

Perspectives in Diabetes

The Rise of Childhood Type 1 Diabetes in the 20th Century

Edwin A.M. Gale

The incidence of childhood type 1 diabetes increased worldwide in the closing decades of the 20th century, but the origins of this increase are poorly documented. A search through the early literature revealed a number of useful but neglected sources, particularly in Scandinavia. While these do not meet the exacting standards of more recent surveys, tentative conclusions can be drawn concerning long-term changes in the demography of the disease. Childhood type 1 diabetes was rare but well recognized before the introduction of insulin. Low incidence and prevalence rates were recorded in several countries over the period 1920–1950, and one carefully performed study showed no change in childhood incidence over the period 1925–1955. An almost simultaneous upturn was documented in several countries around the mid-century. The overall pattern since then is one of linear increase, with evidence of a plateau in some high-incidence populations and of a catch-up phenomenon in some low-incidence areas. Steep rises in the age-group under 5 years have been recorded recently. The disease process underlying type 1 diabetes has changed over time and continues to evolve. Understanding why and how this produced the pandemic of childhood diabetes would be an important step toward reversing it. *Diabetes* 51:3353–3361, 2002

At the start of the 20th century, childhood diabetes was rare and rapidly fatal. By its end, some 3–4 children per 1,000 in Western countries would require insulin treatment by the age of 20 years, and a steady rise in incidence had been reported from many other parts of the world. This increase has been extensively documented over the past two decades, over which time standard means of data collection have been agreed, central registries have been established, and numerous epidemiological studies have been reported (1,2). In contrast, relatively little is known about the frequency of the disease in the early part of the century. It is easy to forget that by 1980 only a handful of studies were available, the “hot spots” in Finland and Sardinia were unrec-

ognized, and no adequate estimates were available for 90% of the world's population (3).

The changing demography of childhood diabetes has major implications for our understanding of the disease. A rapid change in incidence within a genetically stable population implies that nongenetic factors are active and that the influence of genes is relative to population, time, and place. It suggests that something has changed in the environment our children encounter or in the way they are reared. Understanding this historical change would open the way to rational forms of intervention, which could be introduced at the stage of development when they are most likely to prove effective. Seen from this perspective, the central task of diabetes prevention is to understand a historical trend, and to put it in reverse.

It is therefore important to reach a clear overview of the way the disease has changed over time. Did childhood diabetes really become more common in the 20th century? If so, when and where did the increase begin? Is there an overall pattern to the increase? What inferences can we draw concerning its environmental causes? These considerations prompted a reexamination of the older literature. For all its limitations, this contains all that we will ever know concerning the origins of childhood diabetes, and it seemed helpful to try and put this together. I will argue that a number of valuable and neglected sources exist, and that useful inferences can be drawn about the rise of childhood diabetes over the course of the 20th century.

Childhood diabetes before insulin. Diabetes itself was an uncommon diagnosis in the 19th century. The 1892 edition of *Osler's Principles and Practice of Medicine* devotes 10 pages to diabetes, compared with 65 for tuberculosis, and mentions that only 10 of 35,000 patients treated at Johns Hopkins were affected (4). Massachusetts General Hospital admitted 47,899 patients over the period 1824–1898, of whom 172 (0.004%) were diagnosed with diabetes. Of these, 18 were diagnosed under 20 years of age and 3 under 10 years of age. Until 1851, diagnosis was based on the taste of the urine, which may have curbed screening enthusiasm, although the physician in charge “sometimes called upon the house physician to apply this test,” and self-monitoring was occasionally recommended (5). Improved access to urine tests probably accounts for the increased frequency of diagnosis from 1885 onwards, and by 1923, urinary glucose measurement was available in many U.S. drugstores at a cost of 1¢ per test (6).

In 1913, the Professor of Pediatrics at the Harvard Medical School had personal knowledge of 19 cases of

From the Department of Diabetes and Metabolism, Division of Medicine, University of Bristol, Bristol, U.K.

Address correspondence and reprint requests to Edwin A.M. Gale, FRCP, Department of Diabetes and Metabolism, Medical School Unit, Southmead Hospital, Bristol BS10 5NB, U.K. E-mail: edwin.gale@bristol.ac.uk

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childhood diabetes. Despite this limited experience, John Lovett Morse, who wrote the first paper on childhood diabetes in English, was able to draw on a fairly extensive literature in German and French dating back to 1878, and his paper provides a helpful overview of the existing world literature. Morse assembled a total of 989 cases from clinical reports and mortality data. Of these, 162 presented before 5 years of age, 302 from 5–9 years of age, and 525 over 10 years of age (7).

Blood glucose remained difficult to measure and did not become a routine part of the work-up of Joslin's patients until 1915 (8). The introduction of the Folin-Wu method in 1920 enabled blood glucose to be measured on a finger-stick sample (9,10). Even then, blood had to be taken adjacent to the laboratory, since preservatives were not introduced until 1931 (11). Despite reliance on urine tests, the near uniform fatality of childhood-onset cases in series from the preinsulin era testifies that there was little confusion with renal glycosuria. Morse cites Carl von Noorden, the great European authority of the time, who said that "with few exceptions diabetes in childhood knows no cure, no matter how mild it may appear in the beginning, nor how gradual its development in the first months or even years." His experience was that children under age 7 years with the severe form of the disease survived 18 months to 2 years, while those with "mild glycosuria" lived 3–6 years, and that "the usual statement that the younger the child the shorter the course is true" (7). Joslin reported in 1923 that 86% of children presenting under age 16 years had previously died in ketoacidosis (6).

There is of course no way of knowing how many cases of diabetes had been missed, but one small clue suggests that we should not underestimate the diagnostic skills of our predecessors. A strong family history was already recognized as a favorable prognostic marker, and Joslin remarked that "all cases which have come to my attention of youthful patients with diabetes living for very long periods of time have been hereditary" (6). If Joslin was familiar with maturity-onset diabetes of the young, as Tattersall believed him to be (12), this could provide useful internal evidence that type 1 diabetes was truly rare.

How common was childhood diabetes before insulin?

In the absence of epidemiological studies, the only sources available to us are clinic series and mortality statistics. The reported death rate from diabetes for children under 15 years of age was 1.3/100,000/year in the U.S. in 1890, as compared with 3.1/100,000/year in 1920 (6). These results are comparable with those for Denmark, with estimates rounded to 2/100,000/year under age 15 years for 1905–1909 and 4/100,000/year for 1915–1919 (13). Data for Norway can be derived from Gundersen (14) and suggest an incidence rising from 2 to 7/100,000/year over the period 1900–1920.

Clinic series are less helpful, since they typically describe the percentage of referrals in each age category. By 1922, Joslin was able to report that 366 (14%) patients in his personal series had been diagnosed in the first two decades of life, with 149 presenting in the first decade. He also comments that the proportion of children in his caseload was rising, although this may have been due to his special interest in the condition, which was readily

passed on by other physicians because of the "general feeling of the hopelessness of the disease in children." Other series quoted by Joslin give a much lower proportion of children under the age of 10 years, ranging from 0.5 to 1.4% of the total, and one Japanese series of 680 patients contained no children at all. His view was that "the increase in the percentage of cases in the first decade as compared with a generation ago speaks emphatically in favor of the better diagnostic methods of today rather than of actual increase in the frequency of the disease" (6), and at this remove of time we must rest content with this conclusion.

We may therefore conclude from this limited evidence that childhood diabetes terminating in ketoacidosis was uncommon but well recognized in the decades before insulin, that mortality statistics show an increasing incidence over the first two decades of the century, probably due to greater awareness of the condition, and that mortality statistics from the U.S., Denmark, and Norway suggest an incidence range of 2–7/100,000/year under age 15 years for the period 1900–1920.

Incidence between 1920 and 1950. Insulin changed childhood diabetes from a rare fatal disease to a condition in which prolonged survival was possible, and the medal that the Joslin Clinic minted to commemorate this transformation emphasizes the prevailing uncertainty as to the future of children whose lives depended on insulin. It depicts a small boy and his dog in an open boat with the sun rising beside them, and is entitled "explorers of uncharted seas." Meanwhile, the period between the wars saw great advances in public health and the collection of social statistics. A landmark was the U.S. National Health Survey of 1935–1936. This was a doorstep sampling survey of 2.5 million people living in 700,000 households in 83 cities. The reported rate of diabetes for the age-group under 15 years was 0.35/1,000 for boys and 0.41/1,000 for girls (15). In contrast, National Health Interview Surveys undertaken later in the century gave prevalence figures of 1.30 and 1.60/1,000 under age 16 years for 1973 and 1976, respectively, with rates (this time up to age 18 years) of 1.30 for both sexes for 1979–1981 and 1.20 for 1989–1992 (16).

The main source of incidence and prevalence data for this period is Scandinavia. A Norwegian government survey in 1934, based on a questionnaire to doctors, identified a national total of 253 children under the age of 15 years, giving a minimum prevalence of 0.28/1,000, but ascertainment was undoubtedly incomplete (17). More detailed information about the incidence of diabetes in Norway is available from two retrospective surveys in Oslo and Bergen. Westlund examined all cases of diabetes admitted to hospital in Oslo over the period 1925–1954. His main aim was to document the effect of food rationing during World War II on the incidence of diabetes (Fig. 1), and to do this he needed to establish accurate baseline rates both before and after the war. The assumption was that all cases would be admitted to hospital at diagnosis, and the aim was therefore to identify all first admissions. A total of 4,251 individual patients were identified, and the incidence of diabetes under age 30 years remained relatively constant over the period 1925–1954; the average incidence

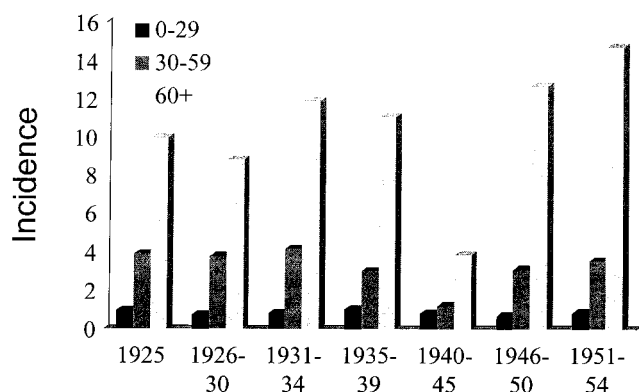


FIG. 1. Incidence of diabetes in Oslo, 1925–1954, per 100,000/year. The rate of onset under the age of 30 years was constant, whereas incidence rates fell rapidly in older age-groups as a consequence of wartime rationing. Redrawn from data in Westlund (18).

under the age of 15 years can be estimated as 4.1/100,000/year from the data provided (18).

Meanwhile, an independent Norwegian survey had been conducted in Bergen. This was then a town of some 100,000 inhabitants with one hospital. Per Hanssen made a heroic effort to identify all cases of the disease over the period 1925–1941. Cases were identified by a retrospective search of hospital admissions from 1910 to 1941 and by examination of a city register established in 1940–1941 to ensure that patients with diabetes received food supplements under wartime conditions. In addition to this, a questionnaire was sent to all doctors in the city asking them to register all cases of diabetes prospectively over a 6-month period beginning March 1941, and death certificates and postmortem reports were also checked for the whole period. This exhaustive search identified 402 patients with diabetes alive in 1941, 46% of whom were receiving insulin and a further 392 who had died over the preceding 16 years. The author concluded that the total prevalence of diabetes had doubled over the 15-year period, but this increase was confined to the older age-groups and, as in the U.S. (19), was attributed to the increasing age of the population. A total of 40 individuals developed diabetes under the age of 20 years, equivalent to an incidence rate (based on the 1934 census) of 7.9/100,000/year for this age-group over the period 1925–1939 (17). Although the confidence intervals around such an estimate will be wide, the overall agreement with the Oslo data is good.

The war also had an indirect impact on Sweden, where, based on ration cards issued in 1942, the State Institute of Human Genetics and Race Biology collected national data on the number of people with diabetes in the population. Ascertainment was checked in Stockholm by a survey of patients receiving hospital treatment over the period 1938–1942, and this identified an additional 14% of patients not receiving ration cards. At that time, the city contained 72 diabetic children under 15 years of age, giving a prevalence of just under 1/1,000 (20). The Pediatric Clinic in Vasterbotten in Northern Sweden retrospectively reported a wartime incidence of 10.2/100,000/year. This estimate is the highest available for the period, and it is therefore of interest that Vasterbotten remained a high

incidence area, with rates rising to 37.9/100,000/year by 1973–1977 (21).

Finland had a wartime registry of patients receiving insulin or diet supplements, but this was frustratingly incomplete. A national population of 3.64 million was reported to contain 250 individuals under 20 years of age with diabetes, equivalent to a prevalence of 0.2/1,000 for this age-group (22). The most striking feature of childhood diabetes was its high mortality, reportedly running at ~70 deaths per year. An informal postwar survey in 1953 used a questionnaire addressed to physicians to identify 663 children born since 1939 who had developed diabetes under the age of 14 years, and a further 169 who had died with a diagnosis of diabetes. The mortality rate is exaggerated by under-ascertainment of living cases, but is clearly very high. A more complete subanalysis based on case records from the Children's Clinic in Helsinki showed that a total of 223 children born after 1939 had attended; of these children, 28 (12.6%) had died by 1953. It should not be forgotten that Finland was embroiled in a desperate struggle for survival during the war years, and living conditions must have been very hard. The author estimated the annual incidence of new cases in 1953 at 12.5/100,000/year (23), around one-third of the number affected by the end of the century.

The Finnish experience suggests that consideration must be given to the two main potential reasons for under-ascertainment of childhood-onset diabetes. Contemporary prevalence estimates will be spuriously low where the mortality of childhood diabetes was high, and death with undiagnosed diabetes will lower both incidence and prevalence estimates. The Industrial Department of the Metropolitan Life Insurance Company collected data concerning mortality rates in families of wage-earners in the U.S. and Canada who participated in their insurance scheme (24). This showed that diabetes mortality in individuals under the age of 20 years fell from 4.1/100,000/year in 1916–1920 to 1.1/100,000/year in 1931–1935, and remained steady until 1945, by which time Joslin was able to comment that “those with onset in childhood have almost ceased to die of diabetes until the duration of the disease has passed twenty years” (25). Westlund found that only eight children with diabetes had died under 20 years of age in Oslo over the period 1925–1961 (26). This may not be the whole story. The Steno Memorial Hospital in Denmark followed 307 patients diagnosed under the age of 31 years before 1933. Some 3–4% of patients died within 15 years of diagnosis, but almost all of these had presented before age 10 years, the 10-year mortality was 20% in those who lived in country areas, and failure to return for follow-up after the initial visit carried a particularly poor prognosis (27). Access to medical care was therefore a major factor in survival, and children with diabetes must have fared badly in rural districts or during periods of hardship or social disruption. Joslin remarked in 1927 that “it is the uneducated, untrained, uncared for child in a family with limited resources who is lost” (28), and this chilling comment also applies at the start of the 21st century. A diagnosis of childhood diabetes still carries a death sentence in parts of sub-Saharan Africa.

It is of course likely that some children died with undiagnosed diabetes and did not feature in the incidence

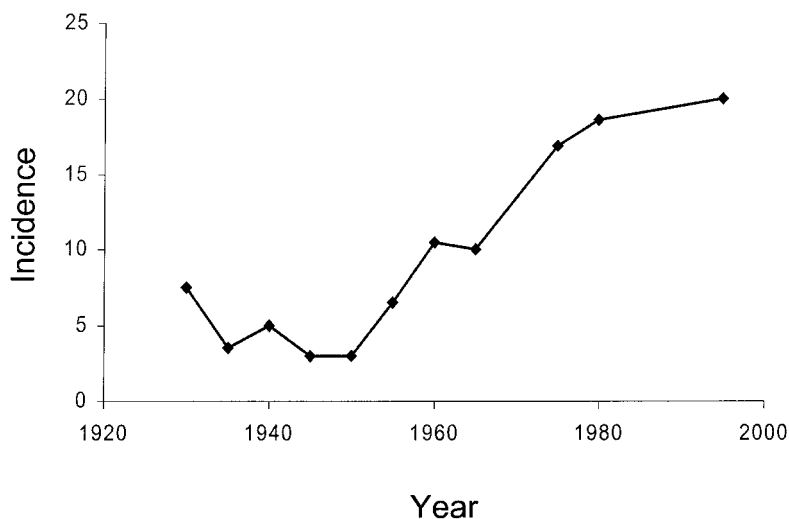


FIG. 2. Incidence of diabetes in children under age 10 years in Norway, 1925–1995. Data from refs. 18,33–36.

or mortality data. Childhood diabetes is still an uncommon condition, and in more recent times, a general practitioner in the U.K. might expect to diagnose three children in a lifetime of practice. Consequently, the diagnosis is often missed at first presentation, especially in the younger age-groups (29). Early-onset diabetes is nonetheless a progressive and ultimately fatal condition that will eventually force itself upon medical attention. Clinical suspicion has always been the mainstay of diagnosis, even in the AutoAnalyzer era, and we should not assume that earlier generations of physicians, who relied almost totally on their clinical skills, were less gifted or motivated than ourselves. Diabetic ketoacidosis can be diagnosed at a glance, or from the other side of the bed curtain by those with the right olfactory apparatus, confirmation by urine testing was simple and sufficient in symptomatic individuals, and mortality in children was low (30). It was also a diagnosis worth making. Readers of Lewis Thomas (31) will recall that few effective therapies existed before the introduction of the sulfonamides in 1937. These he lists: liver for pernicious anaemia, thyroid extract for hypothyroidism, vitamin B for pellagra, vaccination or injection of toxin for diphtheria, and not very much else. Insulin was almost the only therapy that could restore a moribund child to healthy normality, thus placing a high premium on successful diagnosis. The number of missed cases will never be known, but in city areas with good access to medical facilities, the great majority were probably diagnosed correctly.

In summary, studies of the incidence and prevalence of childhood diabetes before 1950 underestimate the true frequency of the condition and must be viewed with caution. Access to medical support was variable, but excellent results were achieved at specialized centers and in regions with good organization of health care. The outlook was not as good elsewhere, and prevalence figures will underestimate the true frequency of the condition. It can however be noted that contemporary estimates from Western countries were generally in good agreement with one another and varied little over the period. The most reliable longitudinal study from Oslo applied the same means of ascertainment over 30 years leading up to 1955 and found little variation in the younger age-groups (18).

We therefore need to look later in the century for a major increase in the incidence of childhood diabetes.

When did the increase begin? A steep rise in the incidence of childhood diabetes undoubtedly occurred in many populations over the latter part of the century. Backwards extrapolation of these trends often implies a zero incidence earlier in the century, which was clearly not the case. We therefore need to look for an upward inflection. The only previous attempt to track the incidence of type 1 diabetes across a century was made by Krolewski et al. (32), who concluded that a sharp upturn in the incidence of insulin-dependent diabetes had occurred in the U.S. around the mid-century. In Europe, the best evidence once again comes from Norway. The 1925–1954 Oslo survey was later extended to 1964, and an additional 3,368 patients were identified; 97% of the records were traced. After exclusion of nonresidents and patients diagnosed outside the city, this number fell to 2,859; 140 were aged under 20 years at diagnosis, and 90–95% of these were started at once on insulin. The incidence increased from a stable baseline of 4.1 cases/100,000/year to a new level of 8.4/100,000/year over the period 1955–1964 (33). This study was later reviewed by Joner and Søvik (34) in the light of their national survey of incidence from 1973 to 1977, and was considered sufficiently reliable to support their own conclusion that a secular change in incidence had taken place over the intervening period. Sequential studies have shown that the incidence of childhood diabetes in Norway increased until the last decade of the century (34–36), giving an S-shaped incidence curve over the 75 years for which information is available (Fig. 2).

Conscript studies lend support to the concept of an upturn in incidence around the middle of the last century. The first national conscript study was performed in Denmark, a country in which, since 1849, all males must appear before a conscript board from age 18 years. Diabetes certified by a physician automatically excludes military service, and the study not only tracked the medical records of almost all cases so recorded to verify insulin treatment, but also combed death certificates for individuals who had died before reaching that age. Successive male birth cohorts over the period 1949–1964 contained 638,718 individuals, of whom 1,652 appeared to have

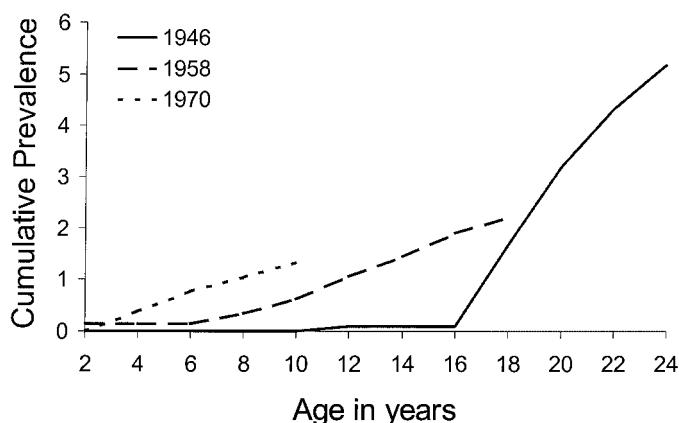


FIG. 3. Cumulative incidence of diabetes from three U.K. birth cohorts. A progressive left shift in age of onset of the disease is shown. Redrawn from data in Kurtz et al. (44).

typical insulin-dependent diabetes by age 18 years, while another 30 had died with diabetes before that age. The cumulative rate of development of type 1 diabetes by age 20 years was 2.37/1,000 for the first eight birth cohorts and 2.90/1,000 for the last eight. Regression analysis demonstrated that the incidence of diabetes doubled over a 30-year period from the 1950s, apparently reaching a plateau in the late 1970s (37). Therefore Denmark, like Norway, showed an upward inflection in incidence around the mid-century and an S-shaped incidence curve over its latter decades.

Three more conscript studies deserve mention. Males in Sardinia are called to medical examination before military service at the age of 20 years, and the prevalence of diabetes at that age has therefore been recorded for successive birth cohorts dating back to 1936. Diabetes was very rare in males born before 1945, but has risen in more or less linear fashion from the 1960s (38), although there are more recent indications of a plateau (2). A conscript study in Switzerland examined files from 514,747 males from birth-year cohorts covering four periods between 1948 and 1972. The number of men with insulin-dependent diabetes by age 19 years rose by 62% over this interval (39). A similar study in the Netherlands reported an average 4.4% increase in risk of type 1 diabetes for each annual cohort of 18-year-old conscripts over the period 1960–1970 (40).

From 1965, drug treatment for diabetes has been free in Finland, provided that a certificate is submitted by a doctor. This has meant almost 100% ascertainment. Retrospective analysis of the period 1965–1984 showed a predominantly linear trend, equivalent to a 2.4% year-on-year increase (41). Finland currently appears to differ from other Scandinavian countries and Sardinia in showing a continued linear increase in incidence (2).

In the U.K., childhood diabetes was considered so uncommon and demanding that ~10% of children were admitted to residential hostels in the 1940s. A 1949 survey of school medical officers identified 183 cases of diabetes, implying that 1 child in 4,300 under age 15 years was affected, although this was undoubtedly an underestimate (42). Three national birth cohort studies initiated in 1946, 1958, and 1970 provide more reliable information. In the first cohort, only 1 child in 5,362 developed diabetes by age

11 years, as compared with 10/15,500 by age 11 years in 1958 and 18/13,823 by age 10 years in 1970. The corresponding prevalence rose linearly from 0.1 to 0.6 to 1.3/1,000, respectively ($P < 0.05$) (Fig. 3). Although small, these prospective studies are of interest because all deaths under 11 years of age were scrutinized with particular care, and none were attributed to diabetes (43,44).

The best U.S. data for this period come from the Erie County Study. This was set up in 1962 to examine the incidence and prevalence of chronic diseases of childhood, and it involved identification of every affected child by retrospective examination of all case notes from hospitals serving a population of about 1 million over the period 1946–1961. Diabetes was estimated to affect 1/1,666 white children under age 16 years, with a total of 352 new cases over the period and five deaths. The incidence rose from 6.6/100,000/year in 1950–1952 to 7.4 in 1953–1955, 10.6 in 1956–1958, and 11.3 in 1959–1961 (45). A later analysis linking the Erie County data with a school survey in Michigan postulated a rising incidence of diabetes in the U.S. (46). There is some doubt as to the quality of ascertainment in these studies, but adequately powered population-based studies are lacking for the period. For example, a study was performed in Rochester for the period 1945–1969, but the town contained only 26,500 inhabitants at the start of this survey (47). The first diabetes registry was established in Allegheny County from 1965 onwards, with reported incidence rates ranging from 10.1 to 16.0/100,000/year according to sex and ethnic background. Although no change in incidence was reported over the period 1965–1976, the sample size was relatively small for time trend analysis, especially when subgroup analysis was undertaken (48).

This analysis therefore supports Krolewski in suggesting that the incidence of childhood diabetes was relatively low and stable until the mid-century, and showed an upturn from the 1950s onwards (32). This appears to have developed around the same time in environments ranging from Northern Europe to the U.S. and Sardinia.

Incidence trends over the past 40 years. More rigorous epidemiological methods came into use in the second half of the century, but reliable data remain scanty for the period 1950–1975, and the rising incidence of the condition was not widely recognized until the 1980s (49). Several of the more useful earlier sources have already been considered. A systematic review considered incidence trends spanning the period 1960–1996 and noted that a significant rise in incidence was recorded for 24 of 37 longitudinal studies from 27 countries, with a similar trend in a further 12; only 1 reported a small decline. The average annual increase was 3.0% (95% CI 2.6–3.3), with a greater relative increase in lower-incidence countries. Extrapolation of these trends indicated that the global incidence of type 1 diabetes would increase by 40% over the period 1998–2010 (1). In line with this, a large European survey for the period 1989–1998 showed a 3.2% (95% CI 2.7–3.7) annual increase, most marked in some Central and Eastern European countries (2). In absolute terms, the increase is similar in the age bands 0–4, 5–9, and 10–14 years, but the most rapid increase relative to baseline was seen in the youngest age-group (50,51). The U.S. stood apart from other parts of the world in reporting a stable

incidence of childhood type 1 diabetes over much of this period (52), but a rapid increase was noted in the Allegheny County population over the period 1985–1989, with an overall increase of 83% for the period 1966–1989. The most rapid increase was noted in nonwhite males and in the 0–4 year age-group (53). The existing capability to monitor the frequency of this condition in the U.S. is limited (52), and the observation that Canada has the third highest rate in the world (54) suggests that North America has not escaped the pandemic of childhood type 1 diabetes.

In summary, the rise in childhood diabetes can be traced back to the middle of the 20th century. Although it is important not to overinterpret limited data, there is some suggestion that a rising incidence first became apparent in those countries with the highest current rates of diabetes and reached lower incidence populations in a later, staggered fashion. Consistent with this, the relative rate of increase is inversely proportional to current incidence (1), suggesting a catch-up phenomenon. The overall impression from combined analysis of many studies is a linear increase, but a saw-tooth pattern often makes interpretation of shorter-term changes uncertain in individual populations. Tuomilehto et al. (41) pointed out that an incidence of 200–300 new cases per year is required to detect an annual increase of 2% with any degree of reliability. It is therefore of note that Norway, with a population large enough to meet this qualification, has shown no increase at all over the past decade (36). A similar effect has recently been reported from other high-incidence areas, Finland excepted (2). It would be premature to conclude that this represents a genuine plateau, but it seems likely that a new equilibrium will eventually be established in most populations. In the interim, a continued linear increase seems inevitable in most parts of the world.

DISCUSSION

A global survey published at the end of the century suggested that no population is exempt from childhood type 1 diabetes, but also documented a >350-fold difference in incidence rates (54). This overview has focused on Europe and North America, since information for the first half of the century could not be obtained from other parts of the world. The best evidence available suggests that childhood diabetes showed a stable and relatively low incidence over the first half of the 20th century, followed by a clear increase that began at some time around or soon after the middle of the century. This increase occurred around the same time in Scandinavia, the U.K., the U.S., and Sardinia but may have occurred later in other parts of the world. The majority of populations studied in the second half of the century have shown a rising incidence until the 1980s. Within Europe, a continued linear increase beyond this point has been reported from Finland, but other high incidence zones appear to have reached a plateau over the past two decades. The overall trend in Europe is however upwards, with the most rapid rate of increase contributed by former communist bloc countries in Central and Eastern Europe (55). Meanwhile, high incidence rates are now reported from a number of non-European populations—Kuwait has the seventh highest rate in the world (54)—suggesting that genetic suscepti-

bility may not vary as widely among ethnic groups as was previously believed.

The aim of this review has been to identify long-term changes in the behavior of this evolving disease rather than try to explain why they occurred. Some implications of this analysis do however deserve brief consideration. To begin with, a rising incidence in a stable population implies an etiological role for environmental factors. Since immune responses heralding later development of type 1 diabetes frequently appear within the first few years of life, the relevant environmental exposures are likely to be encountered very early in development. Since there is also good evidence for a long silent gap between initial exposure and onset of disease, factors modulating the rate at which the disease process unfolds may also be relevant. Genetic susceptibility will determine the probability of an unwanted outcome to the initial exposure, but additional environmental factors, possibly interacting with other genetic influences, may well modulate the rate of progression. For example, rapid growth in early childhood increases the risk of diabetes (56), possibly by increasing the work-load on β -cells, and children grow considerably faster than they did a century ago. In 1970, Swedish boys were (depending on social class) 14.5–16.8 cm taller by age 15 years than in 1883 (57). Early growth velocity and obesity may however be more important than final attained height in predisposing to diabetes (56). For whatever reason, an extremely rapid increase in the age-group under 5 years has been documented in some populations over the past 10–20 years (50,51,53,58).

Many attempts have been made to explain the rise of childhood type 1 diabetes over the past 30 years. A common starting point has been the assumption that something new has entered the childhood environment, and early nutrition or infection have seemed the most promising areas of enquiry. The leading hypotheses have related to early exposure to cow's milk (59) or to enterovirus infection (60). Despite a wealth of indirect evidence, we still lack proof that either plays a major role in causation of the disease, and it has been plausibly argued that both exert their influence via modulation of the developing mucosal immune system (59). Breast-feeding patterns do not reflect changes in the incidence of childhood diabetes. Two of three American women breast-fed in 1911–1955, falling to 22% in 1972, and rising back to 60% in the 1980s and 1990s (61). There is little to suggest that this is in any way related to changes in the incidence of childhood diabetes. Equally, hypotheses based around enteroviral infection must take account of the fact that the proportion of women not exposed during pregnancy is increasing, and that infection in early childhood has become less common in the course of the century (62). These considerations do not exclude arguments based on changing antigenicity of feeds or viruses, or timing of exposure to them, but there is at present little evidence that antigens novel to the 20th century could explain the long-term trends described here.

The alternative possibility is that protective factors have been lost from the childhood environment (63). The hygiene hypothesis, initially developed to explain the parallel rise of asthma and allergy, argues that exposure to a range of infective agents in early childhood is necessary for

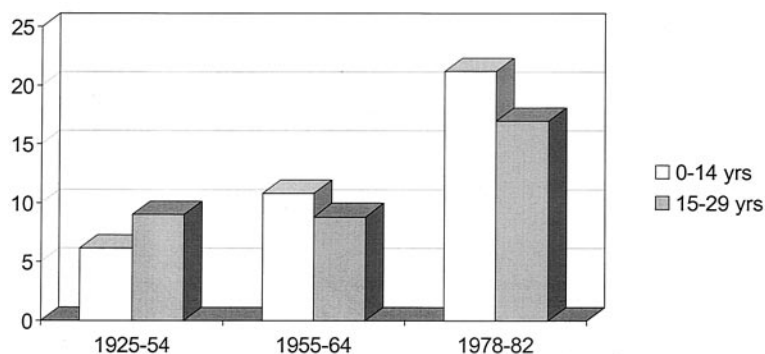


FIG. 4. Incidence of diabetes in the 0–14 and 15–29 year age-groups in Norway at different time points in the 20th century. Data from refs. 18,33,35,76.

successful maturation of the neonatal immune repertoire. In the absence of such exposure, a robust Th1 repertoire does not develop and potentially harmful Th2 patterns of response will persist in genetically susceptible individuals (64). Although this concept may prove unduly simplistic, lack of early stimulation could give rise to a failure of early immune regulation that might, according to genetic susceptibility, permit patterns of response predisposing to autoimmunity or allergy to develop at opposite ends of the Th1/Th2 spectrum (65). A number of recent reviews have attempted to link the rise of asthma and atopy to that of autoimmune disorders such as type 1 diabetes (65,66), and it is therefore of interest that an exhaustive survey of the early asthma literature also concluded that Scandinavia, Britain, the U.S., and Australasia showed an increase beginning in the early 1950s (67). Epidemiological evidence for the hygiene hypothesis is inconsistent for childhood type 1 diabetes, but it is notorious that the NOD mouse is less likely to develop diabetes in the presence of pinworms and other infections (68). Pinworm infestation was common in the childhood populations of Europe and North America around the mid-century, and this potentially protective exposure has largely been lost since that time (69).

Where is the increase coming from? An example may help to illustrate this point. Type 2 diabetes has appeared earlier in successive generations and now presents in teenagers. Although this trend mimics genetic anticipation, it is environmentally mediated, since increasing obesity within the population as a whole means that genetically susceptible individuals develop the disease earlier than they would in a less permissive environment. Has a comparable process, possibly with quite unrelated causes, occurred in type 1 diabetes? This view was first proposed by Kurtz et al. (44) in 1988, based upon the data presented in Fig. 3. An updated version of their proposal, which I refer to as the “spring harvest hypothesis,” would go as follows: we may assume that the number of children with genetic predisposition to immune-mediated β -cell injury has not changed to any great extent over time. A rise in childhood type 1 diabetes might then reflect increased exposure to isolated initiating factors in early childhood. Alternatively, the initial exposure might be widespread or even ubiquitous, resulting in a relatively common but indolent immune-mediated process. A more permissive environment would facilitate this disease process, thus producing a left shift in age at onset. Assuming a finite pool of susceptible individuals within the population, an increase in the younger age-group should be balanced by a

reduction in the older age-group, and there is some evidence that this has occurred. Sequential Norwegian data, presented in Fig. 4, show that the increase in the 0–14 year age-group has overtaken that in the 15–29 year age-group. Recent comparison of incidence trends in the 0–14 and 15–39 year age-groups in Belgium (1989–2000) and in the 0–14 and 15–34 year age-groups in Sweden (1983–1998) has shown that in both cases, the increase in the younger age-group has been balanced by a fall in the older age-group, with no overall increase in incidence (70,71). The incidence of type 1 diabetes in later life remains conjectural, but a Danish study has estimated the lifetime risk as 1.5% (72). Given a susceptible subpopulation of this size, a small shift in the median age at onset could easily manifest as a major change in incidence in the younger age-groups. A further expectation of the spring harvest hypothesis can be tested. There is a strong inverse association between age at diagnosis and prevalence of HLA alleles conferring susceptibility to type 1 diabetes (73). A more permissive environment would be expected to increase the penetrance of susceptibility alleles, and this should be reflected in slow progressive dilution of the highest risk alleles characteristic of childhood-onset disease. Evidence of this effect could be sought in long-term population-based studies.

In conclusion, the quest to understand type 1 diabetes has largely been driven by the mechanistic approach, which has striven to characterize the disease in terms of defining molecular abnormalities. This goal has proved elusive (74). Given the complexity and diversity of biological systems, it seems increasingly likely that the mechanistic approach will need to be supplemented by a more ecological concept of balanced competition between complex biological processes, a dynamic interaction with more than one possible outcome. The traditional antithesis between genes and environment assumed that genes were hardwired into the phenotype, whereas growth and early adaptation to the environment are now viewed as an interactive process in which early experience of the outside world is fed back to determine lasting patterns of gene expression. The biological signature of each individual thus derives from a dynamic process of adaptation, a process with a history. René Dubos (75) expressed this many years ago when he stated that “socially and individually the response of human beings to the conditions of the present is always conditioned by the biological remembrance of things past.” We are indeed part of all that we have met.

The implications of the changing demography of type 1

diabetes for our understanding of the disease are considerable. From the point of view of the geneticist, it means that patterns of inheritance that confer susceptibility to immune-mediated loss of pancreatic β -cells became progressively maladaptive in a late 20th century environment. For the immunologist, it implies that the ontogeny of the immune response in early childhood is changing in such a way that potentially harmful responses are now more prevalent, or more aggressive, in the subpopulation of genetically susceptible children. The task for the epidemiologist is to explain this. For the clinician, it means that childhood diabetes was in the past a partly preventable condition, and could become so again.

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