there were no true differences for any comparison. Thus, your finding of one significant result is entirely consistent with the expected rate of false positive results and cannot be considered conclusive evidence of a true difference. A valid assessment of your data would require an adjustment in the significance level for multiple comparisons,[40] which you did not include in your calculations. It is also possible that more than 27 comparisons could be made when analyzing this data, as an infinite number of possible time periods could be compared, and the presented time-period cutoffs could then be selected based on results, rather than determined a priori. If so, adjustment would have to be made for these additional comparisons. Further, there is no reason to presume a priori that the association is negative or positive; therefore, a two-tailed test, rather than a one-tailed test, is appropriate for all of these comparisons.[41]

For the study by Hummel et al. of 823 children with at least one parent with IDDM, you critique the study (Appendix at 6) based on results presented in a preliminary research letter published by the investigators in 1996.[42] However, in July 2000, the authors published further results from this cohort study after up to eight years of follow up.[43] Ten children were diagnosed with IDDM and 31 children developed anti-islet autoantibodies. No association was found between these outcomes and exposure to HiB vaccine or any other vaccine.

Several expert panels have examined the body of scientific evidence regarding the proposed association between vaccines and IDDM. In 1995, an interagency group involving experts from FDA, the Centers for Disease Control and Prevention, and the National Institutes of Health was convened to examine the hypothesis that childhood vaccines could represent additional risk factors for the development of IDDM in childhood (see Attachment).[44] The group concluded that, "Currently available human and animal data are insufficient to establish a causal association between any childhood vaccines and/or present immunization policies and the risk of IDDM."[45] Since that meeting, two more expert panels have examined this issue and have also concluded that

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[40] See Rosner B. Fundamentals of Biostatistics. 5th ed. Pacific Grove (CA): Duxbury Publishers; 2000.
[41] id.
[42] Hummel M, Ziegler AG. Vaccines and the Appearance of Islet Cell Antibodies in Offspring of Diabetic Parents. Results from the BABY-DIAB Study. Diabetes Care. 1996 Dec; 19(12):1456-7.
[43] See footnote 8 on p. 3.
[44] Attachment to Petition Response: Report of Consultation: Informal Consultation on Vaccines and Diabetes. Summary and Conclusions from Inter-Agency Group. January 30, 1995.
[45] id at 1.

the current scientific evidence does not support a causal association.[46] The Johns Hopkins Institute for Vaccine Safety Workshop on childhood immunizations and type 1 diabetes concluded that no changes in childhood immunization schedules for any vaccines were indicated at this time.[47] In addition, as you note in your petition, the Institute of Medicine exhaustively reviewed the related scientific literature and concluded that the epidemiological evidence favors rejection of a causal relationship between multiple immunizations and an increased risk for type 1 diabetes.[48] Therefore, no expert panel has concluded that the available scientific evidence supports a causal association between the HiB vaccine and IDDM.

B. Response to Requests for Agency Action

Having reviewed the current scientific evidence, we cannot find support for your request that HiB vaccine manufacturers revise their package inserts to include a black box warning that the HiB vaccine causes diabetes and that the risk of vaccine-induced diabetes exceeds the benefit of preventing Haemophilus influenzae type B disease. Therefore, we deny your request. Similarly, we deny your request that package inserts be revised to recommend restricting use of HiB vaccines to those at highest risk for complications from Haemophilus influenzae type B disease, such as users who are immune compromised, and that the risk may still exceed the benefit for these individuals. The available evidence does not warrant requiring manufacturers to include such a recommendation.

You also request that FDA send letters of warning to physicians and state health departments informing them that the risk of diabetes caused by the HiB vaccine exceeds the benefit of preventing Haemophilus influenzae type B disease, and that letters of warning to state health departments should explicitly state that mandatory immunization of the general public with HiB vaccines will cause more children to be harmed than benefit. Because current scientific evidence does not support these actions, we deny your request.

You request that FDA require manufacturers of proposed vaccines to conduct prospective, randomized, blinded clinical trials to prove that a vaccine causes a benefit to health, not just a reduction in infections or infectious complications. We consider statistically significant clinical data showing a reduction in infections or infectious complications to be evidence of a benefit to health. Therefore, we deny your request.

You request that FDA restrict vaccine manufacturers from promoting any vaccine product for general use or lobbying for mandatory immunization until they demonstrate that the vaccine causes a long-term benefit to health. With regard to promotion, section

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[46] See footnote 21 on p. 5, and Attachment to Petition Response.
[47] See footnote 21 on p. 5.
[48] Institute of Medicine (IOM) Immunization Safety Review Committee. K. Stratton, C. B. Wilson and M. C. McCormick, Editors. Immunization Safety Review: Multiple Immunizations and Immune Dysfunction. Washington, DC: National Academy Press: 2002.

505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355) and sections 502(a), (f), and (n) of the Act (21 U.S.C. 352(a), (f), and (n)) prohibit the promotion of a product by a sponsor or any person acting for or on behalf of a sponsor for any indication that is not approved for the product. With regard to lobbying, FDA has no authority under the Act to prohibit lobbying activities.

We also deny your request that FDA require vaccine manufacturers to alert prescribers that the risk of vaccine-induced diabetes is not limited to the HiB vaccine and that this risk may exceed the benefits of other vaccines. You further state that prescribers should be aware that safety testing of vaccines in the past was so severely compromised that the value of the vaccine is in doubt and that prescribers should be told that other autoimmune diseases, beside diabetes, may result from vaccination. Current scientific evidence does not demonstrate a risk of vaccine-induced diabetes in other vaccines, and FDA does not believe that current scientific evidence warrants a change to vaccine labels regarding other autoimmune diseases. Consequently, there is no justification for requiring vaccine manufacturers to notify prescribers as you request.

In your Supplement 1, you request that we modify the package inserts of the HiB vaccines to add that there appears to be a dose response between the number of doses of vaccine given and the development of IDDM. As discussed above, current scientific evidence does not support this conclusion, so we are denying your request.

II. CONCLUSION

The actions that you request FDA to take are based on the purported existence of a causal association between HiB vaccine and IDDM. After reviewing your recent publication, other relevant scientific literature, and prior extensive reviews of the scientific literature by expert panels, we conclude that current scientific evidence does not support the existence of such a causal association. Therefore, as discussed above, we are denying your requests for FDA action.

Sincerely yours,

Jeffrey Shuren, M.D.
Assistant Commissioner for Policy

cc: Dockets Management Branch
(HFA-305)

ATTACHMENT

Report of Consultation

Informal Consultation on Vaccines and Diabetes
January 30, 1995
Solar Building, Room 1A4

Summary and Conclusions from Inter-Agency Group

Executive Summary

A substantial body of biomedical research in the fields of immunology, infectious disease and diabetology has established an autoimmune pathogenetic mechanism as an etiology of insulin-dependent diabetes mellitus (IDDM). A large number of immunologic stimuli and genetic susceptibility factors have been shown to be associated with the risk of IDDM in both animal models and humans. Among these are numerous infectious agents.

A consultation with experts from several agencies of the U.S. Public Health Service and other agencies was convened to consider a recently proposed hypothesis that childhood vaccines could represent additional risk factors for the development of IDDM in childhood (list of participants attached). Following a presentation by the investigator who raised this hypothesis, the biomedical research literature was reviewed, additional information from diabetes and immunization surveillance and clinical research programs was obtained, and a series of meetings and conference calls were conducted to review and evaluate the significance of the hypothesis.

Preliminary conclusions:

1. Currently available human and animal data are insufficient to establish a causal relationship between any childhood vaccines and/or present immunization policies and at the risk of IDDM.

2. Present scientific information does not provide a sufficient basis for a change in childhood immunization policy.

3. Ongoing research that may inform this hypothesis should be encouraged, and the results monitored with respect to implications for the public health. Several appropriate lines for further investigation and follow-up action for the responsible public health and research agencies were identified.

4. Available information should be presented to the immunization policy bodies concerned with issues of vaccine safety for consideration.

Background

Over the past several years, advances in the fields of immunology and infectious diseases have resulted in an enhanced focus on the relationship between autoimmunity and infectious diseases. In some instances, a strong relationship has been found (e.g., diarrheal diseases and arthritis). A literature review (see attachment A) demonstrates that a number of investigators are actively working in this area.

The purpose of this consultation was to consider Dr. Bart Classen's hypothesis that links childhood immunization practices and juvenile-onset insulin-dependent diabetes mellitus (IDDM). Accordingly, on January 30, 1995 an interagency group of knowledgeable scientists and public health authorities was convened to receive more detailed information from Dr. Classen, to review available literature, and to consider the appropriate response to this concern (see attachment B). Participants included experts from the NIH (NIAID, NIDDK, NIDR), CDC (NIP), FDA, NVPO, DoD, and others (see attachment C). Because Dr. Classen considered his research and analysis to result in patentable products, participants were restricted from discussions or consultations with external experts, until his patent application had been filed. A confidentiality agreement was signed (see attachment D), but this was subsequently released by Dr. Classen upon publication of his patent in Europe (see attachment E).

After Dr. Classen's presentation and the ensuing extensive discussion, representatives of the agencies of the U.S. Public Health Service and other federal agencies recommended the collection of additional items of information. These were subsequently discussed in conference calls on March 16 and May __, 1995.

Summary of Findings

1. Etiology of Diabetes Mellitus, Type 1

   There is a significant body of research which establishes autoimmune processes as important in the pathogenesis of type 1 diabetes mellitus. It is equally clear that the etiology of insulin-dependent diabetes mellitus (IDDM) is heterogeneous and multifactorial, including genetic factors (which account for 30-50% of risk) and environmental factors, such as an infectious agent, which may trigger the response in predisposed individuals.

   There exists a substantial long-standing and ongoing research effort, supported by numerous sources, including the NIH and CDC, with the goal of understanding the etiology and pathogenesis of juvenile-onset insulin-dependent diabetes mellitus. These research activities have provided the scientific underpinnings for the research efforts of Dr. Classen and numerous other investigators. Among the lines of current research are issues central to determining whether or not immunization policies and

practices are related to autoimmune phenomena, such as including juvenile diabetes mellitus.

2. Animal Models

There are several well-established animal models for IDDM (BB rats, NOD mice). These genetically defined animals are known to have a high spontaneous rate of IDDM and respond to manipulation of the immune system by a variety of stimuli with an altered (typically increased) frequency of diabetes. Among the multiple factors which have been studied and shown to be associated with changes in outcome in these inbred animal models are:

a) Genetic background
   1) MHC and other loci related to immune function
   2) loci not related to immune function (e.g., pancreatic islet cell antigens)
b) Environmental stimuli
   1) antigens (e.g., bacteria, viruses, fungi, T cells)
   2) adjuvants (e.g., alum, Freund's)
   3) nutritional factors (e.g., dietary proteins, vitamin D)
   4) cytokines, etc.
   5) immunosuppressive agents
c) differences of timing of exposure with respect to immune ontogeny
d) dosage and, perhaps, route of exposure

Preliminary data from Dr. Classen's animal studies are consistent with previous research using well-known animal models, and with extant hypotheses on the pathogenesis of IDDM. From his work, he concludes that childhood vaccines may also produce similar increases in IDDM in these animal models. However, he has not yet developed a specific testable hypothesis for pathogenesis and mechanism of action. A number of suggestions and recommendations to strengthen this line of research were presented to Dr. Classen, including the selection of appropriate control groups and assuring a sufficient follow-up period in his studies. Dr. Classen was urged to submit his research findings formally to the scientific community through publication in peer-reviewed journals. In addition, Dr. Classen was provided information on the grants submission process at NIH.

While animal models of diabetes mellitus may be used to explore the pathogenesis of this disorder and to identify pathogenic mechanisms, issues of genetic predisposition and the plethora of potential stimuli render simple extrapolations from animal models to humans problematic.

3. Epidemiologic Data on IDDM

Epidemiologic studies of IDDM reveal significant geographic, temporal and socio-demographic variations in the frequency of this disorder in human populations. The reported incidence of IDDM varies from 6-42/100,000. Previous epidemiologic and clinical observations support a role for infectious agents in the pathogenesis of type 1 diabetes mellitus (e.g., coxsackie B4 virus).

Furthermore, studies of human diabetic populations reveal differences from controls in the frequency of antibodies to various antigens, as well as distinct differences in the distribution of histocompatibility phenotypes and other immunological characteristics.

(In addition, there is a current trial of BCG vaccination as a diabetes prevention strategy.)

Dr. Classen's ecologic analysis compares national reports on the incidence of IDDM and national recommendations for immunization, suggesting the possibility that in some countries, immunization practices may be correlatable with observed changes in the reported incidence of IDDM. In each of these cases, the possibilities of confounding by alternative environmental exposures must be considered, as well as the existence of alternative hypotheses. Furthermore, information received suggests that changes in immunization policies in Finland and Sweden, as presented by Dr. Classen, need more careful review and documentation (see attachment G).

4. Other Relevant Pathologic Outcome Issues

There is a parallel literature base which suggests that autoimmunity is an important mechanism related to several other disorders, including:

a) rheumatoid arthritis
b) lupus erythematosus
c) demyelinating diseases (e.g., multiple sclerosis)
d) asthma

As a consequence, the health outcome variables which would be of concern may also include other disorders of immunity, including those with a hypothesized autoimmune pathogenesis.

5. Discussion

Unfortunately, neither the currently available animal data nor human ecologic data are sufficient to provide a clear answer to questions about current immunization policies and practices or the contribution of any specific human childhood vaccines currently in use to the occurrence of IDDM.

In order to test the hypothesis and quantify the risk of IDDM related to immunization practices, studies would need to be designed which have the following characteristics:

1) Sufficient power to detect a difference, if one exists, in both animal and human studies.

2) Adequate controls for both animal and human epidemiologic studies.

3) Appropriate epidemiologic study design, including:

   a) Identification of genetic susceptibility factors;
   b) Collection of individual exposure immunization data;
   c) Collection of information on potential confounders;
   d) Study of populations with significant variations in independent exposure variables; that is, a non-biased group of children not immunized;
   e) Collection of accurate information on dependent outcome variables (i.e., diabetes); and,
   f) Utilization of population-based data for determination of rates.

6. Next Steps

A number of different avenues for exploration were discussed by participants. There was a strong consensus, based on both the animal studies and the ecologic data presented, that additional data should be obtained to further evaluate the validity of the hypothesis. In order to facilitate this process, the following suggestions were made.

1) Encourage Dr. Classen to publish his research in peer-reviewed scientific journals to assure validation and extension of his findings and the widest-possible scientific discussions.

2) Encourage Dr. Classen and others interested in this area to initiate research applications to funding agencies, including the NIH. Of interest would be research to clarify the specific mechanisms of action in animal models.

3) The Public Health Service should collect currently available data sources on immunizations and diabetes for possible secondary evaluation of an association between vaccines and/or immunization practices and IDDM (e.g., Finland, Sweden, Allegheny County Pennsylvania).

4) Monitor current ongoing research seeking to identify "diabetes susceptibility genes" in humans and animals.

Other suggestions for possible avenues of research included:

1) Investigate the possibility of using recent or ongoing studies of twins or of high-risk populations, such as siblings of diabetics, for case-control studies.

2) Encourage the inclusion of data on genetic risk factors in human populations (e.g., MHC markers, pancreatic islet cell antigens, etc.).

3) Obtain information on ongoing diabetes prevention trials which may be relevant.

Summary

The interagency group considered the investigator's hypothesis to be biologically plausible but as yet untested in animals or humans. However, Dr. Classen was encouraged to publish this hypothesis to ensure wide discussion of its merits and appropriate further studies. Various relevant lines of research warrant continued consideration by the NIH, CDC, and FDA. Furthermore, the respective agencies should continue to facilitate coordination and communication between all members of the diverse research community. Finally, this evaluation should be shared with other bodies concerned with vaccine safety, for appropriate consideration and actions.

Some consideration should be given as to how the public might be appropriately informed to appropriately balance known benefits against known risks of immunization, and how to put such as yet unconfirmed hypotheses into perspective.

It was the consensus of the interagency group that, while further research should be encouraged, there is at present no clear evidence that would support a change in current immunization policies and practices.

Other Considerations

Attachments:

a) Bibliography
b) Agenda
c) List of Participants
d) Confidentiality Agreement
e) Confidentiality Release from Dr. Classen
f) Other Communications with Dr. Classen
g) Correspondence with Dr. Makela

References stated in citizen petition response letter dated June 26, 2003, to J. Barthelow Classen, M.D., M.B.A., Classen Immunotherapies, Inc.

Docket No. 02P-0349/CP1