Apparent Epidemic of Insulin-Dependent Diabetes Mellitus in Midwestern Poland

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SUMMARY

There is no information concerning the risk of developing insulin-dependent diabetes mellitus (IDDM) in eastern Europe. An IDDM registry has been developed in Midwest Poland for 1970–1984. The risk of developing IDDM in Polish children was determined through utilization of the registry. The incidence of IDDM in Polish children was very low compared with other Caucasian populations. There was a major increase in risk beginning in 1982; the incidence almost doubled from 3.5/100,000 in 1970–1981 to 6.6/100,000 in 1982–1984. The pattern of IDDM in the high-risk period was different from that in the low-risk period, with an altered seasonal pattern and unusual increased incidence in younger children. The rapid increase in incidence as well as altered epidemiologic patterns during this period suggest that major alterations of environmental factors were responsible for the change in risk. *Diabetes* 36:106–13, 1987

The country in which a child is born appears to be a major determinant of the risk for developing insulin-dependent diabetes mellitus (IDDM). Differences in risk as high as 35-fold have been noted around the world (1). An understanding of the geographic differences is likely to provide important insight into the etiology of diabetes. A major problem, however, is that incidence of IDDM is known for <5% of the world's population.

There are only 18 registries evaluating geographic patterns of IDDM (1). Most of these registries are in northern Europe and North America. No study has described the epidemiology of type I diabetes in eastern Europe. The incidence data from Poland would be of particular interest, because Poles differ in terms of genetics (e.g., ABO genotypic frequencies) (2), environment, and socioeconomic conditions from populations studied so far. We therefore evaluated the epidemiology of IDDM (age at onset <17 yr) in a defined population in Midwest Poland.

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METHODS

Survey area and population. Midwest Poland (Wielkopolska) is a historically and geographically defined area precisely equivalent to the Province of Poznan in its borders before June 1, 1975. It occupies 27,000 km^2. An administrative reform took place in Poland on June 1, 1975, resulting in a division of the former Province of Poznan into the current one and four other small provinces. The area of Midwest Poland (A) consisting of the present Province of Poznan (B) and the remaining area (C) is depicted in Fig. 1. The number of residents of each region aged 0–16 yr during the study are included in Table 1.

The population of Midwest Poland represents ~8% of the population of Poland. It is ethnically homogenous and appears to be representative of the demographic pattern of the country in terms of age, sex, and degree of urbanization (Table 2). About 46% of population A, 54% of population B, and 39% of population C reside in towns with populations >10,000, described in this study as urban areas. There are no specific geographic barriers isolating Midwest Poland from remaining parts of the country. However, historical and administrative factors have bound this population to Poznan, the only city in the area.

All children <18 yr old in Poland are admitted to a hospital when diabetes is suspected. The public health system in Midwest Poland has 33 children's hospitals and pediatric departments in general hospitals that might see young diabetics. The Institute of Pediatrics (IP), Medical Academy Poznan, is the referral hospital in the region. There are also 9 diabetic and endocrinological pediatric outpatient clinics in the area. Parents can obtain a monetary allowance and social help by registering a diabetic child in any of the institutions.

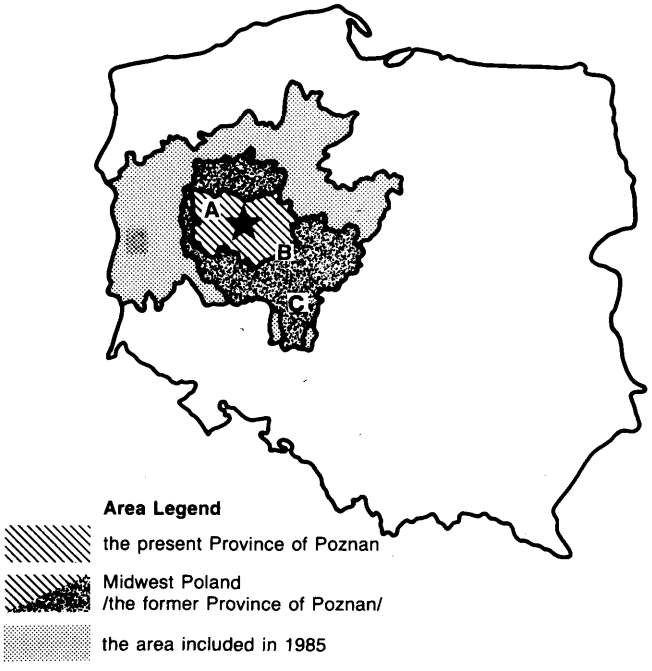

FIG. 1. Survey area according to Midwest Poland Registry. ★, Location of Institute of Pediatrics, Poznan.

Development of the IDDM registry. The IDDM registry is a population-based registry designed to ascertain subjects who fulfill all of the following criteria: *1*) IDDM in accordance with the National Diabetes Data Group recommendations (proneness to ketosis and dependence on insulin at the time of hospital discharge) (3); *2*) age at onset <17 yr; *3*) a Midwest Poland resident at the time of diagnosis; and *4*) onset of diabetes after December 31, 1969, and before January 1, 1985. The registry originates from two sources of data. *1*) The IP Diabetes Roster was initiated in fall of 1979 by retrospective review of records of all patients hospitalized in the inpatient clinics and/or treated in the outpatient clinics at the IP since January 1, 1970. Thereafter, ascertainment has been accomplished by ongoing registration. By September 30, 1985, 354 of the diabetics identified by the IP had met the criteria for entry to the registry. *2*) In 1982 a review of records was conducted at the 32 other hospitals and 8 outpatient clinics in the area. The aim of this review was to ascertain all diabetics aged 0–16 yr at onset and diagnosed after December 31, 1969. The first retrospective review was then followed by annual updating reviews. At all outpatient clinics and hospitals in area B, records were abstracted by us (M.R. or K.D.), whereas at the remaining 21 hospitals situated in area C, records were abstracted by chairmen of the respective pediatric departments. This data source yielded 81 additional cases fulfilling the criteria for entry to the registry. Thus, by these two primary data sources, 435 patients eligible for registration were identified, and >80% of them were seen in the IP.

There were six patients placed on insulin who met criteria 2, 3, and 4 but did not enter the registry. Four were found to have NIDDM of the young (3), and the other two suffered from DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) syndrome. Exclusion of these cases had little effect on the incidence rates.

Potential sources of underascertainment. The review of records at the hospitals located in area B was accurate. In 6 of the 21 hospitals in area C, records before January 1, 1975, were not available. The number of missing cases was estimated by extrapolation of data from the 6 hospitals for the period 1975–1984. The total number of missing cases was seven at most. The percentage of cases reported from the 21 hospitals in area C to the total number of cases registered from 1970 through 1984 was further calculated for the 3-yr intervals. These percentages were 16, 25, 17, 16, and 20; thus, there was little evidence for missing more cases in the earlier years.

It was possible that a diabetic child was diagnosed and followed outside Midwest Poland or that the child was not seen in a hospital or a diabetic clinic. These possibilities, however, were probably minor sources of error, as demonstrated below.

Ascertainment. To determine the completeness of the registry, several procedures were performed to identify IDDM cases from external sources. The first approach was to review files of the Friendly Society for Diabetic Children. This is a help and charity organization completely separate from the primary data sources. In the Friendly Society, 213 cases fulfilled the inclusion criteria. All but one of the eligible cases had been previously identified to the registry. Thus, the degree of completeness could be estimated as approaching 100%.

To evaluate the hypothesis that some adolescents were primarily treated in general departments and were never seen in the pediatric health-care institutions, the records of the Provincial Diabetic Dispensary for Adults were reviewed. The Dispensary had registered 14,621 diabetics by March of 1985; only 19 fulfilled the criteria for entry. Seven of the 19 had not been recorded previously.

Finally, records of 1209 diabetic children aged 0–16 yr treated in the sanatorium Sloneczko, a health resort in Kolobrzeg, during 1970–1984 were reviewed. This sanatorium is situated outside Midwest Poland and admits diabetic chil-

TABLE 1
Number of children aged 0–16 yr who were residents of Midwest Poland (A) and of its constituents, the present Province of Poznan (B) and the remaining area (C), 1970–1984

Year	Midwest Poland	Province of Poznan	Remaining area
1970	694,463	319,000*	375,500*
1971	696,107	310,900*	385,200*
1972	688,127	303,400*	384,700*
1973	681,394	299,100*	382,300*
1974	674,079	295,400*	378,700*
1975	674,200*	295,386	378,800*
1976	677,000*	296,105	380,900*
1977	683,500*	300,776	382,700*
1978	692,000*	307,081	384,900*
1979	705,000*	313,197	391,800*
1980	718,100*	319,058	399,000*
1981	730,800*	325,496	405,300*
1982	745,800*	332,680	413,100*
1983	764,100*	342,823	421,300*
1984	781,300*	351,224	430,100*

*Estimates (±50 people) provided by the Provincial Statistics Bureau in Poznan. Other data taken from official statistical yearbooks of the Province of Poznan that are published annually on the basis of enumeration of the population every 6 mo.

TABLE 2
Comparison of Midwest Poland with total country

	1973		1983	
	Midwest Poland	Poland	Midwest Poland	Poland
Age distribution (yr, %)				
0–4	7.4	7.6	10.5	10.1
5–9	7.5	7.8	9.1	8.7
10–14	8.9	9.1	7.9	8.1
15–19	10.5	10.3	7.1	7.2
Female/male ratio	1.07	1.07	1.05	1.05
Degree of urbanization (% in towns with >10,000 pop.)	40	45	46	50

dren referred by their attending physicians from the whole country. Of the residents of Midwest Poland eligible for registration, 144 were seen at Sloneczko. Only 9 had not been previously registered.

Overall, only 16 patients (4%) were not included in the registry by the primary data sources. Four of the patients originated from population B—2 were treated in the Provincial Diabetic Dispensary and the other 2 were followed by general practitioners and were not hospitalized at diagnosis. The remaining 12 cases came from population C. The 16 cases were included in the study series, which then totaled 451 patients.

Completeness of the primary data sources of 95% (285/299) in earlier years (1970–1981) was slightly lower compared with 1982–1984, when it approached 99% (150/152). Therefore the registry identified at least 95% of the cases.

Virology. In a random sample of 33 children (22%) who developed diabetes in 1982–1984, enterovirus antibody titers were determined. Blood was collected for a maximum of 5 wk after the onset of diabetes. A group-specific complement-fixation test (Enterovirus Complement Fixation Test, Behringwerke AG, Marburg, FRG) was followed by a standard neutralization test for antibodies against Coxsackie B_{1-6} viruses with GMK cells (a cell line derived from African green monkey kidney cells). In both techniques, antibody titer ≥32 was assumed as serological evidence of recent enterovirus infection. All data on reportable viral diseases in population B were obtained from official yearly reports of the Provincial Sanitary and Epidemiology Station in Poznan.

Statistical analyses. Because the number of cases by year was low, the study period was divided into 3-yr intervals to obtain more stable incidence rates. All denominators for incidence calculations by age, sex, and area of residence were provided annually by the Provincial Statistics Bureau in Poznan. For population A (1970–1974) and population B (1975–1984) the exact demographic data were available based on enumeration of the populations performed by local offices every 6 mo. The other data were estimates with an accuracy of ±50 people (Table 3).

The incidence rates were age adjusted, with population A at the end of 1977 as the standard population, and 95% confidence intervals (CI) were calculated (4). Seasonality of onset was assessed through the use of a parametric test (5).

RESULTS

Incidence. Examination of the yearly age-adjusted incidence rates for 3-yr intervals (Table 4) revealed a stable diabetes incidence during 1970–1981 followed by an extremely sharp rise during 1982–1984. When the data were collapsed for the lower-incidence period (1970–1981), the yearly age-adjusted incidence was 3.53/100,000 in contrast with the high-

TABLE 3
Age-adjusted incidence rates ± 95% confidence intervals (CI) for Midwest Poland IDDM cases diagnosed before age 17 yr, 1970–1984

Year	No. male cases (per 100,000)	No. female cases (per 100,000)	Total cases (per 100,000)	Incidence rate	95% CI
1970	11	15	26	3.46	±1.38
1971	12	10	22	3.02	±1.29
1972	4	14	18	2.41	±1.16
1973	6	10	16	2.34	±1.15
1974	14	11	25	3.65	±1.44
1975	18	12	30	4.42	±1.59
1976	14	14	28	4.11	±1.53
1977	12	16	28	4.10	±1.52
1978	19	10	29	4.21	±1.53
1979	15	8	23	3.30	±1.34
1980	17	14	31	4.35	±1.53
1981	10	13	23	3.20	±1.30
1982	22	26	48	6.43	±1.82
1983	26	20	46	6.01	±1.74
1984	31	27	58	7.45	±1.91
Total	231	220	451	4.19	±0.39

TABLE 4
Yearly age-adjusted incidence rates for 3-yr intervals and 95% confidence intervals (CI) for Midwest Poland IDDM cases diagnosed before age 17, 1970–1984

Year	No. of cases	Rate (per 100,000)	95% CI
1970–1972	66	2.97	±0.74
1973–1975	71	3.46	±0.81
1976–1978	85	4.14	±0.88
1979–1981	77	3.61	±0.80
1982–1984	152	6.63	±1.05*
Total	451	4.19	±0.39

*Significantly different from any former period, $P < .05$.

incidence period (6.63/100,000). The variation over time probably was not a chance occurrence, because the CIs (3.13–3.93 and 5.58–7.68, respectively) were not overlapping. Thus, the incidence nearly doubled in the study population during this very short period.

Sex. As shown in Table 5, yearly age-specific and overall age-adjusted incidence rates did not differ significantly between boys and girls in both lower- and higher-incidence periods.

Age at onset. The risk of developing IDDM at a specific age, by period, is depicted in Fig. 2. Boys (Fig. 2*A*) showed two incidence peaks, one at age 6 yr and one at age 13–14 yr. Surprisingly, in boys who developed the disease in 1982–1984, the former peak was even higher than the puberty-related one. However, for girls (Fig. 2*B*) the puberty-related incidence peak was the primary peak. This peak occurred 1 yr earlier in girls diagnosed during 1982–1984 (at age 10–13 yr) compared with those diagnosed in 1970–1981 (at age 11–14 yr).

Of particular importance was that those aged 6 yr were nearly as likely to develop diabetes as those aged 10–14 yr, especially boys (Fig. 3). Interestingly, there was more evidence for this trend during the period of higher risk.

Yearly age-specific incidence rates of IDDM throughout the study were 1–2/100,000 in age group 0–4 yr, 4–5/100,000 in age group 5–9 yr, and 4.5–5.5/100,000 in age group 10–14 yr (Fig. 4). However, two periods of increased incidence occurred, the first during 1975–1978 and the second during 1982–1984. The increased incidence was seen in the 10- to 14-yr age group during 1975–1978, whereas the most marked rise occurred in the youngest children in the period 1982–1984. These changes in incidence were seen in children in the 5- to 9-yr age group 1–2 yr earlier than in teenagers.

Sex and age specificity of IDDM incidence increase. Sex- and age-specific incidence rates in 1982–1984 were generally 1.6–2.2 times higher than those in 1970–1981 (Table 4), but there was a statistically significant 4-fold increase observed in boys aged 0–4 yr. When data for both sexes were collapsed, the increase was significant across the 0–14 yr age range. Thus, both boys and girls aged 0–14 yr were at greater risk for developing IDDM during 1982–1984 in Midwest Poland. However, younger children, especially boys, had the major increase in risk.

Area of residence. Inhabitants of Poznan, the only city in the area, were significantly more diabetes prone than inhabitants of towns with <100,000 population and villages (Table 6). The incidence of IDDM was similar for towns with populations of 50,000–100,000 (4.26/100,000), 10,000–25,000 (3.92/100,000), and <10,000 (3.81/100,000) during the years 1970–1984. Despite major differences in the degree of urbanization between populations B and C, the incidence did not differ significantly.

Seasonality. The month of symptom onset was known in 424 patients. There was a distinct seasonal variation in the monthly incidence of cases ($P < .001$), with the greatest number of cases occurring from September through March in 1970–1981. In 1982, an exaggerated autumn-winter peak was present, which persisted to June of 1983. An atypical seasonal pattern was observed both during 1983, when the nadir occurred in September through November, and during 1984, when the incidence remained fairly stable throughout the year (Fig. 5). The sex difference in the seasonality of onset was only present in children diagnosed during 1982–1984, with a peak incidence in March in boys despite a November peak in girls.

Seroepidemiologic data. The annual incidence of IDDM in population B aged 0–16 yr was compared with the incidence of common viral diseases in the total population B in Fig. 6. Enteroviral meningitis epidemics occurred concurrently in 1982–1984, when the incidence of this type of meningitis in the area exceeded the average for 1975–1981. The incidence of enteroviral meningitis was 6.2, 2.1, and 3.5 times this average for 1982, 1983, and 1984, respectively. Most frequently isolated viruses were ECHO 30 and Coxsackie A_9 (1982); ECHO 6,4 and Coxsackie A_9, B_4, B_3 (1983); and ECHO 30 and Coxsackie B_5 (1984). The 3-mo moving average number of cases of IDDM and enteroviral meningitis in the 0- to 16-yr age group and the total population B, respectively, are shown in Fig. 5. Interestingly, the enteroviral meningitis epidemics regularly preceded periods of increased diabetes incidence by 4–6 mo.

Shortly after presentation, complement-fixing and/or neu-

TABLE 5
Yearly age-specific incidence rates by sex and age for low-incidence and high-incidence periods

Age (yr)	Rates ± 95% confidence intervals (per 100,000)	
	1970–1981	1982–1984
Males		
0–4	1.04 ± 0.54	4.02 ± 1.97*
5–9	4.54 ± 1.21	7.94 ± 2.89
10–14	5.87 ± 1.37	9.19 ± 3.40
15–16	2.51 ± 1.37	5.42 ± 4.34
Age-adjusted rate <17	3.49 ± 0.56	6.67 ± 1.47*
Females		
0–4	1.89 ± 0.76	2.93 ± 1.73
5–9	4.41 ± 1.22	7.32 ± 2.87
10–14	5.70 ± 1.38	10.38 ± 3.71
15–16	1.41 ± 1.04	6.62 ± 4.90
Age-adjusted rate <17	3.57 ± 0.58	6.59 ± 1.51*
Total		
0–4	1.45 ± 0.46	3.49 ± 1.32*
5–9	4.48 ± 0.86	7.64 ± 2.04*
10–14	5.79 ± 0.97	9.77 ± 2.51*
15–16	1.97 ± 0.86	6.00 ± 3.26
Age-adjusted rate <17	3.53 ± 0.40	6.63 ± 1.05*

*Significant increase, $P < .05$.

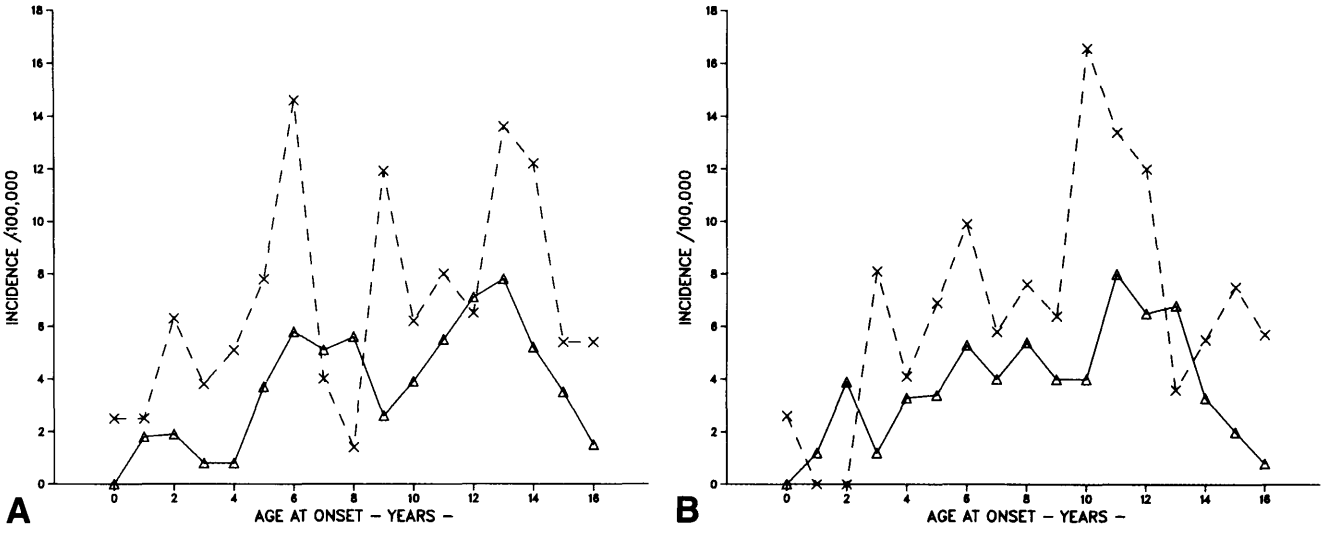

FIG. 2. Age at onset for males (*A*) and females (*B*) in lower-incidence (1970–1981, △) and higher-incidence (1982–1984, X) periods.

tralizing enterovirus antibody titers were elevated in 33% (11/33) of the diabetics diagnosed during 1982–1984 from whom sera were available.

DISCUSSION

Previous reports (6–19) have shown the annual incidence of IDDM to vary from 0.8/100,000 in Japanese aged 0–18 yr (19) to 28.6/100,000 in Finns aged 0–14 yr (6). The few population estimates available have employed differing methodologies, so comparisons are difficult (1).

Completeness of ascertainment has been assessed in some registries and ranged from 65% (15) to 99% (11), as shown in Fig. 7. In our study, validation by external data sources revealed virtually complete ascertainment of cases.

In Europe, 2-fold differences in incidence have been found comparing Finland (6) or Sweden (7) with the other European countries, (8,10–12,15,18). Additionally, an extreme 35-fold difference between Finland and Japan (19) has been recognized (1). Our research is the first with essentially complete ascertainment that demonstrated an area of intermediate risk, although similar incidence has been reported from France (18), Kuwait (16), and Israel (17). These are, however, the lowest reported rates for Caucasian populations; Poland had one-eighth the rate seen in Finland and one-fourth that in the United States. These geographic differences in Caucasians are the largest that have been reported for practically any chronic disease, including cancer, stroke, and coronary heart disease.

It has been suggested that incidence of IDDM in some countries is increasing (10,20,21). Some of the studies have been criticized because of incomplete ascertainment in early years, which may falsely produce an increasing incidence trend. In Midwest Poland there was a doubling of the incidence within 3 yr. No other registry has reported such a marked increase in the incidence over a short period, nor

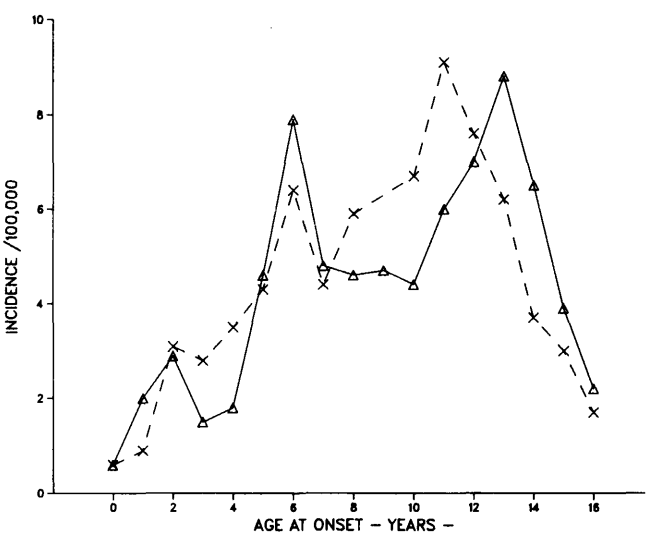

FIG. 3. Age at onset for males (△) and females (X), 1970–1984.

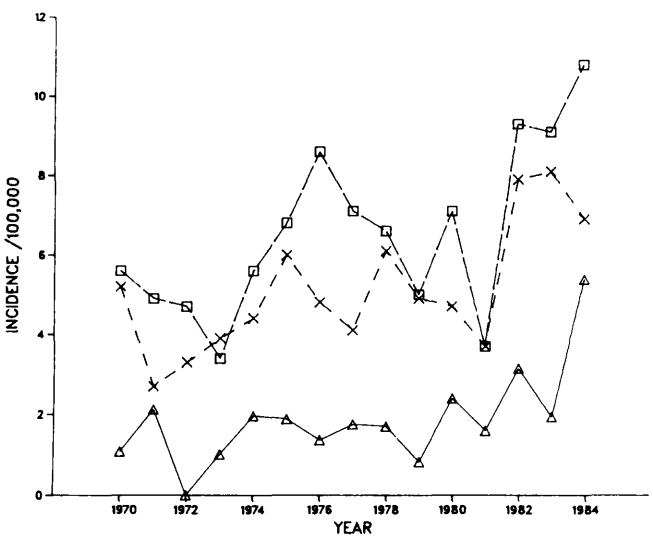

FIG. 4. Yearly age-specific incidence, 1970–1984. Age at onset (yr): △, 0–4; X, 5–9; □, 10–14.

TABLE 6
Incidence (per 100,000) and 95% confidence intervals (CI) for Midwest Poland IDDM cases diagnosed before age 17 by area of residence and period

Area of residence	1970–1981 N	1970–1981 Incidence ±95% CI	1982–1984 N	1982–1984 Incidence ±95% CI	1970–1984 N	1970–1984 Incidence ±95% CI
Poznan*	66	4.94 ± 1.17	38	9.54 ± 3.03	104	6.00 ± 1.15
Towns and villages <100,000 pop.	233	3.34 ± 0.41†	114	6.02 ± 1.11	347	3.91 ± 0.41†

N = number of cases.
*Total population of the city ranged between 472,000 (1970) and 576,000 (1984).
†Significantly different than in the residents of the city of Poznan, $P < .05$.

has any other chronic disease reported such a rapid fluctuation. Such a short-term variation in the incidence clearly indicates that environmental factors play important roles in the pathogenesis of the disease (22,23). Reasons for the epidemic of IDDM are not known. Although enteroviral epidemics preceded periods of increased diabetes incidence by several months, no direct evidence was available for a cause-effect relationship. Nonetheless, this lag time was comparable with duration of the latent period for IDDM estimated from an analysis of diabetic sibships (22).

The proportion of elevated enterovirus-neutralizing antibody titers (33%) in our series was congruent with that observed in newly diagnosed diabetic children, which is presented in a recent review by Barrett-Connor (24). The range of positive Coxsackie titers in newly diagnosed cases has been 14–87% with a median of ~40% (24). Seroepidemiologic evidence for a relationship between enteroviruses in IDDM remains tenuous (22,24) despite conclusions by Barrett-Connor, who indicated that the weight of evidence suggests an association exists. However, Gamble (22) is somewhat more cautious. Note that Coxsackie B virus–specific IgM responses were frequent in diabetic children diagnosed in a part of Sweden during a period of increased IDDM incidence (28). This increased incidence was observed during 1982–1984 not only in Poland and Sweden (28) but also in Finland (29) and Denmark (A. Green, personal communication). If enteroviruses are implicated in the etiology of IDDM, they may have their effect directly through β-cell destruction (22,24). Alternatively, the effect may be indirect through the initiation of immunologic events that lead to β-cell destruction.

Our research suggests the existence of diabetes epidemics superimposed on a basal IDDM incidence, the latter being an age-dependent resultant of a population gene pool and several balanced environmental factors. By balanced environmental factors, we mean the sum of diabetogenic events such as nutrition, chemical toxins, and viruses. If there were several diabetogenic environmental events of a similar magnitude occurring independently, a constant incidence of the disease would be expected. If periodic input from an environmental factor generates the epidemicity of IDDM, a surplus of young patients with short (23) prediabetic periods would be expected during epidemic years rather than cases with long-lasting preclinical autoimmunity. In the population studied the major changes in the incidence occurred in younger children, possibly suggesting a shorter latency in

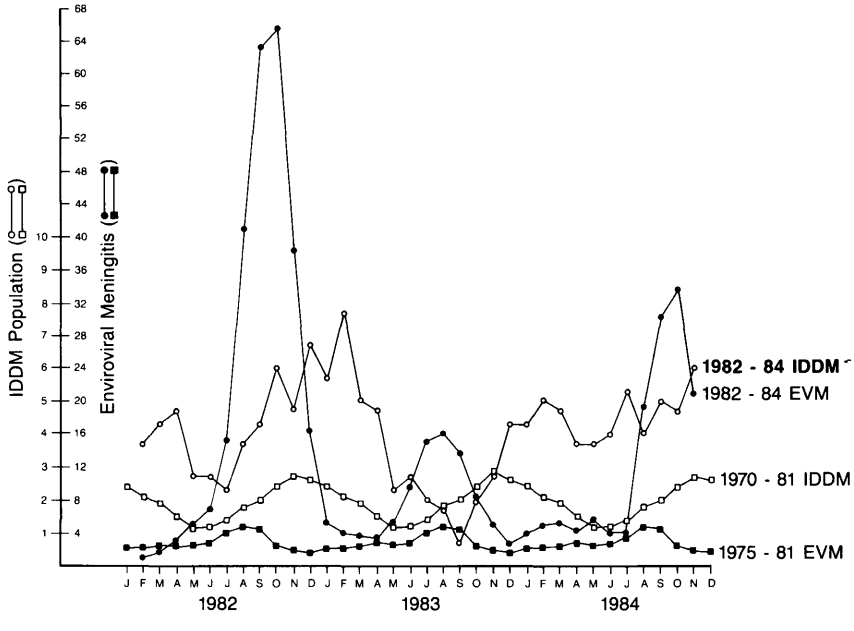

FIG. 5. Seasonal patterns of IDDM and enterovirus meningitis in area B, 1982–1984, compared with 3-mo moving averages in previous years.

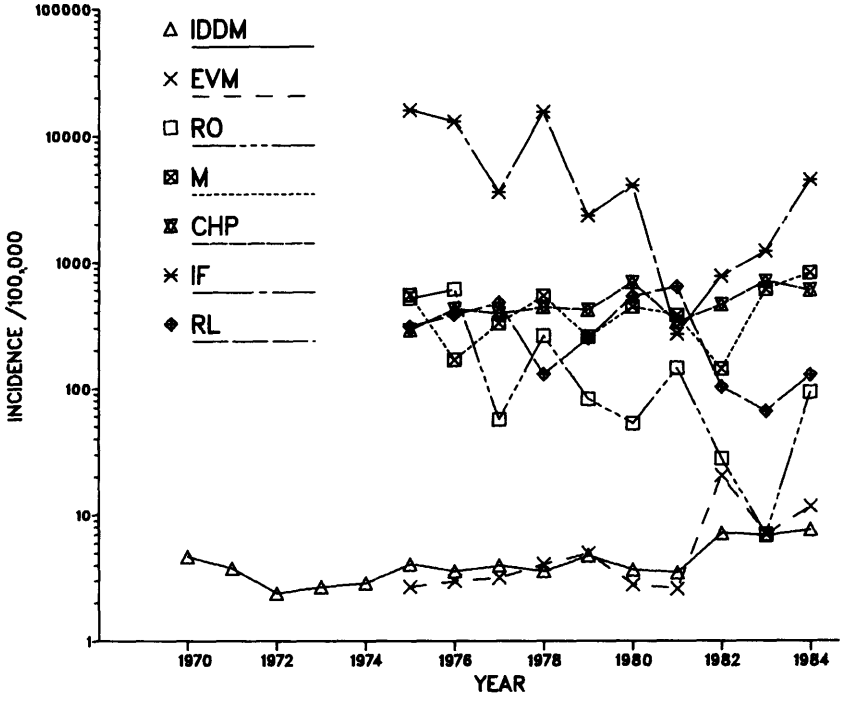

FIG. 6. Annual incidence of IDDM, enteroviral meningitis (EVM), rubeola (RO), mumps (M), chicken pox (CHP), influenza (IF), and rubella (RL) in population B. Data for type I diabetes only for age group 0–16 yr.

those patients. More in-depth analyses of characteristics of diabetes onset and large prospective studies in populations are needed to identify reasons for the epidemic patterns of IDDM.

In our study, analyses were performed to determine whether the periods of lower and higher diabetes incidence differed in terms of the case distribution by sex, area of residence, age at onset, and seasonal trends. No major differences were observed except for the unusual seasonal pattern in 1983 and 1984. Boys aged 0–6 yr were diagnosed most often in the spring during the higher-incidence period of 1982–1984. The seasonal analyses were, however, somewhat hampered by small sample sizes.

An inverse association between incidence of diabetes and population density has been previously demonstrated (10). Nonetheless, no major differences between urban and rural areas were noted by others (11). We found an urban-rural gradient; incidence in a city of population >100,000 was 50% higher than anywhere else in the area. There was no change in the urban-rural gradient during the increased-

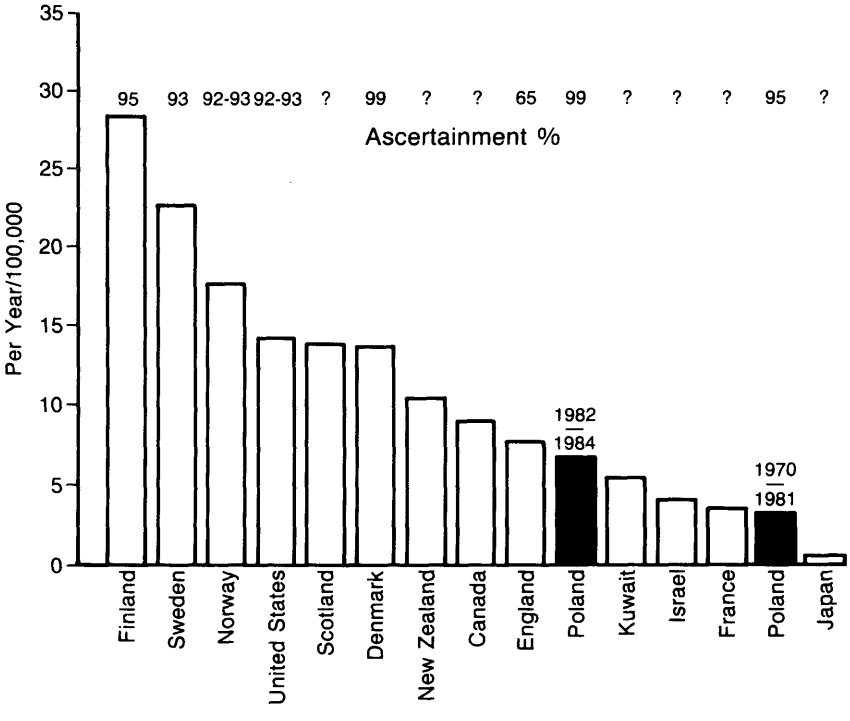

FIG. 7. IDDM incidence across world. Degree of completeness of population estimates is indicated.

incidence period, suggesting that the factors responsible for the urban-rural gradient were not associated with the major increase in IDDM.

The age of onset of diabetes differed markedly in our study from previous findings (6–11,13–15,19). Instead of the gradual increase during early childhood with a peak incidence at ages 11–14 yr and a smaller peak at ages 4–8 yr, the Polish children had two nearly equal peaks, in early childhood and in puberty. The results might be explained by the polio model, where children appear to develop disease earlier in low-risk areas with a lower socioeconomic status (27).

The results thus indicate that in Poland the risk of developing IDDM diabetes is considerably lower than in most other Caucasian populations. Moreover, there appeared to be a rapid increase in the risk of IDDM during a short period, which was probably the result of environmental factors precipitating the disease. The exact source for the increase of IDDM incidence, however, remains to be established.

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