Long-term Study of Mortality and Vascular Complications in Juvenile-onset (Type I) Diabetes

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SUMMARY

A cohort of 372 insulin-dependent diabetic children, diagnosed between October 1949 and December 1960, were followed-up until December 1976 by the same team of physicians. At the time of diagnosis all patients were under 16 yr of age and were given standardized treatment which did not change from 1949 to 1976. The therapy consisted of daily insulin adjustment based on clinical assessment, the degree of physical activity, and the results of semi-quantitative urine tests for sugar and ketone bodies. These tests were systematically performed before breakfast, lunch, and dinner. Diet was normal, unmeasured, rich in carbohydrates (approximately 60%), and quantitatively unrestricted unless the patient was overweight.

Rates for mortality and for the principal complications among this cohort were computed by the actuarial method. During the 26 yr of study, 26 deaths occurred, 16 of which were directly connected with diabetes.

After 16 yr of follow-up, rates of proteinuria and hypertension were 4% and 2.1% respectively. The incidence of retinopathy reached 27%, including 1.5% proliferative retinopathy. After 26 yr, the rates rose to 14% for proteinuria, 16% for hypertension, and 85% for retinopathy, including 18% in the proliferative phase.

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Since the introduction of insulin therapy, several therapeutic approaches have been attempted in an effort to achieve satisfactory metabolic control.[1–4] Long-term results have been reported.[5–10] This paper describes the course of diabetic disease in a cohort of patients managed during 26 yr by the same team of physicians and treated by daily insulin adjustment. Until December 1976 they ate a diet quite comparable to that of nondiabetic French children of the same age. Data are statistically analyzed by the actuarial method.[11,12]

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MATERIALS AND METHODS

Patients. The group includes all insulin-dependent diabetic children (age at onset less than 16 yr, Figure 1), whose diabetes was diagnosed between October 1949 and December 1960. They were followed from the onset of their disease until December 1976 by the Department of Diabetology at the Hérold Hospital in Paris. There were 182 girls and 190 boys.

The selection period was chosen so that it insured sufficient duration of follow-up, at least 16 yr by the end of 1976 and because, at this time, some changes were introduced in the therapeutic approach (see next section). Subjects came from different types of environment and their social, ethnic, and urban/rural distribution corresponded quite well to existing strata in the French population.

Patients previously diagnosed outside the department were excluded.

Treatment. Treatment aimed at the complete elimination of clinical manifestations (i.e., thirst, polyphagia, and ketonuria) and the reduction of diuresis to less than 1 L/m^2 of body surface a day; glycosuria to below 20 g/L (in 24-h urine collection every other month); postprandial blood glucose to less than 250 mg/dl (Nelson-Somogyi method up to 1960, then glucose-oxidase); plasma cholesterol to less than 220 mg/dl; and plasma triglycerides to below 100 mg/dl. These two last biologic tests were carried out at least once a year.

Treatment was unchanged from October 1949 until December 1976 but was slightly modified at the beginning of 1977. Changes included the reduction of simple sugar intake, increased use of multiple daily injections, and administration of monocomponent insulins.

The main features of the program, detailed in earlier reports[4,6,7] were: (1) Step-wise adaptation of insulin dosage to the results of three semi-quantitative urine analyses (Clini-

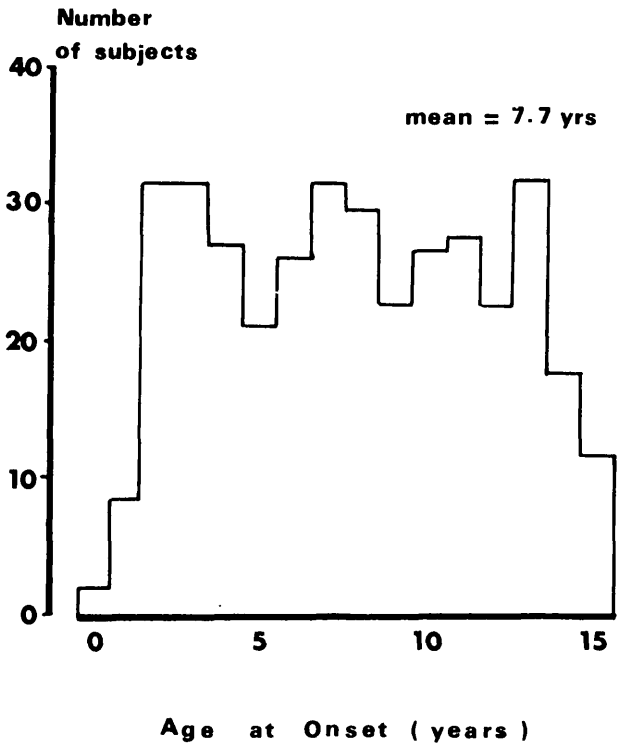


FIGURE 1. Age distribution in the 372 subjects at onset of diabetes.

test and Acetest) performed on the same day and previous day. Sixty-nine percent of the patients were injected with a mixture of regular and protamine zinc insulin before breakfast and, if necessary, with short-acting insulin at noon or in the evening; 24% were given a combined daily dose of long- and short-acting insulin (Novolente), and 6% were injected with intermediate-acting insulin twice a day. Only four subjects required a regimen of three daily injections. Slight hypoglycemia was accepted, but patients were watched closely to avoid as much as possible severe attacks. (2) Except in cases of concomitant obesity (3.6%), the diet was allowed to be free, quantitatively and qualitatively, from October 1949 to January 1977; i.e., small amounts of refined sugars as candies and desserts were allowed. Analyses of data on spontaneous feeding in groups thus treated in France showed that the total calories and the contribution of each nutrient were in the same range as those observed at the corresponding time in nondiabetic children of the same age: 13% proteins, 26% fat, and 61% carbohydrates.[13,14] (3) Year-round regular physical exercise was strongly encouraged.

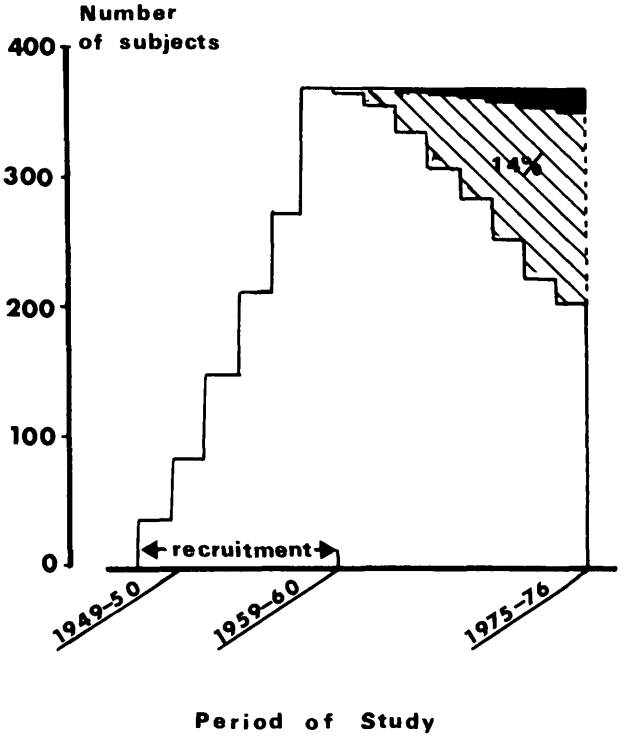
Follow-up. Clinical, biologic, and ophthalmologic examinations were performed from two to four times a year. The results were systematically recorded once a year at the anniversary month of diabetes from 1949 to the end of 1976 on special charts established since 1949 for a prospective study.

Blood pressure was measured under standard conditions in the recumbent position. Values were classified as abnormal when systolic pressure was equal to or greater than 130 mm Hg and/or when diastolic pressure was equal to or greater than 70 mm Hg for 10-yr-old subjects.[15] The corresponding limits were 140 and 90 for subjects under 16 yr of age, 150 and 100 between 16–39 yr, and 160 and 100 for older subjects.[16] Proteinuria, measured at the laboratory by chemical methods, was considered positive when it was consistently higher than 0.2 g/L. Retinopathy was detected by examination made through dilated pupils in the ophthalmologic department of the hospital. The examination was completed each time by retinal photography and classified as follows: stage I = 1 to 4 microaneurysms or a few punctate exudates not interfering with vision; stage II = more than 4 microaneurysms per eye with or without functional disturbance; and stage III = new vessel formation with or without coalescent exudates and hemorrhage, usually combined with substantial impairment of vision. Of the 372 subjects, 146 (39%) were lost to follow-up between 1961 and 1976, mostly because they moved away from Paris. Figure 2 gives the number of subjects observed throughout the entire study. The dotted line corresponds to the theoretical number of subjects, including the dropouts. When the time of dropout was taken into account, the relative loss of information (shaded area = 14%) was not as significant as the percentage of dropouts would suggest. Mean duration of follow-up was 17 yr, i.e., 90% of the subjects were followed-up for 10 yr or more and 33% for 20 yr or more (Figure 3).

Seventy-one of these 372 subjects had poor quality treatment for a long period of time, either because they were not very disciplined or because their diabetes was particularly difficult to control. However, taking into account the arbitrariness of such a classification over such a long time, we decided not to attempt subgrouping and to consider the group as a whole.

Statistical analysis. The main difficulty in estimating mortality and morbidity rates was the lack of information about

FIGURE 2. Number of subjects examined in each 2-yr period of the study. Number of subjects increased from 1949 to 1960, when recruiting stopped. Solid line, number of subjects observed; dotted line, expected number if all subjects had been followed up until 1976. Shaded area, loss of information due to dropout subjects; dark area, deaths.



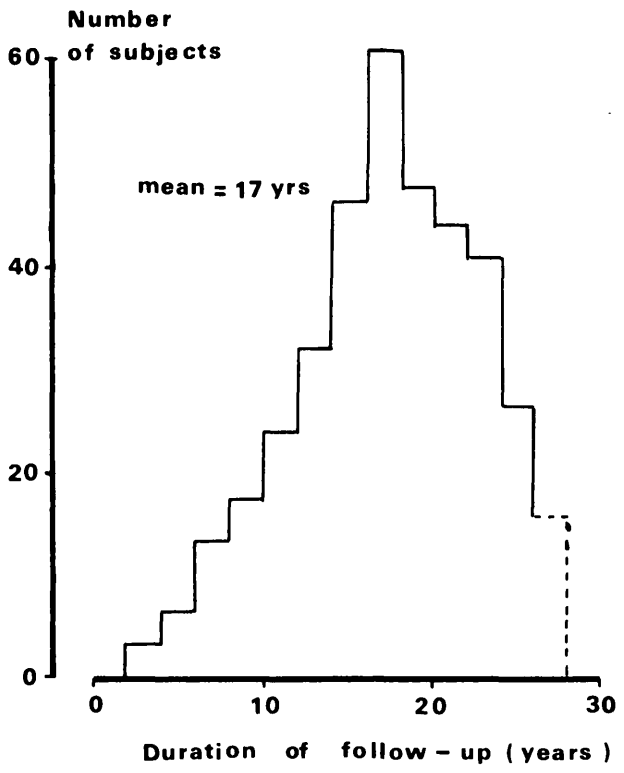


FIGURE 3. Duration of follow-up in the 372 subjects.

dropout subjects lost to follow-up. After thorough study of this problem, statisticians suggested several methods for its solution. Of these, the actuarial method is one of the simplest to use.[11,12] One of its advantages is that it enables every subject in the cohort to be taken into account. Each one contributes to the long-term estimates, even those followed for a short time only. This increases the accuracy of rate estimations and obviates a decline or a fluctuation of rates, always observed when another method is utilized.[6-10] However, to assume that mortality and morbidity are basically similar in dropouts and followed subjects is quite another matter.

RESULTS

Mortality. Twenty-six deaths occurred between 3 and 25 yr after the onset of diabetes. Ages varied from 7–34 yr at the time of death. Ten deaths were unrelated to diabetes; of these, two were due to car accidents, three to septicemias, one to poisoning, two to postoperative accidents, one to multiple sclerosis, and one to an unspecified infectious disease. Sixteen deaths appeared to be related to diabetes and its complications. They comprised four vascular accidents, two cases of chronic nephropathy, three of diabetic coma, and seven of hypoglycemic coma. One of the diabetic coma cases was a patient who took it upon himself to stop his prescribed insulin. Among the seven deaths from hypoglycemia, one was voluntary, and four occurred between 1949 and 1958 before glucagon became available for patients temporarily out of geographical reach of the necessary medical facilities. Two hypoglycemic deaths were recent; one involved a commercial traveller who was found dead in a hotel room, the other a medical student, who one week earlier attended a lecture on diabetes that insisted too heavily on the necessity of permanent aglycosuria. Ten of the 26 deceased patients had exhibited complications of diabetes, which are accounted for in the actuarial analysis.

TABLE 1
Mortality rates per age group

Age (yr)	N	Diabetes (%)	Control (%)
5–9	2	0.53	0.04
10–14	3	0.80	0.035
15–19	5	1.33	0.092
20–24	5	1.33	0.125
25–29	8	2.13	0.115
30–35	3	0.74	0.144

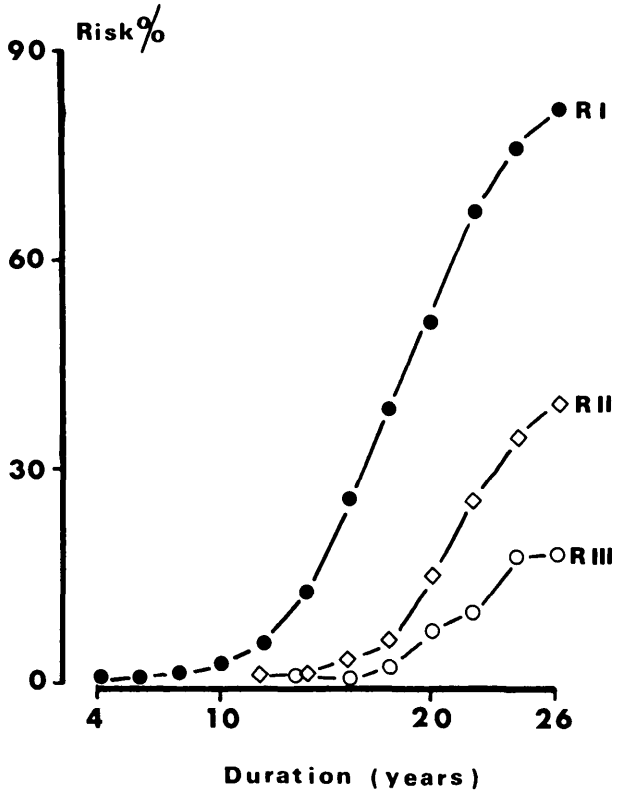
N = number of dead subjects.

Table 1 lists the mortality results as a percentage of the present cohort of diabetics and also mortality in the nondiabetic French population of corresponding ages.

Retinopathy. The cumulative evolution of diabetic retinopathy is shown in Figure 4. All three stages are shown on the same graph. No distinction is made between men and women because the percentages for each sex are practically identical.

One hundred sixty subjects developed at least stage I retinopathy. In this actuarial method the 21 stage III subjects are also included in stages I and II. Similarly, the 48 stage II subjects are included in stage I. Three percent of the stage I cases occurred before diabetes had been present for 10 yr. One stage I case developed after the fourth diabetic year. It is noteworthy that after 10 yr of diabetic evolution a rapid rise in the percentage of retinopathy was observed. Thus, the prevalence of retinopathy was 27% at 16 yr, 53% at 20 yr,

FIGURE 4. Cumulative risk of retinopathy, stages I, II, and III.



and 85% at 26 yr. In stage II, the first case occurred after 12 yr of diabetes and frequency then rose to 16% after 20 yr and 40% after 26 yr.

The first case of stage III retinopathy was observed after 13 yr of diabetes. After 26 yr, the frequency of stage III retinopathy was 18%.

Proteinuria and high blood pressure. Findings are recorded in Figure 5. For these two complications, a scale different from that used for retinopathy was chosen because of the small number of cases occurring during the study, i.e., 27 of proteinuria and 22 of high blood pressure. The two curves are similar and reach a final percentage of 15%.

DISCUSSION

The value of the present findings resides in the fact that from 1949 the same medical team systematically and prospectively collected data from an entire cohort of patients whose treatment and type of diet remained unchanged until the end of 1976.

The rate of stage I retinopathy was certainly underestimated, because the standard optical fundus examination is relatively rudimentary. Retinal angiography was systematically carried out from 1974, when the technique first came into use, but of course it was not available at the start of the study. Nevertheless, the same criteria necessarily had to be applied to all patients participating in the study. Furthermore, it should be noted that although angiography doubles the detection rate for stage I retinopathy during the initial years of diabetes, the method does not significantly alter the detection of stage II and III disease.[17]

Comparison of the dropout group with the set of patients followed-up until 1976 showed a higher proportion of stage I, II, and III retinopathy in the dropouts: 35% as opposed to 23% after 16 yr of diabetes and 62% as opposed to 49% after 20 yr of diabetes. This observation indicates that inclusion of the dropout patients did not reduce the significance of our findings because most of them dropped out after they had already begun to exhibit complications.

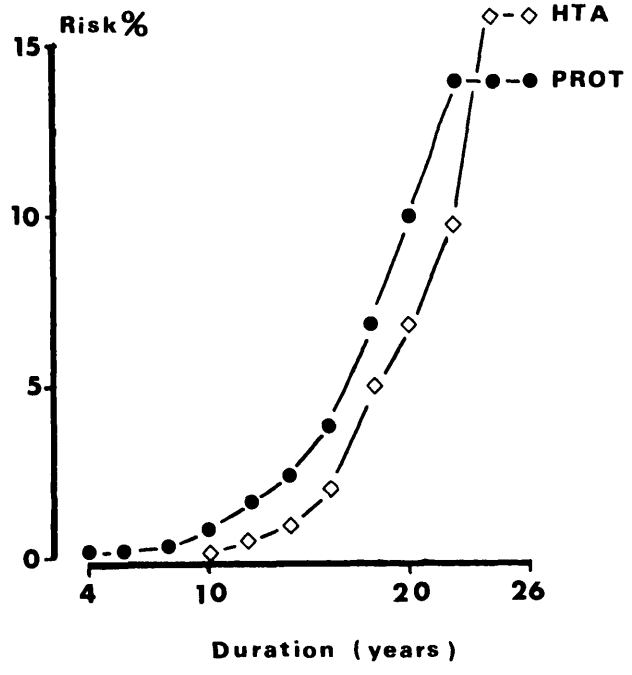


FIGURE 5. Cumulative risk of proteinuria and hypertension.

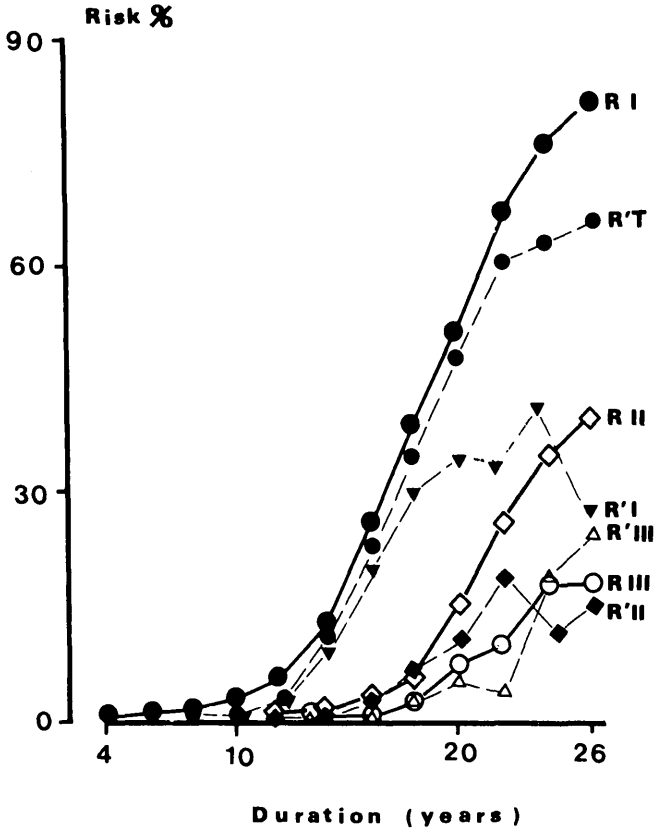


FIGURE 6. Comparison of the prevalence of retinopathies. The symbols R I, R II, and R III stand for retinopathy stages I, II, and III, respectively, as assessed by the actuarial method. R'T, R'I, R'II, and R'III indicate total retinopathy and stages I, II, and III determined by the traditional method (see text).

It should be noted that had we applied the statistical method which most authors use to study the prevalence of complications,[6-9] excluding the dead and the dropout subjects, we would have found completely different results, obtaining an irregular, fluctuating curve. As an example, we have added to the data shown in Figure 2 the percentage curves given by the traditional method of examination for the total number of cases of retinopathy and for stage I, II, and III retinopathy (Figure 6). Such irregular curves give the erroneous impression that the longer the study extends, the percentage of complication decreases. This approach is the rule in most publications, except for Knowles et al.,[5] who used a method comparable to ours.

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