Letter to the editor

Vaccines modulate IDDM

Dear Sir,

Dahlquist and Gothefors [1] recently published Swedish cohort data examining the effect of administering BCG vaccines at birth. Our analysis of their data indicates that immunization at birth caused both a clinically and statistically significant reduction in diabetes mellitus. Our primary concern with the authors' analysis is that it fails to acknowledge that the smallpox vaccine was discontinued in 1976 in Sweden, while the BCG vaccine was discontinued in 1975. The smallpox vaccine was administered in Sweden primarily at 2 months or 9 months of age as compared to the BCG vaccine being administered at birth. Our data (patent application PCT/US 94/08825) from non-obese diabetic (NOD) mice and human ecological studies show that vaccines administered starting after 2 months of life increase the incidence of diabetes thus having the opposite effect of administering vaccines at birth. The Swedish data need to be analysed in a way to compensate for the confounding effect of the smallpox vaccine.

Swedish law until early 1976 required immunization with smallpox vaccine prior to the age of 5 years (2). Unfortunately good records on the acceptance rates in the birth cohorts are not available. Swedish public health officials have indicated that the smallpox vaccine was being increasingly withheld in anticipation of the discontinuation of the law, as it became apparent to physicians that the risk of children developing adverse responses to immunization exceeded the risk of being infected with smallpox. Data from the Netherlands showed this trend clearly. In the Netherlands the smallpox vaccine was given around 9 months of age and was mandatory by age 1 year before the law was repealed on 28 November 1975. The acceptance rates by age 1 year in the Dutch birth cohorts of 1970–1975 were 88 %, 87 %, 82 %, 66 %, 47 %, and 9 % respectively.

Table 1 analyses the differences between the birth cohorts that received BCG, 1973–1974, and those that did not, 1976–1977. Dahlquist and Gothefors' analysis [1] which ignores the effect of the smallpox vaccine is listed as assumption A. Three additional assumptions were included which refrain from comparing the 1973 to the 1977 cohort because the variation in

acceptance rate of the smallpox vaccine between these cohorts is the greatest. The administration of BCG at birth is associated with a drop in the cumulative incidence of diabetes by 32–49 cases of diabetes/100,000 individuals. The most appropriate way to compensate for the confounding effect of the smallpox vaccine would be to compare the 1974 and 1976 cohorts, which show a difference of 48.64 cases/100,000. This data is consistent with ecological data from western Europe looking at published incidence of diabetes in 0–15-year-olds in a group of countries where the BCG vaccine is given at birth (Republic of Ireland, France, Austria, Switzerland, Portugal) and comparing this to the incidence of diabetes in a group of countries which have similar immunization schedules but lacking BCG (Iceland, Netherlands, Spain, Belgium, Luxembourg). The mean annual incidence of diabetes in the two groups was 7.4 cases/100,000 (range 6.8–7.8) and 10.92 cases/100,000 (range 9.8–12.4), respectively. The cumulative effect of administering a BCG vaccine at birth according to this ecological data is 52.8 cases/100,000 (3.52×15 years).

These data are consistent with our findings that administration of a vaccine starting after 2 months of age results in an increased incidence of diabetes. A higher acceptance rate with the smallpox vaccine can explain the higher incidence of diabetes in the 1973 vs 1974 cohorts. While not presenting the data, Dahlquist and Gothefors state that the pertussis vaccine had no effect on the development of diabetes in Sweden. Extrapolation of this report to other pertussis vaccines would be inappropriate since the Swedish pertussis vaccine had little biological activity in regards to protecting against pertussis, efficacy was calculated at 9 %, and lacked an aluminium adjuvant common in many Diphtheria [3, 4] Tetanus Pertussis (DTP) vaccines. Only three doses of the pertussis vaccine were given in Sweden compared to five in the USA. It has been shown that different brands of pertussis vaccines vary in their ability to induce antibodies capable of binding human heat shock proteins. Another reason why Dahlquist's data may differ from our data is that the Swedish control group was likely to have developed pertussis since the disease was endemic in Sweden. We studied the effect of the pertussis vaccine in areas where the incidence of pertussis had been greatly reduced by earlier immunization programmes and the control subjects were protected by herd immunity. Studying the effect of a vaccine on diabetes without ensuring that the control subjects are free of the infection will bias the results, because the natural infection may be as diabetogenic as the vaccine, making the vaccine appear to be safe.

Corresponding author: Dr. J. Barthelow Classen, Classen Immunotherapies, Inc., 6517 Montrose Avenue, Baltimore, MD 21212, USA

Table 1. Analysis of Swedish insulin-dependent diabetes cohort study: the affect of the BCG and smallpox vaccines

Birth cohort	Cases of diabetes	Cohort size	Cumulative incidence/ 100,000	Mean incidence/ 100,000	Difference/ 100,000	P value		
						Normal approximation Poisson distribution		
						1 Tail	2 Tail	
<i>Assumption A: ignore affect of smallpox vaccine</i>								
1973	345	107,582	320.69	311.72	32.22	0.0363	0.0726	
1974	329	108,671	302.75					
1976	342	97,327	351.39	343.94				
1977	320	95,098	336.49					
<i>Assumption B: compare last cohorts</i>								
1974	329	108,671	302.75	302.75	41.19	0.0097	0.0194	
1976	342	97,327	351.39	343.94				
1977	320	95,098	336.49					
<i>Assumption C: compare middle cohorts</i>								
1974	329	108,671	302.75		48.64	0.0028	0.0057	
1976	342	97,327	351.39					
<i>Assumption D: compare first three cohorts</i>								
1973	345	107,582	320.69	311.72	39.67	0.0133	0.0265	
1974	329	108,671	302.75					
1976	342	97,327	351.39	351.39				
Assumptions A–D					Average			
Assumptions B–D					40.43			
					43.17			

This conclusion is misleading and potentially harmful because differences in vaccination scheduling and formulation have been shown to greatly reduce the development of diabetes in animals.

The ability of a vaccine to determine the outcome of 50 cases of insulin-dependent diabetes/100,000 people is clinically very significant, representing 25 % of all cases of insulin-dependent diabetes in many countries. Fifty cases of severe morbidity/100,000 people has caused major changes in immunization practices previously. An international effort has been ongoing for some time to develop an acellular pertussis vaccine because the risk of permanent central nervous system sequelae following the administration of the whole-cell pertussis vaccine is estimated at 0.2 cases/100,000 doses of vaccine administered. The *Haemophilus influenza* vaccine is being promoted for the prevention of *H. meningitis*, a condition that affects 100 in every 100,000 children in the USA. Assuming the *H. influenza* vaccines are 90 % effective and three doses are given, on average each dose prevents 30 cases/100,000 children immunized. We believe the effects of vaccines on diabetes are of tremendous clinical importance and that trials need to be started immediately to address the effect of vaccines on diabe-

tes and other autoimmune diseases. We hope Dahlquist and Gothefors will reanalyse their data by including the 1975 cohort and later cohorts if possible.

Yours sincerely,
J. Barthelow Classen
D. C. Classen

References

1. Dahlquist G, Gothefors L (1995) The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG vaccination. *Diabetologia* 38: 874 (Letter)
2. Lundbeck H (1973) Vaccination programmes in Sweden. *Symp. Series Immunobiol. Standard* 22: 279–286
3. Krantz I, Taranger J, Trollfors B (1989) Estimating incidence of whooping cough over time: a cross sectional recall study of four Swedish birth cohorts. *Int J Epidemiology* 18: 959–963
4. Romanus V, Jonsell R, Berquist S (1987) Pertussis in Sweden after cessation of general immunization in 1979. *Pediatric Infectious Disease J* 6: 364–371

Response from the authors

Dear Sir,

Dr. Classen has reanalysed Swedish data recently presented in a letter to *Diabetologia* [1] where we compared cumulative incidence rates of childhood onset insulin-dependent diabetes mellitus (IDDM) recorded in birth cohorts with a very high compared to a very low coverage of BCG vaccination. He used pairwise Poisson analyses applied to the end-point incidence data. In accordance with our conclusions when analysing mean incidence rates for the two birth cohorts before being compared to the two birth cohorts after the cessation of BCG vaccination in Sweden, he found no statistically significant difference in the two-tailed test (which is the correct test in this case). In addition, Dr. Classen analysed our data by comparing different combinations of birth cohorts except for the years 1977 vs 1973 when the incidence curves were almost identical according to our figures. When performing this kind of multiple analysis a posteriori, it is necessary to adjust *p*-values for multiple comparisons which Dr. Classen did not. Such adjustments would have rendered most of the two-tailed tests statistically non-significant. A more correct analysis, however, to analyse statistically an effect of birth cohorts on these data would be to apply a multivariate Poisson regression analysis considering simultaneously all birth cohorts as independent variable. We have previously published Poisson regression modelling on our Swedish data covering the onset years 1978–1987 and thus including the birth cohorts 1973 through 1977. In this study we found no significant birth cohort effect when taking into account age, sex, calendar year and possible interactions [2]. A similar analysis has been performed and published from Finland [3] with no detectable birth cohort effect despite changes in vaccination programmes during the observation period (1965–1984).

Dr. Classen discusses a possible confounding effect of smallpox vaccine which might counteract the possible protective effect of BCG vaccination. In contrast to most countries Sweden from the early 1960s and onwards vaccinated infants against smallpox during their first 3 months of life usually at 3–7 weeks of age. According to Dr. Classen's theory the gradual discontinuation of an early smallpox vaccination would have increased a possible effect of discontinuing BCG vaccina-

Corresponding author: Dr. G. Dahlquist, Department of Epidemiology, and Public Health, Umeå University, S-90185 Umeå, Sweden

tion rather than the reverse. Dr. Classen also discusses a potential confounding effect of pertussis vaccine which we did not discuss in our letter [1] since pertussis vaccination was stopped in Sweden in 1979. Thus, for the present comparison of birth cohorts given or not given BCG vaccination (1973, 1974 and 1976, 1977) all birth cohorts were given pertussis vaccines of the same kind. Dr. Classen also asks for an analysis of the cumulative incidence of IDDM in the 1975 birth cohort. The reason that we did not include this year was that mandatory BCG vaccination was stopped on 1 April 1975 and during the rest of the year no precise data on the coverage of BCG vaccination were available. Thus, we found it more correct to compare the 2 years immediately before to the 2 years immediately after 1975. Of course we have data on the cumulative incidence rate for this year and in fact this curve would almost exactly cover the curves for 1973 and 1977 as presented in our letter [1].

We do agree with Dr. Classen that for a disease such as diabetes where different environmental factors could either protect or increase the risk it may be difficult in an observational study to exclude that a potential protective BCG effect might be hidden due to the introduction of exposures which might increase the risk. This allows for such exposures being introduced by chance at the same time that BCG vaccination was stopped. We still believe that the Swedish natural experiment does not support the hypothesis that BCG vaccination, at a population basis would prevent a significant number of diabetes cases and the multiple comparisons performed by Dr. Classen on our data a posteriori without correcting for multiple comparison do not change that conclusion.

Yours sincerely,
G. Dahlquist, L. Gotheffors

References

1. Dahlquist G, Gotheffors L (1995) The cumulative incidence of childhood diabetes mellitus in Sweden unaffected by BCG vaccination. *Diabetologia* 38: 874 (Letter)
2. Nyström L, Dahlquist G, Rewers M, Wall S (1990) The Swedish childhood diabetes study. An analysis of the temporal variation in diabetes incidence 1978–1987. *Int J Epidemiology* 19: 141–146
3. Tuomilehto J, Rewers M, Reunanen A, Lounamaa R, Tuomilehto-Wolf E, Åkerblom HK (1991) Increasing trend in type 1 (insulin-dependent) diabetes mellitus in childhood in Finland. *Diabetologia* 34: 282–287

Book review

C. J. Schwartz, G. V. R. Born (eds) *New Horizons in Diabetes Mellitus and Cardiovascular Disease: Current Science Ltd; London; 1995: pp. 224*

Potential buyers/readers should be warned that the editors include microvascular disease under the above heading. Also they have included a number of articles which bear little or no relationship to either, e.g. 'The immune system and diabetes mellitus'; 'Pancreatic transplantation; Implantable insulin pumps, and hybrid artificial pancreas' and 'Alpha-glucosidase inhibition. . .'. There is also an article on 'The impact of diabetes mellitus on public health in Mexico', presumably because the book arose out of a meeting held in Mexico in 1994. Thus, the volume is something of a plum pudding, out of which different readers might pull out different plums (chapters) of interest. For my part I found the chapters dealing

with matters of less general interest to me the more rewarding, because less familiar. Chapters on topics dear to my heart contained no new information or speculation.

Most chapters are reviews of a particular area, e.g. 'plasma lipids in diabetes' and the authors appear to have been encouraged to speculate or hypothesize, to the extent that one, DeFronzo, has written a piece of outright proselytism! If there is one disappointment, it is the inability of some of the researchers in the basic sciences to engage with the clinical and epidemiological nuances of large vessel disease in the main types of diabetes. How, for instance, can hyperglycaemia-induced lipid peroxidation or LDL-glycation possibly account for the fact that in type 2 (non-insulin-dependent) diabetes the risk of macrovascular disease largely precedes the hyperglycaemia (see Stern, Chapter 1)?

I shall find the book useful as a source of reference. I am not sure however, whether I can advise people to buy it.

R. J. Jarrett
London, UK