DIABETIC RETINOPATHY IN YOUNG PERSONS

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INTRODUCTION

Diabetes mellitus in children and young adults during the pre-insulin era was a severe and rapidly progressive disease. The prognosis was grave and the patient usually died in coma within a period of two years. The survival period was so short that retinal lesions rarely developed and this gave rise to the belief that diabetes mellitus was not a cause of retinopathy in the young person (1–5). This tenet has retained its popularity until relatively recent years although occasional cases of retinopathy in young adults thought to be on a diabetic basis were observed from time to time before the introduction of insulin. The rarity of retinal involvement in children with severe diabetes often has been advanced as a strong argument in favor of the thesis that retinopathy in older diabetics represented merely a phase in retinal arteriosclerotic vascular disease perhaps modified in some manner by the presence of diabetes mellitus (6–8).

After the introduction of insulin 28 years ago, it became possible to keep the diabetic child alive and, as additional information concerning the disease accumulated, better methods of treatment evolved. Advances in the field of nutrition, the introduction of more effective insulin preparations, refinements in the handling of the acute complications such as acidosis and coma, and the discovery of potent chemotherapeutic agents with which to combat intercurrent infections are all important factors which have combined to increase the life expectancy of the diabetic child. As the survival period of juvenile diabetics* gradually lengthened, retinal lesions were encountered with increasing frequency even in the absence of hypertension and demonstrable vascular disease.

Today a high percentage of young adults who have been diabetic

*Patients with the onset of diabetes mellitus before the age of 15 are considered to be juvenile diabetics.

since childhood find themselves severely handicapped by crippling vascular disease (9–12). Usually the earliest evidence of pathology in the blood vessels is to be found in the retina, and all too often the early lesions gradually progress to pronounced impairment of vision and eventual blindness. Dolger (10) found this "shocking sequel to retinopathy" in 5 of 55 juvenile diabetics and White and Waskow (12) reported near or total blindness in 15 percent of 200 juvenile diabetics surviving the disease for 20 years or longer.

Therefore it appears that, although great progress has been made in the treatment of childhood diabetes, present-day methods have failed to prevent the development of chronic degenerative vascular changes which appear late in the course of the disease. The question naturally arises as to whether these changes represent merely a complication of the deranged metabolism and are, as such, amenable to control, or whether the accelerated vascular damage is a part of the diabetic process and, therefore, an inevitable process which no known method of treatment will prevent. If the latter view is correct, the patient might well be spared many of the restrictions necessarily imposed in the effort to maintain a high level of control. On the other hand, if complete or physiologic control of the diabetes will retard or avert progressive and irremediable degenerative changes, then a greater effort should be made to attain and maintain physiologic levels of control. That the pendulum is swinging toward the more hopeless outlook is attested by the number of physicians (13–16) who advocate less restrictive measures for treatment of the disease. As yet sufficient information is not available to evaluate properly the outcome of either method, although the recent report by White and Waskow (12) indicates that patients free from degenerative changes after 20 years of the disease are the ones who have maintained the best levels of control.

The present study is an attempt to determine the incidence, the manner of development, and the severity of retinopathy in a group of young persons who have had diabetes mellitus for ten years or longer, and who have maintained known levels of diabetic control. The correlation of retinal lesions with the development of chronic degenerative changes elsewhere in the body is

considered. Furthermore, an effort has been made to determine the effect, if any, of varying levels of control on the development of retinal changes and other types of vascular damage appearing late in the course of the disease.

MATERIAL

The present study is based on retinal lesions and degenerative changes elsewhere which have occurred in 75 young persons who have had diabetes mellitus for ten years or longer. All of the patients have been treated for varying periods of time in the Pediatric Clinic, University Hospitals, Iowa City, Iowa, and were willing to return during the past year for an analysis of their diabetic status. The only requirements for selection of cases were as follows:

1. All patients must have had diabetes for ten years or longer.
2. All patients must be willing to return to the hospital and submit to a detailed physical and laboratory examination. The rarity of retinopathy and other types of degenerative changes in patients of this age obviated the necessity for a control group.

In most instances treatment was started in the Pediatric Clinic soon after the onset of the disease. At the first visit the child was hospitalized until the general condition was satisfactory and control of the diabetes was stabilized. After the child was aglycosuric and free from insulin shock, treatment was continued in the home. The parents were urged to keep a daily home record of the progress of the child. This included entries for diet, insulin requirements, amount and degree of physical activity, the trend of emotional patterns, description of any intercurrent infections, and the result of all urine examinations. This home record was presented for analysis at each subsequent hospital visit and thus became a part of the hospital record. In general the patients returned for evaluation every four to six months, but a few were seen less frequently and at irregular intervals.

Thus, complete hospital records are available for all but four members of the group until they attained the age of approximately twenty-one years. At this time they were discharged to the care of their home physician and subsequently experienced varying levels of diabetic control. In such a case, each patient has answered

a detailed questionnaire covering the period since the last out-clinic visit relative to their diabetic management.

OBJECTIVE OF MANAGEMENT

The objective in treatment of childhood diabetes by the physicians (17–21) in the Pediatric Clinic is based on the premise that the child has normal propensities for health as long as the diabetes is well controlled. Therapy is considered adequate only so long as normal physiologic conditions are maintained. Emphasis is placed on a nutritionally complete diet, similar to a normal diet, and quantitative primarily in respect to calories. Until 1944, regular insulin was used to maintain stability of control and injections were given four times daily, one-half hour before meals and once during the night, usually at 1:00 A.M. Only during the past five years has it been found practicable to use a combination of rapidly acting and slowly acting insulin without sacrificing control. Globin insulin with zinc now is used in place of the evening and night doses of regular insulin.

If treatment of the child was started early in the course of the disease, a high level of control was possible in the well-adjusted home. The longer the diabetes remained incompletely controlled, the more difficult it was to maintain complete control. Obviously it was impossible to maintain it in all cases, and cooperation from parents and child differed widely in the group.

METHOD OF STUDY

In 71 of the 75 subjects examined it was possible to evaluate the control of the disease from one hospital visit to the next by an analysis of the hospital record, home record, questionnaire, and interim history. Each period was given a numerical control rating.

Control rating 0: Good.	Freedom from sugar in the urine except for occasional slight traces. Approximately normal blood sugar levels.
Control rating 1/2: Fair to Good.	Fluctuating from 0 to 1.
Control rating 1: Fair.	Less than one-half of urine specimens free from sugar and small amounts of sugar in the remaining specimens. Slightly elevated blood sugar levels.

Control rating 2: Fair to Poor.	Fluctuating from 1 to 3.
Control rating 3: Poor.	Varying amounts of sugar in the urine continuously. Elevated blood sugar levels.
Control rating 4: Very poor.	Continuous gross glycosuria. High blood sugar levels.

The numerical control rating for the total period of observation was computed in the following manner: The control rating for a given period was determined and multiplied by the duration of that period in years. The sum of the control ratings for each period equals the numerical control rating for the entire period of observation. For example:

Three years with control rating	0 = 0
Four years with control rating	½ = 2
Three years with control rating	1 = 3
Four years with control rating	2 = 8
Two years with control rating	3 = 6
One and one-half years with control rating	4 = 6
Numerical control rating for total period of observation	=25

The examination included a determination of visual acuity, ophthalmoscopic examination of the eye grounds through dilated pupils and slit-lamp biomicroscopy of the anterior segments with particular attention to the lens.

Changes in the retinal arterioles were graded according to the classification recommended by Wagener, Clay, and Gipner (22).

Generalized Narrowing of Arterioles

Grade 1. Reduction of caliber of arterioles to 3/4 average caliber or 1/2 caliber of veins.
Grade 2. Reduction of caliber of arterioles to 1/2 average caliber or 1/3 caliber of veins.
Grade 3. Reduction of caliber of arterioles to 1/3 average caliber or 1/4 caliber of veins.
Grade 4. Arterioles thread-like or invisible.

Focal Constrictions or Focal Sclerosis of Arterioles

Grade 1. Localized narrowing to 2/3 caliber of proximal segment of arteriole.

Grade 2. Localized narrowing to 1/2 caliber of proximal segment of arteriole.
Grade 3. Localized narrowing to 1/3 caliber of proximal segment of arteriole.
Grade 4. Arteriole invisible beyond point of constriction (or in case of focal sclerosis visible only as a thin, fibrous cord).

Generalized Sclerosis of Arterioles

Grade 1. Brightening or increased luster of the arterioles; mild depression of the veins at the points of arteriolar crossing, with reduction in visibility of those portions of the veins which underlie the crossing arterioles.
Grade 2. Burnished coppery color of arterioles, with definite depression of underlying veins, widening of the apparent arteriolovenous crossing spaces, and almost complete invisibility of those portions of the vein which underlie the crossing arteriole.
Grade 3. Polished silver color of the arterioles, widening of the apparent arteriovenous crossing spaces with a change in the course of the veins (right-angled crossing), complete invisibility of those portions of the veins which underlie the crossing arterioles and distal dilatation of the veins.
Grade 4. Arterioles visible only as fibrous cords without blood stream.

Aside from venous changes, few arteriolar changes were encountered in this group of patients and the classification was useful mainly as a means of excluding arteriolar disease. Slight or questionable exaggeration of the light reflex without accompanying changes in transparency or crossing were considered insufficient evidence for the diagnosis of sclerosis.

The types of retinopathy encountered were classified according to the method used by Wagener (9). It is as follows:

1) Hemorrhages only;
2) Central punctate retinopathy, that is, a combination of hemorrhages and exudates;
3) Mixed vascular retinopathy, that is, retinal lesions caused by hypertensive vascular changes superimposed on already existing diabetic retinopathy;
4) Venous disease and proliferating retinopathy;
5) Hemorrhages or central punctate retinopathy plus toxic cotton-wool patches;
6) Toxic retinopathy.

The systemic blood pressure was considered elevated if the systolic pressure exceeded 140 mm. of mercury or the diastolic pressure was 90 mm. of mercury or over.

Laboratory studies included determinations of the non-protein nitrogen, serum proteins, blood sugar, and fat. The urine, of course, was examined for the presence of albumin. Roentgenographic studies of the pelvis, left leg, and foot were made for evidence of calcification in the blood vessel walls. Examination of the heart included electrocardiographic and roentgenographic examinations.

DEVELOPMENT AND COURSE OF RETINOPATHY

At the present time there remains little doubt that diabetic retinopathy is a specific entity dependent in some manner on vascular damage associated with diabetes mellitus. The young diabetic presents an excellent opportunity to observe the development of retinopathy without the complicating factor of vascular changes and retinal lesions secondary to hypertension. Although no single case has been followed through all the progressive stages of the retinopathy it has been possible to gain a rather clear clinical picture of the sequence of the retinal lesions.

Venous dilatation is often the earliest ophthalmoscopic finding. Both the large veins and small venules become engorged. Myelius (23) and Ballantyne (24) have stressed the importance of this early change and the latter author estimates that it occurred in approximately one-third of his cases. Since there is evidence that the vascular changes in diabetic retinopathy affect the veins rather than the arterioles, Ballantyne feels that venous dilatation is an important early sign of stasis in the venous circulation of the retina. This abnormality was noted in ten members or 13.3 percent of the present group without any other evidence of retinal involvement.

The appearance of one or more deep, punctate hemorrhages usually in the perimacular area must still be considered the first definite evidence of retinopathy. Nettleship (25) stated that the round, deeply situated hemorrhages in diabetics were often derived from capillary aneurysms, and recently it has been shown histologically that many of the pin-point red dots are actually micro-

aneurysms. Jonas Friedenwald (26), while making a study of diabetic retinas in 1936, recognized these lesions and Ballantyne (24) later gave a detailed clinical and histological description of the aneurysms. The latter author states that

> . . . the aneurysms are situated in the inner nuclear layer and are globular distensions of the capillaries which form a link between the first capillary plexus, in the ganglion cell layer, and the deeper plexus situated at the outer boundary of the inner nuclear layer; that is, the aneurysms are situated between the pre-capillaries on the arterial side and those on the venous side of the circulation. . . . The formation of the capillary aneurysms seems to require the operation of two factors, weakening of the resistance of the capillary walls and a relative increase of pressure within the vessel.

More recently Friedenwald (26), by use of the Hotchkiss fixed carbohydrate stain and flat retina preparations, again beautifully demonstrated these lesions. He states,

> In the diabetic retinopathy the aneurysms are regularly present by dozens, sometimes by hundreds, and their pattern with the surrounding exudates and hemorrhages appear, so far, to provide a characteristic picture.

Similar preparations of flat retinas from non-diabetics disclosed only an occasional aneurysm of this type.

In general, the appearance of the familiar, yellowish-white, "waxy" plaque deep in the retina represents a later stage in the development of the retinopathy. In the cases of retinopathy occurring in this group of patients, exudates never were found to precede the appearance of hemorrhages or microaneurysms. The exact origin of these lesions remains unsettled, although Waite and Beetham (27) expressed the opinion that they resulted from hyalinization of hemorrhage. According to Elwyn (28), the deep deposits follow deficient oxidation of the retinal tissue and Ballantyne (24) suggested that at least some of the punctate white areas might be the thickened hyalin wall of microaneurysms, while others might result from thrombosis of the microaneurysm with consequent cicatrization. Clusters of exudate surrounding microaneurysms were found by Friedenwald (26) with such frequency that he believed they resulted from leakage of plasma

through the aneurysmal wall. At first punctate, the deposits in time form clusters, clumps, and masses, usually but not always situated in and around the macular area. They may present a variety of patterns and often simulate a circinate figure but seldom, if ever, form a macular star.

In young diabetics, these retinal lesions occur almost invariably in the presence of ophthalmoscopically normal arterioles and in the absence of edema of the retina and nerve head. Clinically, they are identical with the lesions encountered in older diabetics without hypertensive vascular changes.

In some instances, usually after diabetes has been present for several years and associated with widespread vascular damage elsewhere in the body, particularly in the kidney, the systemic blood pressure becomes elevated and hypertensive vascular changes may be seen in the fundus. These changes are generalized arteriolar sclerosis, arteriolar narrowing and localized constrictions, and may be severe enough to produce retinal lesions characteristic of hypertensive retinopathy. These lesions, consisting of edema, superficial striate hemorrhages, and cotton-wool patches, when superimposed on a diabetic retinopathy produce the clinical picture of a mixed diabetic and hypertensive retinopathy. This mixed type of retinopathy reported by Wagener (9) occurred in 4.6 percent of his 1945 series of cases. In the present group it was found in one patient, an incidence of 1.3 percent.

In general, the retinal lesions progress slowly and good vision may be retained for many years unless the foveal region becomes involved. The late stage of retinopathy is heralded by the onset of retinal and vitreous bleeding and deterioration of useful vision. Preretinal hemorrhages may break through into the vitreous with resultant retinitis proliferans, retinal detachment, and disorganization of the retina.

In a small percentage of cases gross changes in the large and medium sized veins overshadow the picture. These venous changes present a varied ophthalmoscopic picture consisting of irregular dilatations and constrictions, deposition of a yellowish-white granular material along the vessel wall, bizarre irregularities and new vessel formations, and the appearance of networks or fanlike

figures of new vessels in and on the surface of the retina. Often attached to the nerve head, the network of new vessels may proliferate for a considerable distance into the vitreous and become the source of recurrent vitreous bleeding. Many of the venous changes have been shown by Klien (29), O'Brien and Allen (30), Agatston (31), Gibson and Smith (32), and Ballantyne (24) to depend on a process of phlebosclerosis. Usually considered a late complication, these changes may from the onset assume a dominant role and progress to blindness with alarming rapidity.

INCIDENCE OF RETINOPATHY

The incidence of retinopathy in young diabetics is increasing from year to year. Although an occasional case was reported during the preinsulin era, such cases were exceptional and, in general, it was believed that diabetic retinopathy occurred only in the older age groups. Spalding and Curtis (35) examined 307 diabetics in 1927 and found no instance of retinopathy in patients under 30 years of age. In 1929 Cammidge (36) reported on 1,000 diabetics and found one case of retinopathy in a 19-year-old girl, but all the other patients with retinal lesions were over 35 years of age. As late as 1931, Shepardson and Crawford (37), reporting on the ocular findings in 68 unselected cases of diabetics found retinal lesions in only one case less than 40 years of age. Waite and Beetham (27) in a survey of over 2,000 diabetics published in 1935 found an incidence of 1.9 percent in patients under 30 years of age. In 1942 O'Brien and Allen (38) examined 555 young diabetics less than 30 years of age and found typical diabetic retinopathy in 4 percent of the subjects. In 1945 Wagener (9) reported retinal complications in 8.3 percent of patients under 30, and, furthermore, found retinopathy in 76 percent of young persons who had had diabetes for ten years or longer. White and Waskow (12) have recently found retinopathy in 80 percent of 200 juvenile diabetics surviving the disease for twenty years or longer.

RESULTS OF STUDY

Sex: Males and females were almost equally distributed in the group, there being 40 males and 35 females.

Age: The average age for the group at the time of last exami-

TABLE 1. AGE DISTRIBUTION OF 75 JUVENILE DIABETICS

10–14 yrs.	*15–19 yrs.*	*20–24 yrs.*	*25–29 yrs.*	*30–31 yrs.*
5	18	25	21	6

nation was 22 years; no patient was older than 31 and the youngest patient was 12 years old (Table 1).

Types of Degenerative Changes

In Table 2 are listed the types of degenerative changes encountered at the last examination of 75 juvenile diabetics.

Retinopathy

Forty of the subjects were considered to have normal fundi, although in 10 of these varying degrees of venous dilatation was evident. The remaining 35 patients, 46.6 percent, had retinal lesions considered characteristic of various phases of diabetic retinopathy. Of this group, 27 had only hemorrhages, microaneurysms, or both, varying in number from a single lesion in one or the other retina to large numbers in the perimacular area or scattered throughout each retina. Five patients presented the typical picture of central punctate retinopathy—hemorrhages and microaneurysms, plus punctate exudative lesions. One patient presented a mixed diabetic and hypertensive retinopathy and another member of the group had a typical punctate retinopathy plus numerous cotton-wool patches without arteriolar changes. Only one patient had far advanced retinal changes which consisted of preretinal hemorrhages, massive proliferative changes and retinal detachment (Table 3).

TABLE 2. TYPE AND INCIDENCE OF DEGENERATIVE CHANGES IN 75 JUVENILE DIABETICS

Degenerative Change	*Males*	*Females*	*Total*	*Percent*
Retinopathy	22	13	35	46.6
Cataracts	6	5	11	14.6
Calcification of blood vessels	6	6	12	16.0
Hypertension	2	1	3	4.0
Nephropathy (Albuminuria)	1	2	3	4.0
Abnormal Electrocardiogram	0	0	0	—

TABLE 3. TYPES OF FUNDUS PICTURE ENCOUNTERED IN 75 JUVENILE DIABETICS

Fundus	*Number of Patients*	*Percent*
Normal fundi	40	53.3
Hemorrhages or microaneurysms or both	27	36.0
Central punctate retinopathy	5	6.6
Mixed vascular retinopathy	1	1.3
Venous disease and proliferative retinopathy	1	1.3
Hemorrhages or central punctate retinopathy plus toxic cotton-wool patches	1	1.3
Toxic retinopathy	0	0

Cataracts

Although the study was not primarily concerned with the development of cataractous changes, lens opacities considered to be on a diabetic basis were noted in 11 patients, an incidence of 14.6 percent. The degree of change varied from minute flocculi usually associated with iridescent crystals to advanced changes which had reduced the visual acuity in one eye to 3/60. One patient had previously undergone needling operations with resultant normal vision, but an after-cataract had subsequently reduced the visual acuity in one eye to counting fingers. All but 2 of the 11 patients had a retinopathy in addition to the lens changes, and all of the patients had had varying periods of poor control. One of the 2 patients without retinopathy had a numerical control rating of two, and the periods of poor regulation were short but severe. The lens changes presented by this patient were early, consisting of numerous punctate opacities in the anterior and posterior cortex with a few iridescent crystals.

Visual Acuity

The central visual acuity was reduced in one or both eyes of 5 patients to 6/9 or less. Two of these had a monocular convergent squint with amblyopia ex anopsia and one patient had posterior subcapsular lens opacities which reduced the visual acuity in one eye to 3/60. Another patient had previously undergone needling operations for diabetic cataract with resultant normal vision, but an after-cataract had developed in one eye which had reduced the

vision to the ability to count fingers. Only one patient had retinal changes due to diabetes sufficiently advanced to cause reduction of vision. This patient had a numerical control rating of 63, the highest in the group, and at each examination was found to have gross glycosuria and a high blood sugar level. The right eye was blind and the vision of the left was hand movements only. Ophthalmoscopic examination disclosed numerous preretinal hemorrhages, massive proliferative retinopathy, and retinal detachments in each eye.

Severity of Diabetes

All members of the group were severe diabetics. Using the insulin dosage per 24 hours as the criterion for severity of the diabetes, it was found that the requirement ranged from 30 units to 108 units, and the average for the group was 60 units. Although insulin requirement was the major factor in classifying patients as to relative severity of the disease, other factors such as age, body build, caloric intake, amount of physical activity and the presence of infection were taken into consideration. Twenty-two percent were classified as very severe; 60 percent as moderately severe, and 18 percent as less severe. No statistical significance was found to exist between the severity of the diabetes and the development of retinopathy (Table 7).

Age of Onset of Diabetes

The age of onset of diabetes for 26 members of the group was four years or less; for 28 patients five to nine years, and for 21 patients ten to fourteen years. The earliest age of onset was one year and all subjects had diabetes by the time they reached the age of fourteen. The average duration of the diabetes was approximately equal for each of the three groups. Retinopathy had developed in 7 patients, 26.9 percent, with the onset of diabetes one to four years; 17 patients, 60.7 percent, with age of onset five to nine years; and 11 patients, 52.3 percent, who developed diabetes at age ten to fourteen years (Table 4). The group with the earliest onset of the disease had a considerably lower incidence of retinopathy than the two other groups. However, the age of onset was found to be statistically significant only at the 20 per-

TABLE 4. AGE OF ONSET OF DIABETES, DURATION OF THE DISEASE AND DEVELOPMENT OF RETINOPATHY IN 75 JUVENILE DIABETICS

Age of onset	*0–4 yrs.*	*5–9 yrs.*	*10–14 yrs.*
Number of patients	26	28	21
Average duration of diabetes in yrs.	15.0	16.5	13.6
Number with retinopathy	7	17	11
Percent retinopathy	26.9	60.7	52.3

cent level, as shown in Table 7. It is believed that the lower incidence of retinopathy in this group may be explained by the fact that during childhood it is easier to obtain cooperation than it is during adolescence.

Duration of the Diabetes

All of the subjects in the group had had diabetes mellitus for ten years or longer. In Table 5 is shown the relationship between retinopathy, duration of the disease and age of the patient.

The importance of duration of the disease as a factor in the production of retinopathy is shown clearly in this table. Also, it is evident that the rapid increase in the incidence of retinopathy is out of proportion to the accompanying increase in the age of the patient. This finding is in accord with the observations of other workers who have investigated the subject. It is to be noted, however, that in this series there is a proportional increase in the average control rating. This may indicate that, as the patient grows older, economic and social factors make it increasingly difficult to maintain a high level of control. The close correlation between the development of retinopathy and duration of diabetes also is shown in Table 7.

TABLE 5. RELATIONSHIP BETWEEN RETINOPATHY, DURATION OF DIABETES AND AGE OF PATIENT IN 75 JUVENILE DIABETICS

Duration of disease in yrs.	*10–14*	*15–19*	*20–25*
Number of patients	37	27	11
Number of patients with retinopathy	9	17	9
Percent retinopathy	24.3	62.9	81.8
Average age, each group	19.7	23.8	28.0
Average control rating, each group	5.8	12.9	21.0

Control of the Diabetes

In the manner previously described, it was possible to give 71 of the 75 patients a numerical control rating for the entire period of observation. Four patients were excluded from this part of the study because of insufficient data. Table 6 shows the relationship between the levels of control and the development and stage of

TABLE 6. RELATIONSHIP OF LEVEL OF CONTROL TO DEVELOPMENT AND STAGE OF RETINOPATHY IN 71 JUVENILE DIABETICS

Numerical Control Rating	*Normal Fundi*	*Hemorrhages and/or Microaneurysms Only*	*Central Punctate Retinopathy*	*Mixed Vascular Retinopathy*	*Hemorrhages or Central Punctate Retinopathy plus Toxic Cotton-Wool Areas*	*Venous Disease and Proliferative Retinopathy*
60–64	—	—	—	—	—	1
55–59	—	—	—	—	—	0
50–54	—	—	—	—	—	0
45–49	—	—	1	—	—	0
40–44	—	2	0	—	—	0
35–39	—	2	1	—	1	0
30–34	—	4	0	1	0	0
25–29	1	6	0	0	0	0
20–24	2	7	1	0	0	0
15–19	10	4	0	0	0	0
10–14	7	1	0	0	0	0
5–9	10	0	0	0	0	0
0–4	9	0	0	0	0	0
Totals	39	26	3	1	1	1
Average Control Rating	10.7	25.0	37.0	32.0	35.0	63.0

the retinopathy. Although there is some overlapping, it is clear that the members of the group free from retinal changes are the ones who have maintained the highest levels of control and the patients with the most advanced retinopathies are those with poor control levels. The one patient in the series nearly blind from advanced retinal changes was the only one of the group with continuous gross glycosuria and constantly high blood sugar levels. The close relationship which exists between development of

TABLE 7. TEST OF ASSOCIATION BETWEEN RETINOPATHY AND SPECIFIED VARIANTS OF DIABETES MELLITUS

Retinopathy	*Chi-square*	*Degrees of Freedom*	*Significance*
Age at onset[a]	13.5	10	At the 20% level
Severity of disease[b]	4.5	10	None
Duration of disease[c]	30.6	10	Beyond the 1% level
Level of control[d]	35.3	10	Beyond the 1% level

[a]All patients in the group had diabetes before 14 years of age.
[b]All patients had severe diabetes. They were divided into three groups—very severe, moderately severe and less severe.
[c]All patients in the group had diabetes for 10 years or longer.
[d]This represents an over-all evaluation for the entire period of observation.

retinopathy and level of control of the diabetes also is shown in Table 7. This factor was found to be significant beyond the 1 percent level.

Calcification of Blood Vessels

Twelve subjects presented calcification of the walls of blood vessels, an incidence of 16 percent, as determined by roentgenographic examination of the pelvis, left leg or foot. Eleven of the 12 patients presented retinopathies which ranged from the early stage consisting of hemorrhages or microaneurysms or both, to the patient with advanced retinitis proliferans and retinal detachment. In general, this group of patients was characterized by long periods of poor control, although one patient 22 years of age who had had diabetes for 18 years had a control rating of 14. This patient showed very early calcification of a small vessel lying between the first and second metatarsals and was free from other demonstrable degenerative changes, including retinopathy (Table 8).

Hypertension

Three patients were found to have an elevation of the systemic blood pressure. One of these was a borderline case; the recorded blood pressure was only 140/88. The retinal vessels in this case were considered normal but an early central punctate retinopathy was present. Another patient presented a mixed hypertensive and diabetic retinopathy with well marked arteriolar changes which

TABLE 8. COMPARISON OF CALCIFICATION OF BLOOD VESSELS, DEVELOPMENT AND STAGE OF RETINOPATHY AND LEVEL OF CONTROL IN 71 JUVENILE DIABETICS

Numerical Control Rating	*Normal Fundi*	*Hemorrhages and/or Microaneurysms Only*	*Central Punctate Retinopathy*	*Mixed Vasuclar Retinopathy*	*Hemorrhages or Central Punctate Retinopathy plus Toxic Cotton-Wool Areas*	*Venous Disease and Proliferative Retinopathy*
60–64	—	—	—	—	—	1[a]
55–59	—	—	—	—	—	0
50–54	—	—	—	—	—	0
45–49	—	—	1[a]	—	—	0
40–44	—	2[b]	0	—	—	0
35–39	—	2[b]	1	—	1[a]	0
30–34	—	4[b]	0	1	0	0
25–29	1	6	0	0	0	0
20–24	2	7[a]	1	0	0	0
15–19	10	4	0	0	0	0
10–14	7[a]	1	0	0	0	0
5–9	10	0	0	0	0	0
0–4	9	0	0	0	0	0
Totals	39	26	3	1	1	1

[a]One patient in this group had calcification of blood vessels.
[b]Two patients in this group had calcification of blood vessels.
NOTE: One patient was excluded from the table because data were insufficient to establish accurate control rating.

were recorded as Grade 2 sclerosis and Grade 2+ generalized narrowing. In the third case it was impossible to grade the arteriolar changes because of the hazy media and advanced proliferative changes in the retina. Each of the three patients had maintained very poor control levels and received control ratings of 49, 31, and 63 respectively.

Albuminuria

Three members of the group had albumin in the urine and each was found to have a retinopathy. One patient had a mixed diabetic and hypertensive retinopathy and the other 2 had only hemorrhages or microaneurysms, or both. Two of the patients showed cataractous changes but only one had calcification of the blood vessel walls. Each of the 3 had elevated cholesterol valves

and 2 had low plasma albumin. All had poor control ratings which were 22, 31, and 36, respectively.

Electrocardiographic Studies

Electrocardiograms were normal for all patients.

Non-protein Nitrogen Values

The non-protein nitrogen determinations at the time of the last examination showed essentially normal values for all members of the group. Of the 5 patients with hypertension or albuminuria, or both, only one had a mild elevation of the non-protein nitrogen; this patient had the poorest control level in the group.

Plasma Albumin Levels

Thirty-eight patients, 51 percent, had plasma albumin levels lower than 4 gm. per 100 ml. Twenty-three of these patients, 60 percent, presented varying stages of retinopathy. Six patients had plasma albumin levels lower than 3 gm. per 100 ml. and 5 of these had a diabetic retinopathy. Of the 5 patients with hypertension or albuminuria, or both, 4 had low plasma albumin values and the others had a low normal value.

Serum Cholesterol Values

Serum cholesterol values for 71 of the 75 patients were determined at the time of the last examination. Forty-one patients, 58 percent, had a value higher than 230 mg. per 100 ml. and 15 patients had a value higher than 300 mg. per 100 ml. Twenty-six, 61 percent of the 41 patients, with elevated cholesterol values had varying stages of retinopathy. Ten, 66 percent of the 15 patients with cholesterol values over 300 mg. per 100 ml, had a retinopathy. Of the 5 patients with hypertension or albuminuria, or both, all had marked elevation of the serum cholesterol values.

DISCUSSION

The results of a study of a group of 75 juvenile diabetics surviving the disease for ten years or longer are presented. It was pointed out that the child with this disease seldom lived longer than two years during the preinsulin era and consequently retinal

lesions were rarely encountered. After the introduction of insulin and with subsequent improvement in treatment, it became relatively easy to keep the diabetic child alive. As the survival period lengthened, it soon became evident that diabetic retinopathy not only occurred in the young person but that the incidence was steadily increasing. In a recent publication, White and Waskow reported an incidence of 80 percent retinopathy in 200 juvenile diabetics who had survived the disease for 20 years or longer; furthermore, retinal damage associated with diabetes had produced near or total blindness in 15 percent of this group of patients. We encountered retinopathy in 46 percent of our group and one patient had retinal lesions sufficiently advanced to interfere with central visual acuity.

The question has arisen as to whether or not retinopathy and other degenerative lesions are merely complications of deranged metabolism or are inevitable changes, the so-called concomitants of the disease. If the former view is correct, then high levels of diabetic control should be the objective of management, but if the latter thesis is accepted then less rigid methods of treatment might be employed. In this study a close correlation was found to exist between the level of control and the development of retinopathy. In general the patients who were free from degenerative changes after ten years or more of the disease were the ones who had maintained consistently high levels of control, and the patients with demonstrable degenerative lesions were the ones with poor control levels. It is recognized that the number of patients studied is not sufficient to warrant sweeping conclusions, but the findings indicate that until additional knowledge is available good control offers the best method of averting or retarding the development of chronic vascular changes.

In this study degenerative changes in the eye were encountered far more frequently than any extraocular type of lesion. In only three patients free from retinal changes was it possible to demonstrate any other type of vascular damage. Therefore, ophthalmoscopic examination is an advisable procedure for the early recognition of chronic degenerative changes. Early recognition is important because there is some evidence that the early retinal lesions may be reversible and thus amenable to treatment. But,

as Folk and Soskin (39) have pointed out, careful and frequent examinations are necessary if the retinopathy is to be discovered in the early stages. Visual acuity is a poor index of retinal involvement because only in the advanced stage is there likely to be any interference with vision.

The significance of low albumin and high cholesterol values is not clear from a study of this series of cases. The values recorded represent a single determination taken at the time of the last examination and may not be a true indication of actual conditions. However, where the deviation from normal values was marked, almost invariably some type of vascular degeneration could be demonstrated and a poor control level was the rule. When the deviation from normal was slight, no correlation was found between level of control and development of degenerative changes. The recent encouraging reports of other writers (40–43) indicate that this aspect of the problem may prove a fruitful field for further investigation.

CONCLUSIONS

1. Retinopathy is the earliest demonstrable evidence of chronic degeneration in juvenile diabetes. The incidence is much higher than any other type of recognizable degenerative change.

2. The incidence of retinopathy is steadily increasing.

3. Venous dilatation may precede or accompany the retinopathy but visible alteration of the retinal arterioles was not encountered during the early stages.

4. Central visual acuity is a poor index of retinal involvement, inasmuch as the foveal region is seldom disturbed until late in the course of the retinopathy.

5. Detailed and frequent ophthalmoscopic examinations are necessary to detect the early retinal lesions.

6. A close correlation was found to exist between the development of retinopathy and the level of control of the diabetes.

7. Duration of the disease was significant in the production of retinopathy. However, the mounting incidence of retinal lesions with the increased duration of the disease was accompanied by a proportionate decrease in the level of control.

8. Age of onset and severity of the diabetes are not significant factors in the development of the retinopathy.

9. Until additional knowledge concerning the treatment of diabetes in childhood is available, a high level of control appears to offer the best means of averting or retarding chronic degenerative changes.

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