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Prognosis of Diabetics with Diabetes Onset before the Age of Thirtyone

I. Survival, Causes of Death, and Complications

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Summary. A follow-up on three hundred and seven patients diagnosed before 1933 and before the patient was thirty-one years old was conducted as of 1.1.1973, i.e. after at least forty years of diabetes. All patients were seen at the Steno Memorial hospital and were referred from all parts of Denmark. A small proportion of the patients (5.9%) could not be traced. Of the remaining two hundred and eighty-nine patients 40% were alive. Three-hundred and six patients were insulin dependent, 87% being treated with insulin twice daily. More than 50% survived their diabetes for more than thirty-five years. The mortality rate was 2–6 times that in an age- and sex-matched non-diabetic population. In 31% of the deceased patients the cause of death was uraemia; in 25% myocardial infarction. The excess mortality among patients exhibiting persistent proteinuria before forty years of diabetes was 3–4 times higher than in patients who did not have proteinuria after forty years.

16% of the whole study population became blind, and another 14% had severely impaired vision; 21% exhibited objective signs of myocardial infarction, 10% of stroke, and 12% had gangrene or had undergone amputation of the foot or lower leg; 38% had proteinuria and 22% uraemia. Death with or from hypoglycaemia was more common than death in ketoacidotic coma. Clinical manifestations of late diabetic complications were considerably less common in patients who were still alive after more than forty years of diabetes than in patients who died before their fortieth year of diabetes.

Key words: Prognosis, insulin, juvenile diabetes, mortality, cause of death, diabetic complications.

Before the beginning of the insulin era, the prognosis of juvenile insulin-dependent diabetes mellitus was extremely poor, with early death in ketoacidotic coma [1]. After Banting and Best's isolation of insulin in 1922 it was hoped that – if insulin was given in the correct dosage – young people who developed diabetes would be able to live an approximately normal life. In the course of the 1940's, however, it became apparent that this was not so: the expectation of life was diminished and the quality of life was impaired by the development of late diabetic complications [1, 2, 3, 4, 5]. It has been difficult to obtain a quantitative elucidation of these factors in young diabetics, because it is not until now that a sufficiently long time has elapsed after the discovery of insulin for the full natural history to be apparent. The object of the present study was to elucidate the length of life, the causes of death, and the quality of life in a group of juvenile diabetics attending a hospital specializing in diabetes, in whom diabetes mellitus was diagnosed prior to 1933.

Material

307 patients (164 men and 143 women) who had been admitted to the Steno Memorial Hospital between 1933 and 1973 with onset of diabetes mellitus before the age of 31 and prior to the year 1933 were studied. We tried to follow this group either until death or until 1.1.1973. The onset is defined as the year in which the disease was diagnosed (Fig. 1). It will be seen that 26 patients had the disease diagnosed before insulin first came into use in Scandinavia in 1923. Figure 2 gives the age at onset. According to the age at onset the patients have been divided into 3 groups: patients whose disease began

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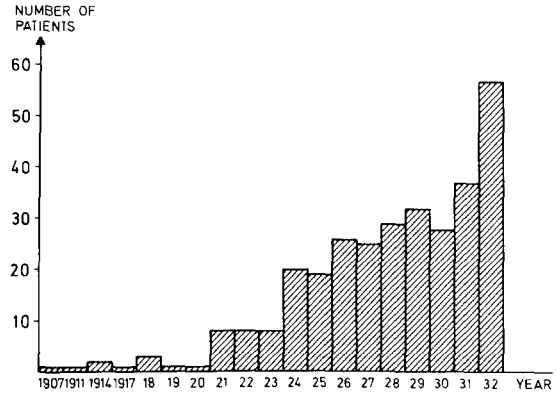

Fig. 1. Year of onset of diabetes in 307 patients with juvenile diabetes

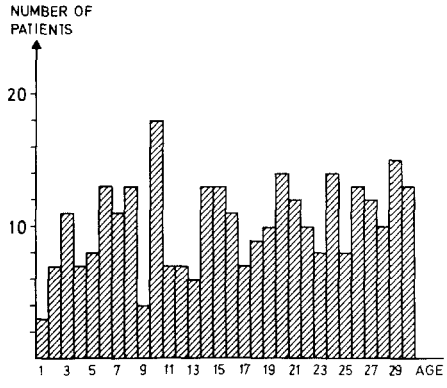

Fig. 2. Age at diagnosis of 307 patients with juvenile diabetes

Table 1. Time between diagnosis and first admission to the Hospital

Years between diagnosis and first admission to the Steno Memorial Hospital	Number of patients
0–5	54
6–10	79
11–15	47
16–20	34
21–25	30
26–30	23
31–35	27
> 35	13

Table 2. Institution of insulin therapy in relation to time after onset of diabetes. In 26 cases diabetes was diagnosed before insulin was available

Years between diagnosis and onset of insulin treatment	Number of patients	Per cent insulin treated
0 –1/2	167	55.0
1/2–2	95	86.0
2 –5	27	95.0
> 5	17	99.7

between the ages of 0–10 years (n = 96), 11–20 years (n = 97), and 21–30 years (n = 114).

The patients were from all parts of Denmark, but predominantly from Greater Copenhagen, 44% being domiciled in the metropolitan area (compared with 24% of the current Danish population). Referral to the Steno Memorial Hospital, a hospital specialising in the care of diabetics, is always through a general practitioner or a hospital. Treatment in the Steno Memorial Hospital has always been free of charge for the patients. However, it is difficult to rule out possible bias in referral practice.

All the patients were included in the study at first admission to the Steno Memorial Hospital. The duration of diabetes prior to the first visit to the Steno Memorial Hospital is shown in Table 1: 180 (59%) patients were referred with a duration of diabetes of 15 years or less, i.e. before the occurrence of subjective late diabetic complaints.

Before the first admission to the Steno Memorial Hospital nearly all the patients had been treated by general practitioners. After the first admission to the Steno Memorial Hospital 93 of the 307 patients were followed by their own doctor, in many cases supported by other institutions. The remaining patients (214) were later re-admitted or supervised for varying periods in our Out-patient Clinic. The decision as to whether each patient was still to be supervised in the Steno Memorial Hospital was in the hands of his own doctor, a new referral being demanded if continued supervision was to be established.

All the patients, except for a woman whose diabetes began at the age of 27, were treated with insulin, 12.4% injecting once daily and 87.6% twice daily. If insulin was given once a day, NPH-insulin (made of porcine (85%) and bovine (15%)) or zinc-insulin (lente®) made of porcine (30%) and bovine insulins (70%) was used. If insulin was given twice daily NPH-insulin was given twice daily in every case, in 51 per cent of cases combined with approximately 30% of short acting insulin in the morning. Usually two thirds of the daily insulin requirement was given in the morning and one third before supper. Zinc-insulin preparations were only used in 3% of cases. Insulin therapy was instituted in 55% at the time of diagnosis; by 5 years after diagnosis 95% were on insulin (Table 2). In one female, with onset at age 16, insulin therapy was discontinued after 32 years of diabetes, since when the patient has been controlled on tolbutamide. In one male with onset at age 20, insulin was discontinued after 25 years' treatment, and in a third patient with onset at 27 years of age, insulin treatment was interrupted for 8 years. The remaining 303 patients received continuous insulin therapy.

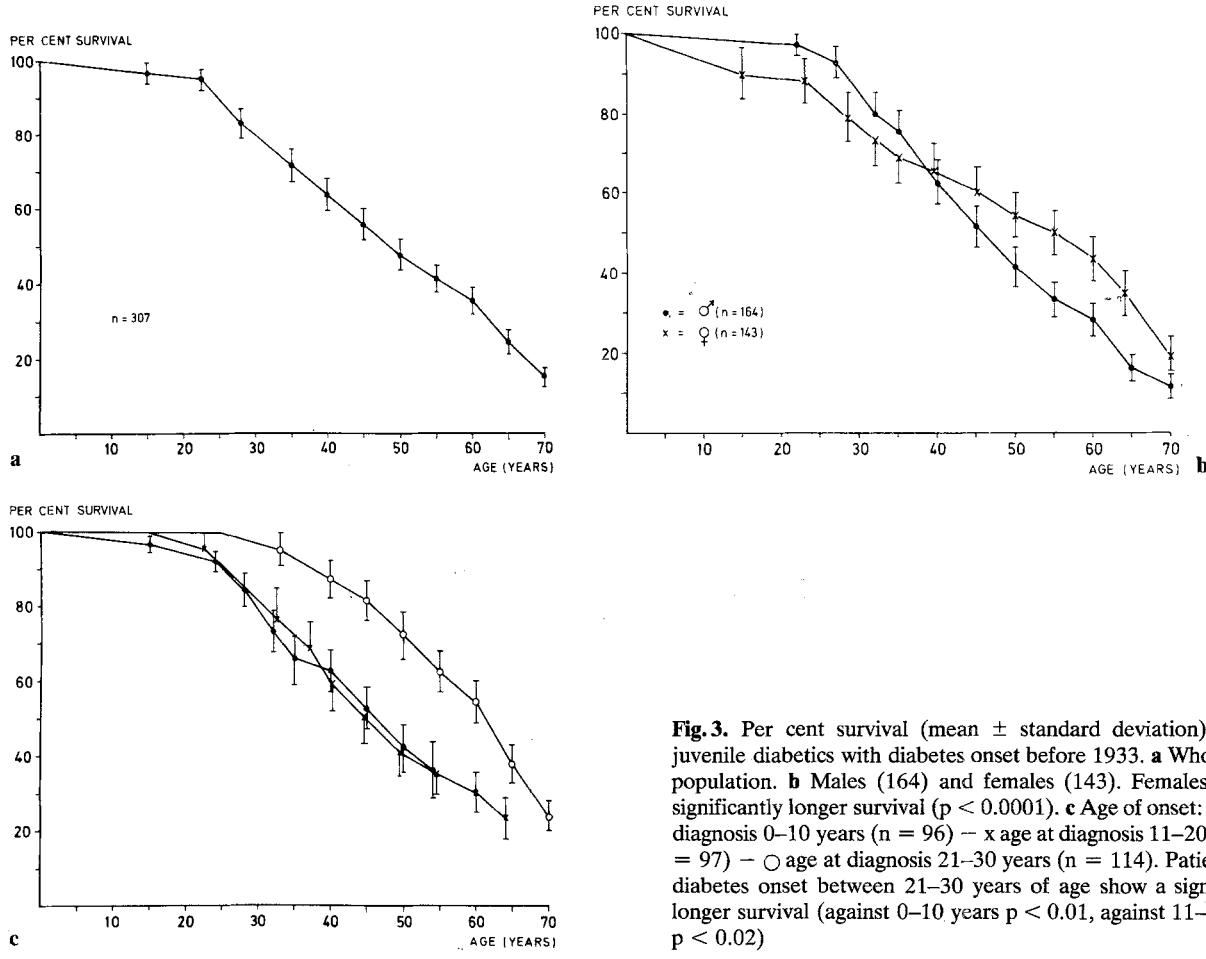

Fig. 3. Per cent survival (mean ± standard deviation) of 307 juvenile diabetics with diabetes onset before 1933. **a** Whole study population. **b** Males (164) and females (143). Females show a significantly longer survival ($p < 0.0001$). **c** Age of onset: ● age at diagnosis 0–10 years (n = 96) – x age at diagnosis 11–20 years (n = 97) – ○ age at diagnosis 21–30 years (n = 114). Patients with diabetes onset between 21–30 years of age show a significantly longer survival (against 0–10 years $p < 0.01$, against 11–20 years $p < 0.02$)

Eighteen (5.9%) of the 307 patients could not be traced because of changes in name, emigration, etc. The remaining 289 were followed until death (173 patients) or until 1. 1. 1973 (116 patients or 40%).

Method

For assessing *survival* three parameters were used:

(1) Age at death or at termination of the study (Fig. 3).

(2) Duration of diabetes (Fig. 4).

(3) Relative survival, i.e. survival in relation to the general population of the same age and sex. This calculation was based upon the comparable mortality rates per thousand for the total population of Denmark given in the Danish Year books of Statistics (Statistisk årbog) (Fig. 5).

To describe the duration of survival, decrement analyses were used [6] and for comparison of the two decrement curves Gehan's Wilcoxon test [7, 8]. A modification of these methods was used which pays regard to the unknown lifetime of some of the patients and to the fact that entrance to the study could be later than the beginning of the studied lifetime [8].

Co-variation analyses were made by the Spearman rank correlation, using the t-test, the chi-square test, and the Kruskal-Wallis test.

To assess the *cause of death* a copy of the death certificate was procured, showing the cause of death and the underlying disease. In the case of patients dying in hospital (one hundred and twentytwo patients or 71%) the information from the death certificates was supplemented with clinical data from the hospital where the patient had died. In any case full agreement was found between clinical records from hospitals and cause of death given on death certificate. For sixtytwo (35%) of the one hundred and seventythree dead patients there were also autopsy reports.

The *quality of life* comprised an evaluation of morbidity (visual acuity, renal function, cardio-vascular function) and, for the living patients, an evaluation of general condition, working capacity and social status. Morbidity was evaluated during the year before death or, in the case of the survivors, around

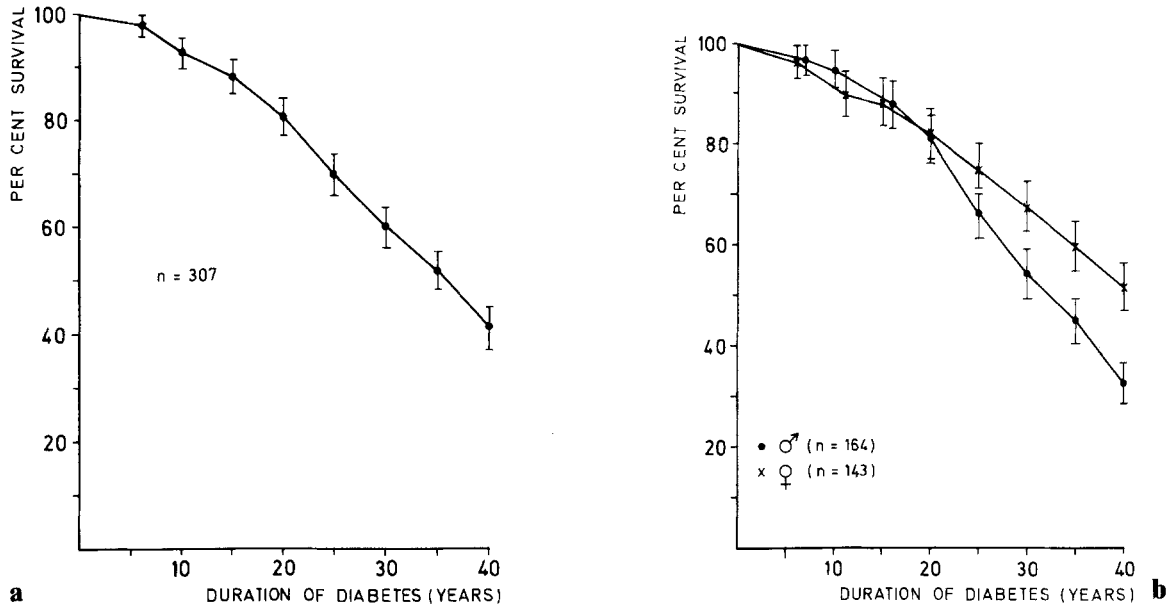

Fig. 4. Per cent survival (mean ± standard deviation) of 307 juvenile diabetics followed for 40 years. **a** Whole study population. **b** Males (164) and females (143). Females show a significantly longer survival ($p < 0.0005$)

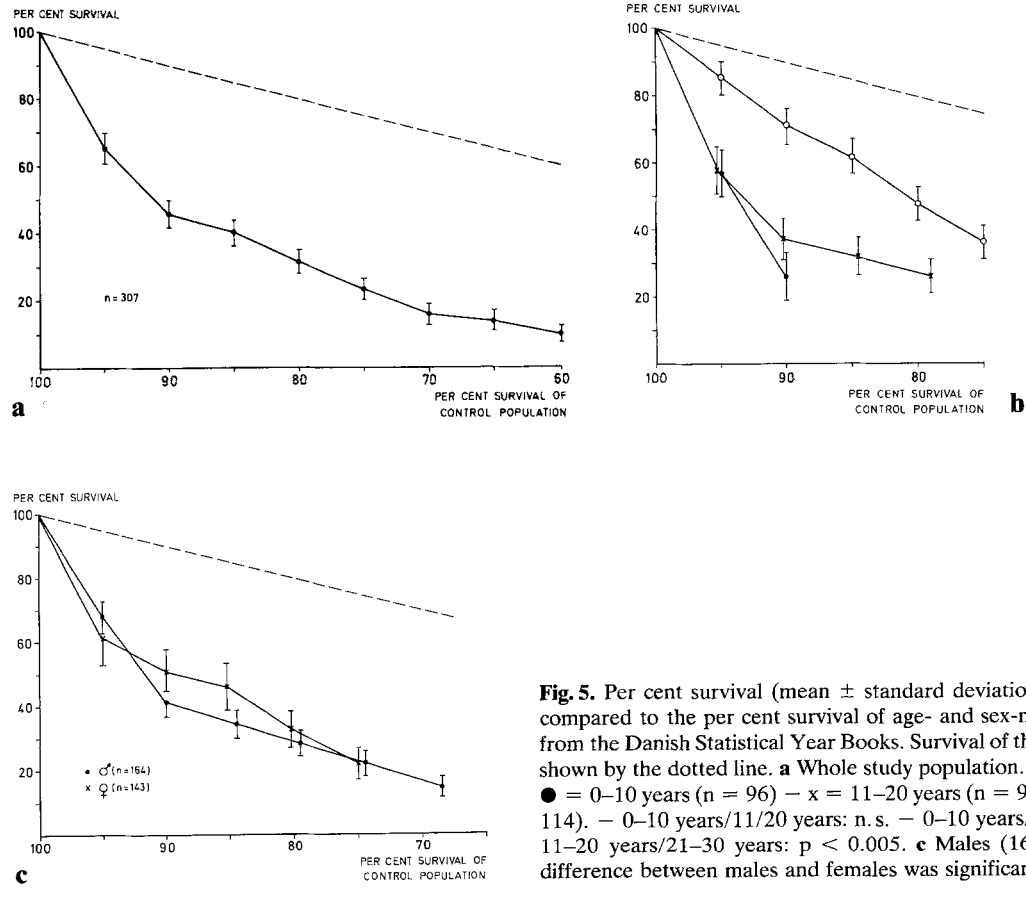

Fig. 5. Per cent survival (mean ± standard deviation) of 307 juvenile diabetics compared to the per cent survival of age- and sex-matched non-diabetics taken from the Danish Statistical Year Books. Survival of the non-diabetic population is shown by the dotted line. **a** Whole study population. **b** According to age at onset: ● = 0–10 years (n = 96) − x = 11–20 years (n = 97) − ○ = 21–30 years (n = 114). − 0–10 years/11/20 years: n.s. − 0–10 years/21–30 years: $p < 0.0001$ − 11–20 years/21–30 years: $p < 0.005$. **c** Males (164) and females (143). The difference between males and females was significant ($p < 0.01$)

Table 3. Cause of death in study population

	Per cent of deaths		
	Diabetics mean age 49 range: 16–77 n = 173	General population 1972[b]	
		age 35–59 n = 7279	all ages n = 50445
Uraemia (nephritis & nephrosis, B 38)[a]	31	0.3	0.1
Myocardial infarction (ischaemic heart disease, B 28)[a]	26	20.9	31.3
Infections (B 1–18 + B 31–33)[a]	9	4.1	6.4
Cerebrovascular insult (cerebrovascular disease B 30)[a]	7	4.4	10.1
Malignant neoplasms (B 19)[a]	4	34.9	23.4
Suicide (BE 49)[a]	3	8.5	2.4
Motor vehicle accidents (BE 47)[a]	1	3.6	2.4
Hypoglycaemia, possibly	5	0	0
Diabetic coma	2	0	0
Others & unknown	12	23.3	23.9

[a] Statistical classification of causes of death (WHO, Geneva 1967). Abbreviated list
[b] Source: Statistisk Aarbog, Danmark 1972.

1.1.1973, partly on the basis of information from our own case records and those from other hospitals (153 cases), partly by written inquiries (49 cases) to the patients and partly by personal interviews and examinations of the patients (62 cases). Apart from the 18 patients that could not be traced, it was not possible to procure relevant data for twenty of the deceased patients and for five of the survivors. In another 5–10% the data were incomplete. The following factors were examined:

Visual Acuity: Impaired vision = unable to read the daily paper without a magnifying glass. Blindness = vision < 6/60.

Renal Function: Impaired renal function = serum creatinine persistently > 2.0 mg/100 ml (measured by the Jaffé method), or blood urea persistently > 60 mg/100 ml (measured as per van Slyke). Proteinuria = Albustix or Heller positive (> 50–100 mg protein/1000 ml urine) urine for more than 1 year.

Cardio-Vascular Functions: The presence of gangrene, amputation below-knee or above-knee, objective evidence of previous or present stroke with limb paralysis, objective evidence of myocardial infarction (typical ECG changes combined with pyrexia, chest pain and/or elevated glutamic-oxalacetic acid transaminase or finding at autopsy).

Results

Life Expectancy: (Figs. 3–5.) Figure 3 a shows that 50% of the patients who developed diabetes before the age of 30 died before reaching the age of 50, while women survived for longer than men (Fig. 3 b), and those diabetics who developed their disease between the age of 21 and 30 lived longer than those who developed it earlier (Fig. 3 c).

Figure 4 sets out the importance of the duration of diabetes to survival. Almost 50% of the patients had died after 35 years of diabetes, irrespective of whether the diabetes had developed during the age range 0–10, 11–20, or 21–30. Women, however, survived longer with their diabetes than men (Fig. 4 b). The relative survival is presented in Figure 5a–c. At a time when only 10% of the general population had died, more than 50% of the diabetic population had succumbed. Figure 5 b shows that patients whose diabetes had begun between the ages of 20 and 30 had a significantly longer relative survival than had patients with diabetes onset before the age of 20. There is also a significant difference between the two sexes with respect to relative survival (Fig. 5 c); the longer survival and the longer duration of diabetes cannot be explained solely on the basis of greater longevity among women in general.

Causes of Death (Table 3): It will be seen that about 30% of diabetics died from renal failure and about

Table 4. Complications in juvenile diabetics (n = 264)[a] developed in the course of 40–50 years of study

	yes n (%)	no n (%)	doubtful n (%)
Blind	43 (16.3)	194 (73.5)	27 (10.2)
Impaired vision[b]	81 (30.6)	133 (50.6)	50 (18.8)
Myocardial infarction	55 (20.9)	202 (76.5)	7 (2.6)
Cerebral vascular disease	25 (9.5)	232 (87.9)	7 (2.6)
Amputation/gangrene	32 (12.1)	221 (83.7)	11 (4.2)
Proteinuria	101 (38.3)	138 (52.3)	25 (9.4)
Impaired renal function[c]	57 (21.6)	179 (68.2)	27 (10.2)

[a] 43 patients were not included: 18 were lost to follow-up, and insufficient data was available on 20 of the deceased patients and 5 of the survivors

[b] Blind or unable to read the daily paper without a magnifying glass

[c] see text page 367

Table 5. Prevalence of complications of surviving juvenile diabetics (n = 111) 40–50 years after onset of diabetes

	yes n (%)	no n (%)	doubtful n (%)
Blind	9 (8.1)	101 (91.0)	1 (0.9)
Impaired vision[a]	19 (17.1)	91 (82.0)	1 (0.9)
Myocardial infarction	10 (9.0)	99 (89.2)	2 (1.8)
Cerebral vascular disease	4 (3.6)	107 (96.4)	0
Amputation/gangrene	8 (7.2)	103 (92.8)	0
Proteinuria	8 (7.2)	89 (80.2)	14 (12.6)
Impaired renal function[b]	0	97 (87.4)	14 (12.6)

[a] blind or unable to read the daily paper without a magnifying glass

[b] see text page 367

25% secondary to myocardial infarction, whereas stroke was a fairly uncommon cause of death. The incidence of suicide was not higher than in the non-diabetic population. On the other hand, death in hypoglycaemia was more common than death in ketoacidotic coma. Table 3 also includes the distribution of the causes of death in Denmark in the general population in 1972. Since, however, the diabetic deaths were distributed over the years 1935–1972, and since the distribution of the causes of death has not been constant through these years, a comparison can only be made with reservations.

Morbidity (Table 4): At least 16% of the juvenile diabetics became blind and another 14% had such severe visual impairment that they were unable to read their daily paper without a magnifying glass. About 40 per cent of these patients had only been

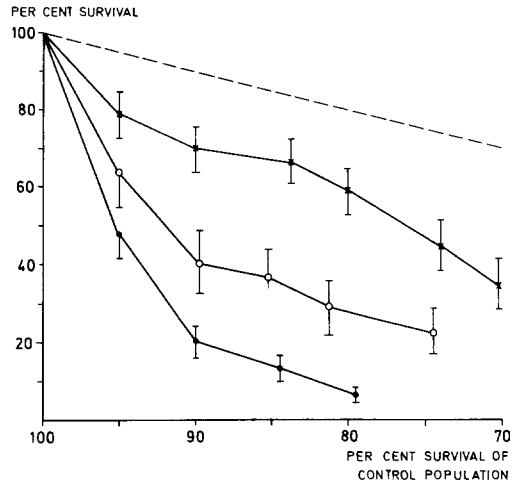

Fig. 6. Per cent survival (mean ± standard deviation) of 307 juvenile diabetics with diabetes onset before 1933, compared to the per cent survival of age- and sex-matched non-diabetics (dotted line). Group 1 (x) (n = 162): patients who did not develop proteinuria until 1973. Group 2 (●) (n = 99): patients who developed proteinuria before 1973. Group 3 (○) (n = 46): patients in whom development of proteinuria before 1973 was unknown. Group 1/group 2: $p < 0.0001$, Group 1/group 3: $p < 0.0001$, Group 2/group 3: $p < 0.0005$

blind for a short time, e.g. during terminal uraemia. At least 21% of the juvenile diabetics had impaired renal function, and the majority of this group developed uraemia before 1. 1. 1973. Approximately 20% had myocardial infarctions before 1973, whereas 12% had to undergo amputation and 10% had a stroke before 1973. More than 50% of the patients had not developed proteinuria.

Quality of Life of Survivors (Table 5): The majority (78%) of patients who survived after having had diabetes for more than 40 years were managing on their own, although 44% were receiving disablement pensions. Nearly 68% were feeling well in all respects, while 47% were capable of working. Of the patients who had survived for 40 years with juvenile diabetes (Table 5) the prevalence of serious diabetic complications was considerably lower, as might be expected. Only about 10% of these patients had serious complications (i. e. blindness and/or hemiparesis and/or amputations).

Figure 6 illustrates the importance of diabetic nephropathy to survival. Whereas patients who did not develop proteinuria in the course of 40–50 diabetes years had an excess mortality (compared with the background population) of only about 200%, the excess mortality among patients who developed persistent proteinuria was about 800%.

Discussion

As stated in the introduction the present study comprises a consecutive series of diabetics who fulfilled, when first seen in the Steno Memorial Hospital, the following two criteria: [1] Diabetes diagnosed before 1933 and [2] age below 31 years at time of diagnosis. This definition of juvenile diabetes is perhaps open to discussion. According to the WHO definition, juvenile diabetes is diabetes arising before the age of 15 [9]. However, diabetes beginning between the ages of 15 and 30 does not differ, pathophysiologically or genetically, from early diabetes. It is characteristic of practically all cases of diabetes in Denmark occurring prior to the age of 30 that they require insulin therapy and that insulin dependent diabetes differs genetically from non-insulin-dependent diabetes [10]. Besides, our investigation confirms that, assessed by the duration of diabetes, the prognosis is identical for patients whose diabetes has set in at the ages 0–10, 11–20, and 21–30. The degenerative effect on the body of the disease appears to be extremely well programmed, as about 50% of the patients had succumbed after about 35–40 years of diabetes, irrespective of whether the disease had started at the age of 5 or at the age of 25. Thus, it may be justifiable to consider patients with diabetes beginning before the age of 30 as one group.

The distribution by sex and age at onset is in agreement with recent Danish findings [11]. We made no attempt to exclude cases with maturity-onset diabetes in the young (MODY), but 3–5 of the 307 may have had this type of diabetes, as they could do without insulin for long periods. The fact that only 55% of the patients were started on insulin at the time of diagnosis presumably reflects attitudes towards insulin therapy in the 1920's. Therefore, Table 2 illustrates how many years elapse after diagnosis before the insulin deficiency has become total. This is in agreement with the insulin requirement per kg body weight in children, which also rises (from 0.6 units/kg to 0.9 units/kg) in the course of the first 5 years with diabetes [12]. All 18 patients whose diabetes had been diagnosed prior to 1922 (Fig. 1) had severe disease in 1923 and were immediately started on insulin.

It is probable that referral of patients to the Steno Memorial Hospital (which is a diabetes hospital serving the whole country) involves some selection of patients whose diabetes is difficult to control. There has been no selection on the basis of the patients' income, more likely a selection of patients who were more ready to do something themselves about their disease. The material also has a non-random geographic distribution, with over-representation of patients living in the Copenhagen area.

One hundred and twentyseven (41%) of the patients were not referred to the Steno Memorial Hospital until their diabetes had existed for 15 years. Among these patients there may be an over-representation of patients with late diabetic complications. Indeed, later studies have shown that patients referred for the first time to the Steno Memorial Hospital after diabetes for more than 15 years' duration have a significantly poorer survival ($p < 0.05$) than patients referred within the first 15 years of their diabetes. The reason why only 6 patients were referred to the Steno Memorial Hospital with newly diagnosed diabetes is that the Hospital was founded in 1932. It cannot be excluded that the frequency of death in diabetic coma would rise and the survival curves would be somewhat lower, if all patients had been followed from the time of diagnosis.

It is difficult to compare survival in the present juvenile diabetics with that of juvenile diabetics elsewhere, as to our knowledge no such data has been published. According to Goodkin [3], the excess mortality from juvenile diabetes (diabetes arising before the age of 20) exceeds 1000% in the course of 20 years after onset, while in the present study it reached a maximum of 750% (Fig. 5 b). The excess mortality in diabetics with onset between the ages of 0–10 and 11–20 was identical, while it was significantly lower in patients who developed their disease between the ages of 21 and 30. The lower excess mortality in this decade is, however, due to the higher mortality in the general population, not to a lower mortality among the diabetics in this age group. Women with juvenile diabetes had a significantly better prognosis than men, and this is manifest also in a significantly lower excess mortality (Fig. 5 c).

The distribution of the causes of death corresponded largely to that reported by Joslin [4] for juvenile diabetics except that in the present study there were fewer deaths from uraemia and diabetic coma. The values reported here, however, have to be considered as preliminary, as 40% of the patients were still alive at the time of the study. It is a debatable matter whether 8 of 173 died *of* hypoglycaemia or *with* hypoglycaemia.

Tables 3,4, 5 and Figure 6 illustrate the importance of diabetic nephropathy to the course of life of juvenile diabetics. Only about 10% of the juvenile diabetics living more than 40 years with diabetes showed proteinuria, whereas at least 61% of the deceased patients had had persistent proteinuria. It is surprising that as many as 16% of the juvenile diabetics went blind. As already mentioned, however, a large number of them developed their blindness while uraemic. We have previously demonstrated that proliferative retinopathy leads to blindness sooner in patients with diabetic nephropathy than in

patients without nephropathy [13]. About 40% of the blind patients were not even blind for long enough (about half a year) to come under the National Care of the Blind.

In conclusion, the present study has shown that juvenile diabetes has a high excess mortality, due mainly to the development of diabetic nephropathy. On the other hand, the study has shown also that not less than 40% of the juvenile diabetics lived for more than 40 years with their disease and that of these patients 78% were managing on their own.

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