Natural Course and Prognosis of Juvenile Diabetes

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One thousand seventy-two juvenile patients of the Joslin Clinic have now lived for more than twenty years. Since in the United States today there are some one hundred thousand individuals who also are surviving childhood diabetes, a summary of the unique experiences of these long-term cases appears to be of value. What is their present status? Why did they develop diabetes? What was the entire course of their disease? How did they grow and mature? What complications did they develop? How did they die and, finally, what can be done toward the solution of their problems?

Status. These 1,072 patients comprise 28.7 per cent of the 3,732 juvenile cases treated at the Joslin Clinic up to Aug. 1, 1955. Their present status shows that 82 per cent (879 patients) are living, 16 per cent (169 patients) have died, and 2 per cent remain untraced.

Present age and duration. These patients are, of course, no longer children. The oldest (also treated by Dr. John Williams) at fifty-six years of age has survived his diabetic adolescence, youth, middle age, and is now entering the technical old-age period. The majority (61 per cent) are now between 30 and 39 years of age, with 18 per cent between ages 20 and 29, 20 per cent between ages 40 and 49, and 1 per cent now over age 50. The duration of diabetes to Jan. 1, 1956, or to death varied from 20 to 42 years; 70 per cent survived 20 to 29 years and 30 per cent over 30 years, including 3.2 per cent over 35 years.

Achievements. Their struggle to survive and their struggle to achieve, even after the development of multiple disabilities, was amazing. A famous case of pituitary dwarfism, reported by Beck and Suter,[1] totally blind and with renal failure, earned his PH.D. degree. A total comprising 30 per cent received college education; 5 per cent did graduate work. They achieved a high socio-economic level. Their occupations compared more than favorably with the Minnesota scale[2] for urban populations for males. Those in professions, 26 per cent, exceeded the number expected in the general population, 6 per cent, by more than four times.

By age at onset and sex distribution, they are typical of all juvenile diabetics. The peak for age at onset was eleven years and the sex distribution was even. For the most part their attitude and that of their parents had been one of acceptance of the problem. The patients' cooperation in the measuring of food, performance of tests and regulation of insulin was good. Their past treatment, however, had not been uniform, since the group includes all patients registered in the clinic—those under continuous care, those seen occasionally, those seen only once in consultation, as well as those who came for terminal care. Management with respect to caloric prescription, partition of diet, type of insulin and frequency of insulin injections was varied.

Etiology. Because of the many opportunities to recheck family histories, the hereditary predisposition to diabetes was revealed in 57 per cent. The data compiled from these long-term cases again support the thesis that the transmission is through Mendelian recessive genes.[3] Thus, in spite of the advancing age of their parents, only 13 per cent had one or more diabetic parent. Although one patient could trace her diabetic ancestry for five generations, three-generation cases were exceptional. Compared with an expectation of 22 per cent diabetes[4] in their life span for the children of a single diabetic parent, only 1 per cent had offspring with diabetes. Four per cent of the girls had diabetic sisters and 5 per cent had diabetic brothers. Six per cent of the boys had diabetic brothers and 4 per cent had diabetic sisters. The prenatal maternal influence upon diabetes production[5] was not shown at the time of this study, for the number of diabetic fathers equaled the number of diabetic mothers. The peculiar age behavior of diabetes was again indicated in the family histories, 1 per cent of the cases showing it in direct descendants, 13 per cent in the parent group and 18 per cent in the grandparent group.

Natural course of diabetes. The natural course of

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diabetes, recognized by those who see many of these cases,[6] is shown in its entirety in this long-term group. The onset of their symptoms occurred typically in a day, week or month. The first recognition in many was in diabetic coma. Despite this virulence of the early course, remissions of the diabetic state occurred in one-third. On occasions the remission was so marked that the standard glucose tolerance test returned to normal. Gradually the insulin requirement increased to one-half unit per pound of body weight. Intensification of the diabetic state appeared to be affected more by linear growth than by gain in weight. It was also intensified by the intercurrence of infections of the common types as well as by bouts of ketoacidosis. The requirement for insulin at the completion of growth and development (age twenty) was compared with the last recorded doses. Although as adults 75 per cent of the females and 56 per cent of the males required less insulin than before age twenty, the decrease of dose in units was slight. Insulin requirement fell 50 per cent in only 5 per cent of males but in 20 per cent of females.

Examination of the pancreatic islets in thirty-one autopsied cases, with ages between 20 and 41 years and duration of diabetes between 20 and 31 years, showed diminution in islet size, number and cellular differentiation in 93 per cent. None showed hypertrophy or hyperplasia. These changes are not reported in short-term juvenile diabetics. The clinical course of these patients along with the pancreatic assays (by Wrenshall),[7] blood assays (Bornstein),[8] the histological reports (Bell),[9] and the findings of Warren,[10] all imply that the total or near total diabetic state is eventually acquired by the juvenile patient.

Growth. The linear growth of these patients was for the most part satisfactory. The median height finally attained by the males was 68 inches and by the females 63 inches, comparable to general experience. Perhaps because they were treated in part with undernutrition in the preinsulin era, 7 per cent of the males did not attain an adult stature of 63 inches and 8 per cent of the females did not attain a height of 60 inches.

The weight after age twenty was maintained at a normal or more often a sub-normal level in nearly 90 per cent (51 per cent of the males and 45 per cent of the females were five or more pounds below weight). Only 14 per cent of females and 13 per cent of males were five or more pounds above weight for height.

Menses. Sterility. Pregnancies. Although very few American girls have not menstruated before age fourteen,[2] only 28 per cent of these patients had matured at that age. The median age for their first menses was fifteen. However, there was no evidence of hypo-ovarianism in their later life. Sterility was *no* problem. Among 473 pregnancies, including reported and observed cases, their fetal wastage was high, 40 per cent, compared with the expected of 13 per cent. Their abortion rate was two and one-half times normal and their perinatal loss was six times the normal. The reported infancy death rate was 0.4 per cent and the incidence of gross anomalies only 2 per cent (both probably below the actual figures).

The harmful influence of maternal diabetes upon fetal salvage is suggested by the contrasting figures on the perinatal losses of the wives of the diabetic males in this series. They reported the loss of 3 per cent, exactly that of the general population.

Complications. In varying degrees of intensity and frequency these 1,072 patients had developed the major complications of diabetes: coma, infections, neuritis and vascular damage. Severe ketoacidosis or coma had occurred in 52 per cent of the females, multiple attacks in 18 per cent. The incidence in the males was 39 per cent, with 12 per cent having multiple attacks.

In the order of descending frequency they had abscesses and carbuncles, pyelonephritis, tuberculosis and osteomyelitis (in an incidence of 33, 12, 4 and 0.5 per cent respectively for the females; 30, 2, 4 and 0.8 per cent respectively for the males). Neuropathy had occurred too often, in 26 per cent of the females and 20 per cent of the males. Acroneuritis was the form observed most commonly, with gastrointestinal neuropathies in second place. Such malignant neuropathies as Argyll Robertson pupils, tabetic bladders, and Charcot joints occurred infrequently, in only 0.3 per cent, 0.3 per cent and 0.5 per cent respectively.

From incidence, disability and mortality, vascular damage was by far the most important complication. At thirty-five years' duration nearly all showed lesions; 94 per cent had calcified arteries, 93 per cent retinopathy, 59 per cent neovascularization, 53 per cent hypertension, and 44 per cent had nephropathy. These lesions were not observed in the first five years of diabetes, rarely found in the first ten years, but by fifteen years, 19 per cent of those examined had retinopathy, 14 per cent calcified arteries, 7 per cent proteinuria, 4.5 per cent hypertension and 3 per cent proliferans.

The lesions were rare under age twenty but were prevalent by age thirty (63 per cent had retinopathy, 46 per cent had calcified arteries, 29 per cent had retinitis proliferans, 34 per cent had albuminuria, and 40 per cent hypertension). Although the incidence of the disabilities arising from the vascular lesions for the

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TABLE 1

Age and duration of 879 juvenile diabetics surviving more than twenty years

Present age				
Years 20-29 per cent	Years 30-39 per cent	Years 40-49 per cent	Years 50-56 per cent	Total
18	61	20	1	100%

Present duration					
Years 20-24 per cent	Years 25-29 per cent	Years 30-34 per cent	Years 35-39 per cent	Years 40-42 per cent	
31	40	24	<5	<0.2	100.2%

TABLE 2

Occupations of males among 879 juvenile diabetics surviving twenty years (Minnesota Scale for Urban Populations)

	Expected per cent	Actual per cent
Professional	6	26.3
Semiprofessional	13	18.1
Clerical	29	22.7
Farmers	0.4	2.3
Semiskilled	29	16.8
Slightly skilled	13	6.9
Day labor	8	5.3

TABLE 3

Total incidence of vascular lesions by age

Age Years	Albumin per cent	Blood pressure per cent	Retinitis all types per cent	Retinitis proliferans per cent	Calcified arteries per cent
0-9	0	0	0	0	0
10-19	4.2	1.8	4.8	0	6.5
20-29	18.5	16.7	63.2	28.7	45.5
30-39	34.7	40.3	84.4	53.1	83.3
40-49	37	51.9	88.0	58.4	95.0
50+					

TABLE 4

Total incidence of vascular lesions by duration

Duration years	Albumin per cent	Blood pressure per cent	Retinitis per cent	Retinitis proliferans per cent	Calcified arteries per cent
0-4	0.8	0.5	0	0	0
5-9	1.5	1.2	2.5	0	1.7
10-14	7	4.5	19	3	14
15-19	18	15	59	18	44
20-24	41	32	82	47	73
25-29	39	44	88	46	88
30-34	44	53	93	59	94
35-39	63	70			

TABLE 5

Causes of death 169 cases (16% of 1,072)

	Number	Per cent
All causes	169	100
Diabetic coma	1	0.6
Cardio-renal-vascular	148	87.5
Arteriosclerotic Cardiac	8	4.7
Angina pectoris or Coronaries	45	26.6
Nephritis	86	50.9
Apoplexy	9	5.3
Infections	5	2.9
Tuberculosis	2	1.2
Accidents	3	1.8
Suicide	1	0.6
Murder	1	0.6
Appendicitis	2	1.2
Sepsis	1	0.6
Necrotizing papillitis	1	0.6
Hypoglycemia	1	0.6
Unknown (diabetes)	3	1.8

TABLE 6

Age and duration at death (169 cases)

Age at death				
Years 20-24 Per cent	Years 25-29 Per cent	Years 30-34 Per cent	Years 35-39 Per cent	Years 40+ Per cent
2	20	43	25	10

Duration at death				
Per cent	Per cent	Per cent	Per cent	Per cent
64	25	11	0	0

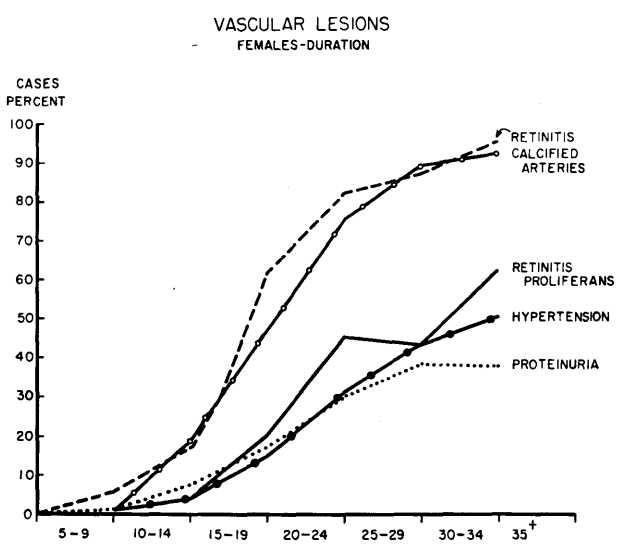

FIGURE 1

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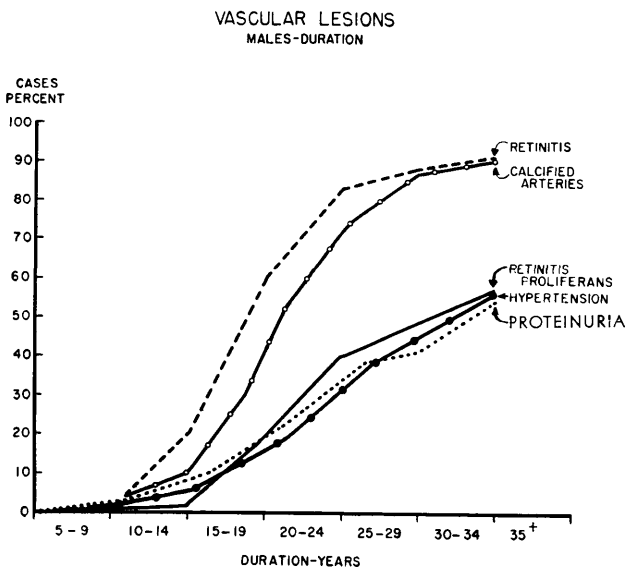

FIGURE 2

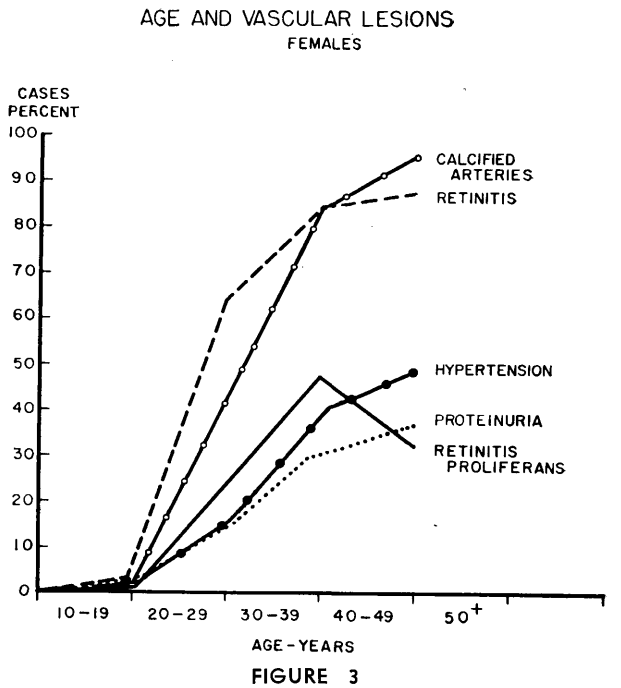

FIGURE 3

entire series of living and fatal cases is appreciable (uremia in 9 per cent, blindness in 6, myocardial infarction in 6, cerebrovascular accident in 2 and gangrene in 0.5 per cent), there is increasing evidence that certain numbers of these patients show a stationary status of their vascular lesions. This favorable course can be evaluated best in the retina.

Although it is evident from the foregoing that all of the vessels of these young patients are involved in all

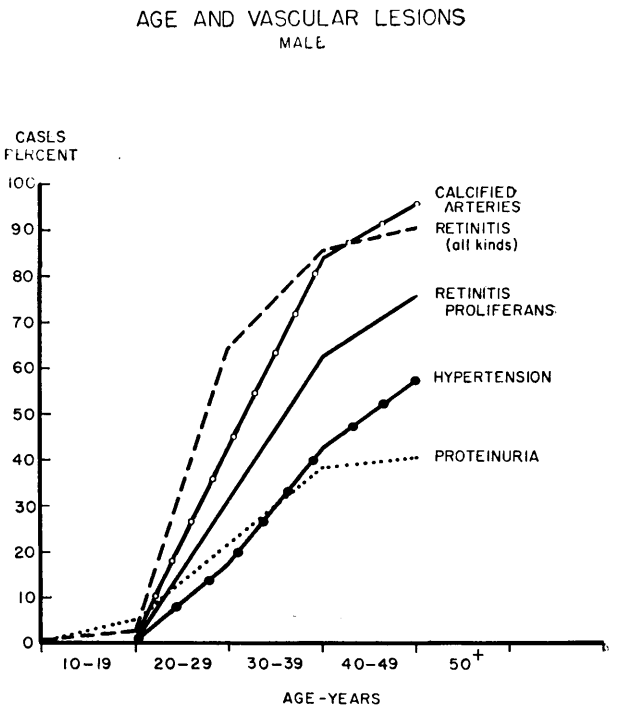

FIGURE 4

types of sclerosing processes, the significant, progressive and lethal lesions involve the arterioles, capillaries and venules. These small vessels can be observed at the microscopic level in the bulbar conjunctiva. Such examinations have been made upon this group by Ditzel[11] and have shown two types of patterns. One is characterized by the loss of venular tone and by venular dilatation. The second is characterized by increased arteriolar constriction. The changes are followed by intravascular aggregation of erythrocytes, by perivascular edema and by hyaline deposition. Long-term diabetics show these abnormal responses, and untreated and uncontrolled cases to an exaggerated degree. It is significant that these changes were also observed in children of diabetic mothers, 16 per cent in those with normal glycemia, 51 per cent in those with hyperglycemia.

Because Fanconi[12] reported 100 per cent mortality from nephropathy in juvenile diabetes before the twentieth year of the disease and because he attributed it to the low protein content of his diets, the dietary management of these patients was reviewed.

Patients were classified according to presence or absence of vascular lesions, as perfect, minimal, moderate, and severe. *Minimal* lesions included microaneurysms and/or calcified arteries; *moderate* included blotchy hemorrhages; and *severe* included proteinuria and neovascularization in the retina. The weights and prescribed diets and insulin were compared. There were

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no significant differences and, in this group, vascular lesions did not appear to be iatrogenic in origin.

Unusual procedures. The most remarkable procedures experienced by this group were the removal of a pheochromocytoma, an aorta graft and a single transplantation of fetal pancreas. These two last procedures were done recently and the influence upon the diabetic state has not been revealed.

Mortality. Cardio-renal-vascular lesions have replaced nearly all other causes of death, accounting for 87.5 per cent of the total. Nephropathy alone accounted for one-half of the deaths. The changing status with respect to causes of death was shown by the near disappearance of coma, sepsis and tuberculosis, formerly the chief causes of death. In this group they accounted for 0.6 per cent, 0.6 per cent, and 1.2 per cent. The median age at death was 32 and median duration 22 years.

DISCUSSION

Two major problems confront us: (1) the acceleration of vascular lesions; and (2) the progression of the diabetic process to a total diabetic state. Of the four possibilities which suggest themselves in the interrelationship of diabetes and vascular damage—(1) gene linkage, (2) physical signs, (3) a complication, or (4) any combination of these—our data support the last. The children of our diabetic mothers have shown the vascular pattern characteristic of diabetes. These individuals may be pre-diabetics; on the other hand, they are heterozygotes who may carry the vascular changes, hyperglycemia and/or glycosuria as part of the inherited recessive defect. Poor chemical control of diabetes markedly affected the vascular responses. Poor control has been reported in our cases[13] as showing a statistically significant correlation with the frequency and severity of vascular lesions in youth. Reversible vasomotor vascular changes can be seen in the bulbar conjunctiva. The end result of these abnormal reversible vasomotor changes is stasis, probably leading to hypoxia and starvation, sequelae, which, dependent upon degree and chronicity, will produce degenerative changes.

The presently available appropriate mixtures of regular and intermediate acting insulins in split doses have already increased the facility with which chemical control of juvenile diabetes can be achieved. Prescription of diets moderate in carbohydrate will also avoid the wide undesirable fluctuations of the levels of blood glucose.

The search for inhibitors of insulinase,[14] islet cell stimulators,[15] and technics for pancreatic grafts continues. Fifty per cent of a pilot group of former juvenile patients receiving estrogen during pregnancy showed a 50 per cent drop in insulin requirement contrasted with a 5 per cent drop in the diabetic males in this series. One fifteen-year-duration case so treated showed islet hypertrophy and hyperplasia (this case not included in the presently discussed autopsied reports).

Cortisone in small doses had no effect upon the natural course of diabetes in a group of young diabetic children. A group of adolescents have remained in the remission phase in a study of less than three years and are still sensitive to sulfonyl compounds.

Since November 1955 five patients, including one in this series, have had implants of the pancreatic tissue of their nonsurviving newborn infants. Sufficient time has not elapsed for proper conclusions to be drawn.

CONCLUSION

Of 1,072 juvenile diabetics surviving twenty years, 82 per cent are living. Their predisposition to diabetes was hereditary. Their disease followed a natural course from virulent onset to favorable remission to a total state. The problems of growth and development have largely resolved themselves. The successful control of former lethal factors—coma, sepsis and tuberculosis—is shown conclusively. Nephropathy has replaced other causes of death. Although new data on the possible mechanism of production of vascular damage and its regulation are suggested, poor chemical control of diabetes remains an important contributing factor. Present forms of available insulins control diabetes with greater facility than those used in this series of patients, and programs to alter the course of diabetes, especially those applicable in the remission phase, are in progress.

SUMMARIO IN INTERLINGUA

Curso Natural e Prognose de Diabete Juvenil

Ex un serie de 1.072 diabeticos juvenil qui ha supervivite vinti annos, 82 pro cento vive al tempore presente. Lor predisposition a diabete esseva hereditari. Lor morbo sequeva un curso natural ab declaration virulente a remission favorabile a un stato total. Le problemas de crescentia e de disveloppamento se ha resolvite in grande mesura. Le subjection de previemente letal factores como coma, sepsis, e tuberculose ha demonstrabilemente succedite. Nephropathia occupa le loco de altere causas de morte. Ben que nove datos relative al mechanismo possibile del production de lesiones vascular e etiam al regulation de ille mechanismo ha essite presentate, le inadequate adjustamento chimic de diabete remane un importante factor contributori. Le nunc disponibile formas de insulina es plus efficace in le regu-

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lation de diabete que illos usate in le serie de patientes hic reportate. Programmas destinate a alterar le curso de diabete, specialmente durante le phase de remission, es in progresso.

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DISCUSSION

LAURANCE W. KINSELL, M.D., (*Oakland, California*): Dr. White, I enjoyed your paper very much. I wonder if you would have available the figures for insulin requirement in this group. The first six months, the first year, the second and third year following onset of diabetes.

ALLEN GOLD, M.D., (*Montreal*): Cortisone is mentioned as a beta cell protector. Would Dr. White care to elucidate this further?

REED HARWOOD, M.D., (*Boston*): I would like to ask Dr. White to tell us a little bit more about remissions in juvenile diabetics. Is it frequent for diabetics over twenty who have had severe onset of diabetes subsequently to get along without insulin for any time?

CECIL STRIKER, M.D., (*Cincinnati*): I would like to ask Dr. White whether there was any correlation between the need for increase in insulin and the high incidence of complications. For example, the incidence of those things that worry us, namely, kidney lesions.

HENRY T. RICKETTS, M.D., (*Chicago*): Dr. Striker's comments remind me of a comment I would like to make. Dr. White said, I believe, that as measured by glycosuria and hyperglycemia control in many of these patients was different, and I wondered what other measurements of control she would like to apply.

PRISCILLA WHITE, M.D.: I thought you were going to answer that last question, Dr. Ricketts.

I think that the juvenile patient, somewhere between the third and the fifth year of diabetes in almost all instances, becomes a total or near-total diabetic. The insulin requirement is high and remains high in these patients nearly all of whom did develop some vascular lesions.

I think these patients with relatively good control, of course, survive much longer. Our really bad actors have often died between the fifteenth and the twentieth year of their disease. The fact that they lived so long was partly an indication of relatively good control.

Cortisone was attempted in these fresh cases of diabetes preferably in their remission phase because of the experimental work of Houssay. In his experimental work on diabetic animals he found that if he gave, along with insulin, estrogen or cortisone, hydrocortisone, thyroxin, in very small doses, that within six months clinical evidence of diabetes had disappeared. When the pancreas was examined, hypertrophy and hyperplasia of islets was demonstrated.

We had, of course, been using large amounts of estrogenic nature in our former juveniles who subsequently became pregnant and thought that there was some indication of a drop in insulin requirement in these patients. One patient coming to autopsy did have hypertrophy and hyperplasia so that gave us the courage to try this experiment in the juvenile patients.

The remission phase of juvenile diabetes occurred in one-third of the patients in this long-term group, and I think that is a fairly good estimate of its frequency. In some patients the diabetes may have started in diabetic coma, and yet they will go into a remission phase. In some instances, the standard glucose tolerance test may become normal, and yet subsequently the disease becomes intensified, runs its natural course, and subsequently these patients later develop the vascular complications of the disease. I have a record of the insulin requirement of these long-term cases by yearly, six months' and three months' intervals.

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