The Development of Diabetic Retinopathy

Effects of Duration and Control of Diabetes

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Evolution in the treatment of diabetes mellitus has been marked by a succession of problems brought to notice by newly acquired knowledge or by change in the course of the disease resulting from better therapy. For example, improved treatment has brought longer life to diabetic patients, but in the second and third decades of their disease they often become subject to degenerative vascular lesions. Determination of the exact nature of these lesions is one of the important problems of the present. The fundamental question is whether the degenerative diseases which accompany diabetes are a part of its natural history or whether they are complications. If the first viewpoint is proved correct, the diabetic patient must be regarded as facing the inexorable course of an unalterable disease. Contrariwise, if the other concept is the true one, degenerations, when the pathologic physiology of their production is understood, should be preventable.

It has been recognized for many years that diabetics are prone to develop vascular disease at an early age and at a rate exceeding that of persons without diabetes. The arteriosclerosis and atherosclerosis which are part of this process differ not at all from those seen in nondiabetic individuals except in certain clinical features. Although both are of interest to the student of diabetes and of utmost importance to the patient, there are other degenerative lesions which lend themselves more readily to investigation. Among these is diabetic retinopathy which begins as a visible capillary micro-aneurysm. This lesion, which occurs in the renal glomerulus and is suspected of being present in other places, may be regarded as peculiar to diabetes. From the standpoint of the investigator it is well adapted for study. Other lesions might be chosen such as the diabetic cataract, intercapillary glomerulosclerosis or polyneuritis, but the first of these occurs with relative infrequency and may regress even after a considerable period; and the others are difficult to diagnose accurately in the early stages or may be confused with similar diseases. The retina is easily examined and the progression of retinopathy has been well established. For these reasons we have chosen retinopathy as an index of the presence and degree of degenerative disease. Our studies have been concerned with factors which might influence its development. Our subjects are a group of juvenile diabetics who have been followed in the clinics of the University Hospitals for periods from ten to thirty years.

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COMPOSITION OF THE GROUP

Patients are accepted into the study group when they enter the second decade of diabetes. The course of their disease from its onset is a matter of written record. The group now numbers 132 of whom 69 are men and 63 are women. Periodic visits to the clinic afford the opportunity to examine each patient carefully, to evaluate the control of the diabetes in the interval since the last visit and to make laboratory observations.

The data to be presented here are for the most part limited to the period ending September 1954. At that time the median age of the group was 24.3 years. Figure 1 shows the age distribution of the group.

All are juvenile diabetics who developed their disease before the age of fifteen years except three who became diabetic in their sixteenth year and one whose first symptoms appeared just after his nineteenth birthday. The earliest onset in the group was at the age of six months. Figure 2 shows the number who developed diabetes in

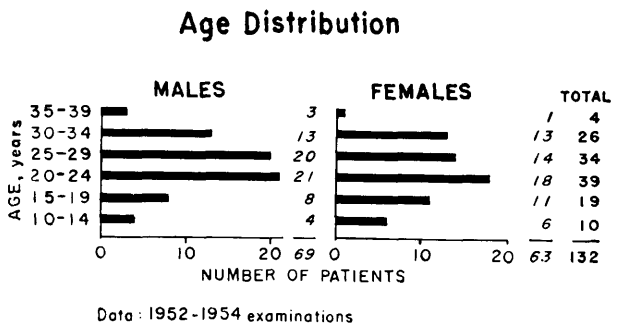

FIGURE 1

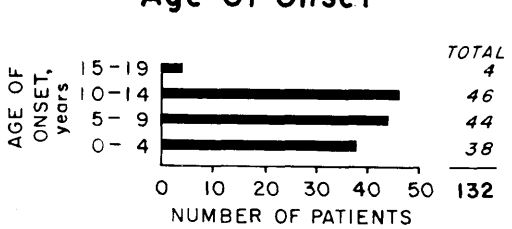

FIGURE 2

each of four age periods of five years. All, as is generally true in juvenile diabetes, have a moderately severe to severe form of the disease as indicated by insulin dosage and insulin-weight ratios before attaining adulthood.

The plan of treatment in all had as its goal the achievement of normal growth and development and exact control of diabetes. To this end diets were designed to insure proper growth. These were complete in all respects.[1] As the patients matured diets were changed to fit adult requirements, energy demands and work schedules. Total dosage and distribution of insulin were ordered with the intent of bringing about excellent control as measured by normal blood sugar levels, freedom from glycosuria, absence of hypoglycemia and avoidance of ketosis at all times. Not all patients achieved this goal constantly but, in striving for it, many have attained a very good degree of control for many years. Some, however, have fallen short and, although we regard this as a joint failure, it does afford the opportunity to make certain comparisons.

PREVIOUS STUDY

In 1949 we reported upon a group of seventy-five diabetic patients who had had their disease for more than ten years.[2] All were juvenile diabetics and their characteristics and the objectives of their treatment were those described for the present group. In fact, the majority are included in the present study. Our conclusions at that time were that, so far as retinopathy is concerned, its occurrence and severity are not related to sex, severity of the diabetes nor age of the patient at onset. Two factors seemed to influence the appearance and progression of the retinal lesions and these were the duration of diabetes and the degree of control achieved. When these were tested, statistically significant degrees of correlation were found in both instances. The value for the relationship between duration of diabetes and the presence of retinopathy was significant at the 1 per cent level of confidence and that for the relationship of the degree of control to retinopathy was significant beyond the 1 per cent level. From this could be concluded only that both factors were of importance in the development of retinopathy.

The question of the relative importance of the two could not be settled. It was known that the average time required after the onset of diabetes for retinopathy to appear is thirteen years.[3] The median duration of diabetes in the group was 15.2 years which was close to the average time required for the development of retinopathy. It was obvious that this study would have to be continued in order that, as time passed, the influence of the period required for retinopathy to appear could be eliminated. In this way the true relation of duration of diabetes to development of degenerative disease might become evident. At the same time a re-evaluation of the influence of control could be made. A clear distinction between the relative importance of these two factors could help answer the fundamental question of whether degenerative disease is a part of the natural history of diabetes or a potentially preventable complication.

With this objective the study was continued. Those persons who had been subjects previously were followed and others were added to the group as they passed into the second decade of their disease in order that more valid comparisons could be achieved not only by study of the former subjects over a longer period but by increasing the number of observations.

METHOD

For the purpose of statistical analysis it was necessary to group our observations into classes. There were three items which had to be so treated. The first of these was duration of diabetes which was calculated to the nearest year. Thus the value of 16 was taken for the duration of disease in all patients whose onset of diabetes had been from 15 years and 6 months to 16 years and 5 months before their last examination. The presence and degree of retinopathy were depicted by a scale ranging from zero to nine in which zero denotes a normal retina and nine proliferative retinopathy. Descriptions of the various stages are given as follows.

CLASSIFICATION OF RETINOPATHY

0—normal.

1—venous dilatation.

2—few punctate hemorrhages and/or capillary aneurysms.

3—many punctate hemorrhages and/or capillary aneurysms.

4—early central punctate retinopathy.

5—advanced central punctate retinopathy.

6—central punctate retinopathy plus pre- or subretinal bleeding.

7—central punctate retinopathy plus cotton-wool patches.

8—mixed diabetic and hypertensive retinopathy.

9—proliferative retinopathy.

To designate the degree of control of diabetes achieved over the entire duration of disease the over-all control rating was computed. This is derived from the interval control rating which is a number designating a certain degree of control. An interval control rating was assigned at each evaluation of the patient to describe the degree of control achieved since the last examination. The over-all control rating is the sum of the products of the interval control ratings and the number of years over which each obtained. The scale of interval control ratings and an illustration of the computation of the over-all control rating are given below.

Interval Control Rating:

0—Freedom from sugar in the urine except for occasional slight traces. Approximately normal blood sugars. (good)

1/2—Fluctuating from rating 0 to 1.

1—Less than one-half the urine specimens free from sugar and small amounts of sugar in the remainder. Slightly elevated blood sugars. (fair)

2—Fluctuating from rating 1 to 3.

3—Varying amounts of glycosuria constantly. Elevated blood sugar levels. (poor)

4—Continuous gross glycosuria. Elevated blood sugar levels. (very poor)

Computation of Over-all Control Rating:

Seven years with rating 0	= 0
Eight years with rating 1	= 8
Four years with rating 3	= 12
Over-all Control Rating	= 20

After tabulation of the data in this fashion scattergrams were constructed by plotting the degree of retinopathy against either duration expressed in years or against degree of control as expressed by the over-all control rating. Analysis of these graphs by the method of Pearson gave the relationship between the two items being tested expressed as the coefficient of correlation.

RESULTS

First to be considered was the original group of 75 patients studied in 1948 and reported upon in 1949. In our previous publication[2] the correlations were done by the chi square method and, for purpose of comparison, it was necessary to calculate the coefficient of correlation by the method chosen for the present investigation. When this was done with the data collected in the period ending in 1948 good correlation was found, as before, between degree of control and retinopathy and between duration of diabetes and retinopathy. The ***r*** value for the relation between control and retinopathy was 0.749 which is significant beyond the 1 per cent level of confidence. That for the relation between duration and retinopathy was 0.334 which is significant at the 1 per cent level. This bore out the conclusion previously reached that both duration of diabetes and degree of control influenced the appearance and severity of retinopathy although the latter was of somewhat more significance. The scattergrams on which these calculations are based are shown in figure 3.

It was desired to study these patients again at a later date and for that purpose the evaluation period of March 1, 1952, to Sept. 1, 1954, was chosen for the collection of data. During that time 66 of the original 75 patients returned for examination. In that interval two died of renal failure (intercapillary glomerulosclerosis) at the ages of 31 and 33 years and with a duration of diabetes of 21 and 22 years respectively. These two patients were included in the series. Another who died at home shortly after his last examination of cause unknown to us was included also. Two patients were excluded from the series because at the last examination they had a duration of diabetes slightly less than fifteen years. One had retinopathy and one did not. There were, then, paired data available for 64 of the original 75 patients.

All had a duration of diabetes exceeding 15 years with a range of 15 to 29 years. The median duration for the group was 21 years which is well above the 13 years known to be the average time required for the development of retinopathy. When the data from these examinations were analyzed by the methods described above it was found that the presence and severity of retinopathy still correlated inversely with the degree of control of diabetes. The coefficient of correlation was 0.651 which is significant beyond the 1 per cent level of confidence. However, no correlation could be found between retinopathy and the duration of diabetes. The ***r*** value was 0.171

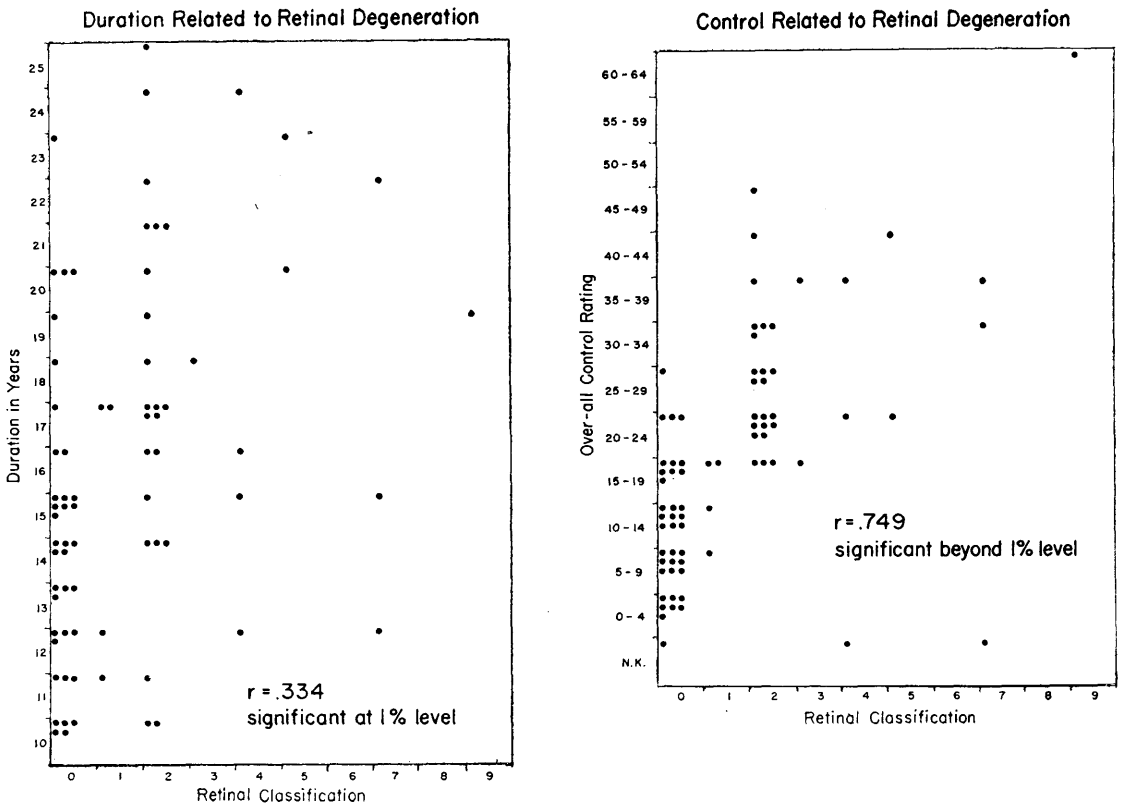

FIG. 3. Relation of duration and control to retinopathy in 75 patients—1948 study.

which is not significant. Thus, in the same group of patients the passing of an average of five years eliminated duration of disease as a factor in the development of retinopathy. The scattergrams for this analysis are shown in figure 4.

The data collected for the entire group of 132 patients (including the 66 from the previous study) were then analyzed in the same manner. The use of a larger number of subjects offered the opportunity to test the validity of the analyses performed for the smaller series. Reliable paired data were available for 123 patients. The correlation between degree of control and retinopathy was found to be good. The ***r*** value was 0.661 which is significant beyond the 1 per cent level. The coefficient of correlation between duration and the development of retinopathy was 0.318 which is significant at the 1 per cent level of confidence. It must be noted that the duration of diabetes in this group ranged from 10 to 29 years with a median of 16.5 years. The scattergram for this group is shown in figure 5.

Finally a scattergram was constructed in which the presence and degree of retinopathy were plotted against the duration of diabetes at the time of the last examination of each patient who had been studied at any time in the period between March 1948 and December 1955 inclusive. This was done in order to include those patients who had disappeared from the series through failure to return or, more particularly, through death from complications of diabetes, and who had been excluded from the previous analyses. In this final group there were 140 subjects who had a duration of diabetes of more than 10 years and for whom there were paired data. In 93 instances the duration of disease exceeded 15 years. When the correlation between duration and the presence of retinopathy was studied for the entire group it was found to be good. The ***r*** value was 0.270 which is significant beyond the 1 per cent level. However, when a similar analysis was done for those patients who had passed the fifteenth year of their diabetes at the time of the last examination the results were entirely different. The coefficient of correlation was 0.079 which is not significant. It should be mentioned that, of the four who are known to have died, three are included in the group above fifteen years' duration. Figure 6 shows these relationships.

INCIDENCE OF RETINOPATHY

The incidence of the various stages of retinopathy in

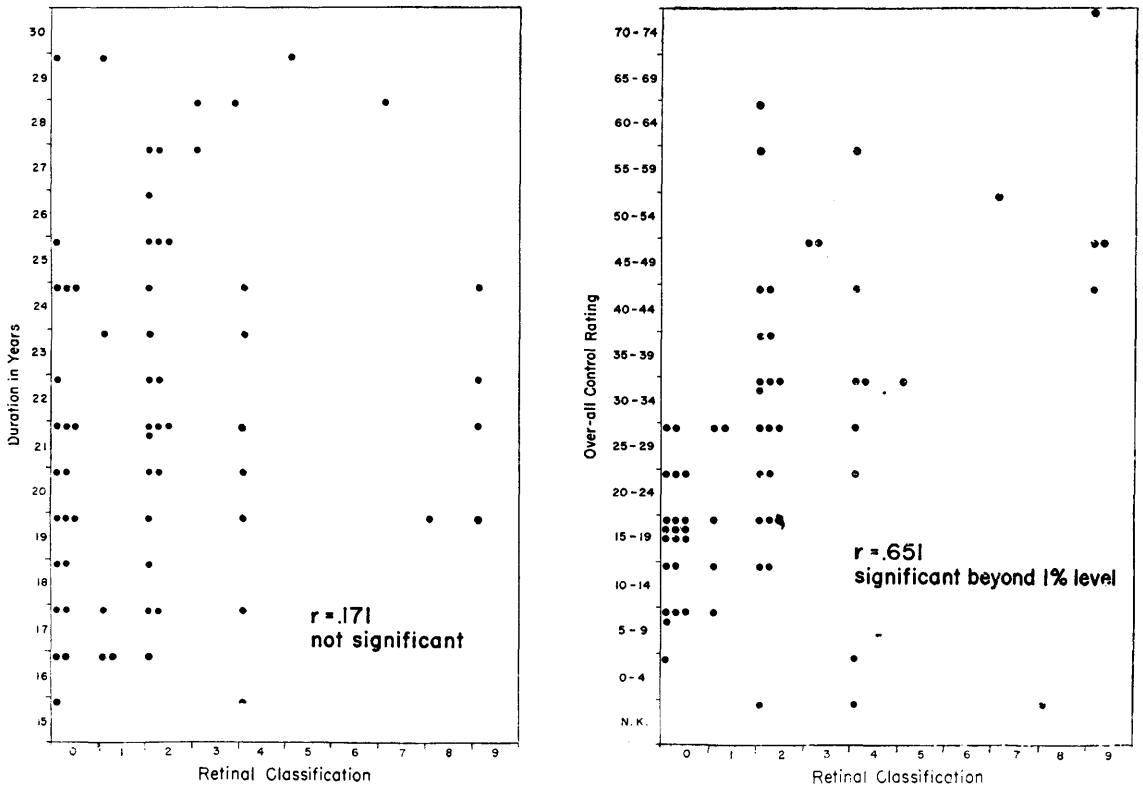

FIG. 4. Relation of duration and control to retinopathy five years later in 64 of the original 75 patients.

140 patients at the time of their last examination is shown below. The duration of diabetes in this group ranged from 10 to 29 years.

Normal Retinae	54	38.5 per cent
Dilated veins only	14	10.0 per cent
Micro-aneurysms only	48	34.3 per cent
Advanced Retinopathy	24	17.1 per cent

It has been our practice to regard venous dilatation as the first stage of diabetic retinopathy. However, if the usual criterion, the appearance of the capillary micro-aneurysm, is accepted 48.5 per cent of this series had normal retinae.

DISCUSSION

The question of whether retinopathy and other degenerative disease accompanying diabetes may be prevented or delayed by properly ordered treatment has been the subject of much investigation without a universally accepted decision. Probably the answer will not be achieved until the pathologic physiology of degenerative lesions is completely understood and causative factors are clearly related to their effects. In the meantime one must treat diabetic patients and choose between the two viewpoints concerning the nature of degenerative disease. One is that diabetics must inevitably develop degenerations for they are a natural part of diabetes. The other is that they are complications which may be prevented. Reports of investigators offer varying conclusions.[4, 5, 6, 7] A series of papers from the Joslin Clinic emphasize that good control is of utmost importance in the prevention of degenerative vascular lesions. Others hold the same opinion. The opposite viewpoint has also been presented by many in reports such as that of Larsson[7] and others. They concluded from a study of 257 juvenile diabetic patients that increased incidence of vascular lesions did not follow degrees of control lesser than those advocated by others. They did emphasize that diabetic patients must be closely supervised. A review by Engleson[8] summarizes the literature up to 1954 and offers the conclusion that there is better evidence for more exact control than there is against it.

Our present study was designed to separate, if possible, the influences of duration and degree of control on the development of diabetic retinopathy. The subjects were grouped in four different ways but, no matter what division was made, there always existed a highly significant correlation between degree of control and the incidence and severity of retinopathy. Patients with good control had a much lower incidence of retinopathy than those with lesser degrees of control and retinal lesions

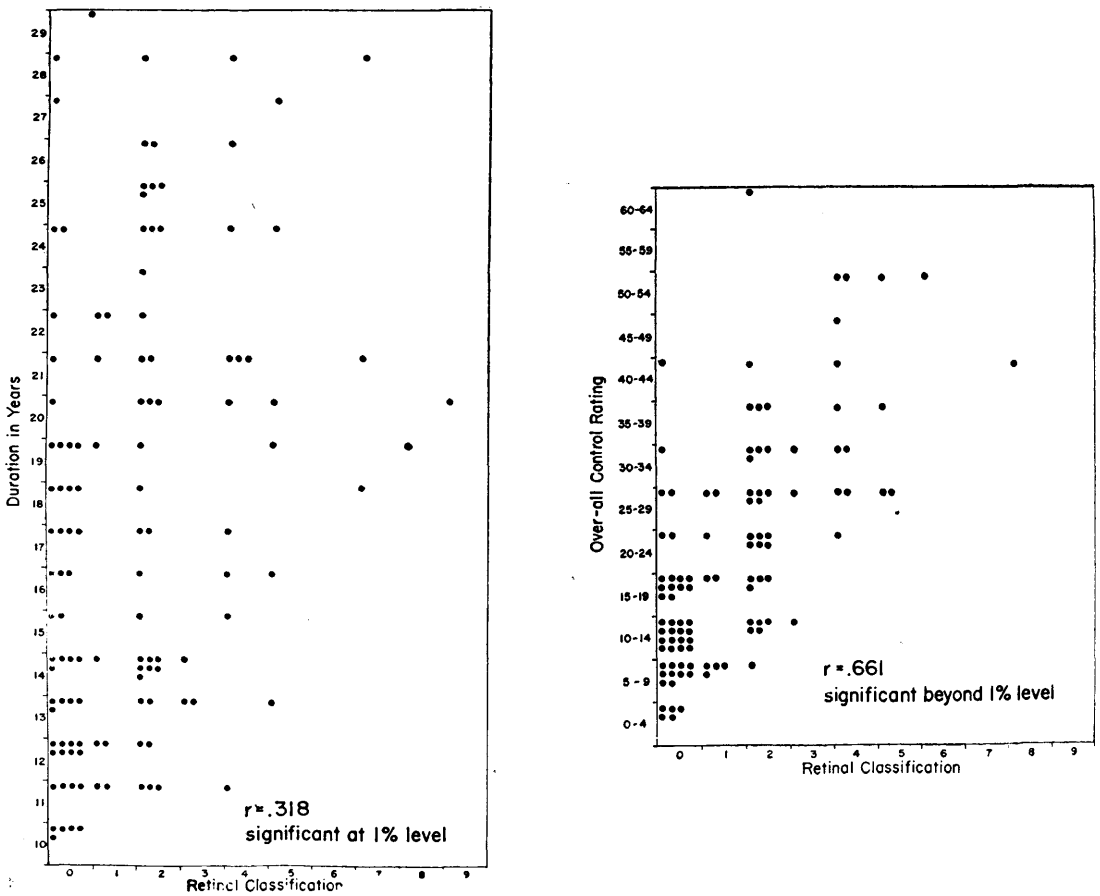

FIG. 5. Relation of duration and control to retinopathy in 123 patients—1954 study.

tended to be more severe in those with poorer control.

The influence of duration also was investigated in the four groupings of patients. In our original study[2] duration of diabetes correlated well with the incidence of retinopathy. Recalculation of that data by our present method confirmed this observation. However, when these same subjects were observed an average of five years later, there was no demonstrable relationship between duration of diabetes and the incidence and severity of retinopathy. This was striking because, if retinopathy were an inevitable concomitant of diabetes, it should have been observed with greater frequency and severity as the duration of the disease increased. Observation of exactly the opposite argues against duration of diabetes being a strong influence in the production of degenerative disease and against vascular disease being a part of the natural course of diabetes. A possible explanation of why this was not evident previously is found in the fact that retinopathy, when it occurs, appears on the average thirteen years after the onset of diabetes. In our 1948 study the median duration of diabetes was 15.2 years so that statistical analysis might have reflected the time required for retinopathy to develop rather than the true influence of duration on its incidence. At the time of the second study of this group the median duration of diabetes was twenty-one years which possibly eliminated the factor of the time required for retinopathy to appear.

Analysis of the data from 123 of the larger series of 132 patients with a median duration of their disease of 16.5 years gave a correlation coefficient between duration and retinopathy significant at the 1 per cent level of confidence. This was similar to that found in the original study. Finally all patients were grouped according to their duration of diabetes at the time of their last examination. The relation between duration and incidence and severity of retinopathy was determined for all 140 patients and again for only those whose diabetes had been present for more than 15 years. In the first instance the correlation coefficient was 0.270 which is highly sig-

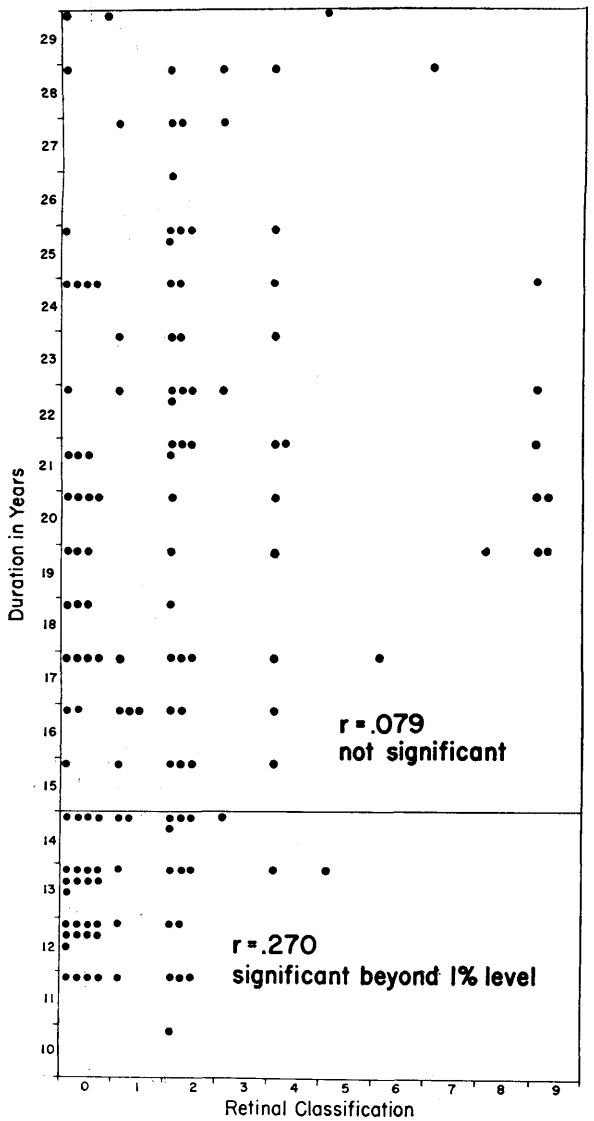

FIG. 6. Relation of duration and control to retinopathy in 140 patients—last examination.

nificant. When the 93 subjects whose duration exceeded 15 years were similarly tested the correlation coefficient was 0.079 which is of no significance. This demonstrated again that study of a group of diabetics whose mean duration of disease significantly surpasses the required time for the development of retinopathy fails to show any relationship between duration and retinopathy.

Thus, except for the time required for it to appear, the only constantly identifiable factor in the development of retinopathy is the degree of control of the diabetes. This is an observation concerning the conditions under which retinopathy occurs and not an explanation of the mechanism of its production. Elucidation of this must await a better understanding of the pathologic physiology of diabetes and of vascular disease. It may be suggested, however, that observable differences in the physiology of well controlled and poorly controlled diabetics may provide information useful in this respect.

SUMMARY

Observations on a group of 140 juvenile diabetic patients with a range of their disease from 10 to 29 years have been made. The data were analyzed for the relationship of duration and control to the development of retinopathy. Highly significant correlations between degree of control and incidence and severity of retinopathy were demonstrated. When groups of patients whose duration of diabetes exceeded fifteen years were studied no correlation between duration and retinopathy was found. From this it was concluded that:

1. Except for the time required for its appearance (average thirteen years) duration of diabetes is not an important factor in the development of retinopathy.

2. The only identifiable factor bearing a constantly significant relationship to the incidence and severity of retinopathy is the degree of control of the diabetes.

3. Differences in the pathologic physiology of well controlled and poorly controlled diabetic patients may provide information useful in the explanation of vascular degeneration.

SUMMARIO IN INTERLINGUA

Le Importantia Relative de Duration e Controlo in le Disveloppamento de Retinopathia Diabetic

Esseva observate un gruppo de 140 patientes diabetic juvenil in qui le duration del morbo esseva inter 10 e 29 annos. Le datos esseva analysate pro determinar le relation inter duration e controlo e le disveloppamento de retinopathia. Esseva demonstrate correlationes multo significative inter grado de controlo e frequentia e le severitate del retinopathia. Nulle correlation inter duration e retinopathia esseva trovate in le studio de gruppos de patientes in qui le duration de diabete excedeva dececinque annos. Ab iste factos nos concludeva que:

1. Con le exception del tempore requirite pro su apparition (dece-tres annos al media), le duration de diabete non es un factor importante in le disveloppamento de retinopathia.

2. Le sol factor identificabile que ha un relation constantemente significative con le frequentia e severitate de retinopathia es le grado de controlo del diabete.

3. Differentias in le physiologia de patientes diabetic sub bon controlo e mal controlo pote provider informationes utile in le explication de degeneration vascular.

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DISCUSSION

HENRY DOLGER, M.D., (*New York City*): I am amazed at the contrast in these two papers. The last one is probably the most adynamic view of the subject I have ever heard. In contrast, Dr. White presents the most ideal, dynamic attitude towards diabetes. If one is to limit the objective criteria of vascular damage just to retinopathy, it is true that in thirteen years one will see just various graduations of degenerative change. But it is obvious to all of us here, as Dr. White has shown, that it's first retinopathy, then arterial renal lesion, and thirdly generalized vascular disease.

I go back to Dr. White's paper of ten years ago. Her report at that time indicated that 94 per cent of the juvenile patients had vascular damage. Ten years later, today, with what she calls better control, the results are still 94 per cent; so where are we ten years after better control?

GEORGE M. GUEST, M.D., (*Cincinnati, Ohio*): In studies of the sort reported by Dr. White earlier and now by Dr. Hardin, I should like to suggest that more attention should be paid to the exceptional cases among the large groups of patients classified according to the authors' standards as "well-controlled" and "poorly controlled." The figures on the incidence of complications, higher among the poorly controlled groups than among the well-controlled groups are of course impressive; but let us bear in mind that within both groups there are notable individual exceptions. Individual behavior cannot be prophesied from statistics on group behavior. Among presumably well-controlled patients complications of degenerative organic disease do sometimes occur early; and, on the other hand, some notoriously undisciplined and badly controlled patients have gone longer than thirty years with no discernible degenerative cardiovascular-renal-ocular lesions. The individuals within these large groups, however subdivided, have in common one principal characteristic, namely, the diagnosis of diabetes mellitus. Apart from that item in their medical histories they probably differ among themselves in their physiological and biochemical patterns and genetic traits as much as do a similar number of individuals in the nondiabetic population. Recognition of exceptions, with regard to the development or nondevelopment of complications in individual diabetic patients emphasizes our great need for more knowledge of many fundamental factors that are involved in the pathology of concomitant features of the disease. There is a great need for study of genetic factors that may determine the development of chronic cardiovascular-renal-ocular disease apart from the genetic trait or traits that may determine diabetes mellitus.

JOSEPH L. IZZO, M.D., (*Rochester, New York*): There is one point I would like to have cleared. I was in the back of the room and was unable to get a close look at the charts. I would like to know what is the magnitude of your positive correlation coefficients? Those that were positive, how highly positive were they? I thought some of them, although they were significantly positive were of very low order, some around 0.2 or 0.3.

ELIZABETH F. TULLER, PH.D., (*Boston*): Dr. White mentioned some of the work that Dr. Ditzel has been doing in our laboratories with conjunctival studies as another way of investigating vascular changes in diabetes. (DIABETES *3*:99-106, *4*:474-76.) These studies may also be useful in the problem of the relationship of duration to vascular lesions as well as to control. It thus might be well to point out two items, one from his work and one from our protein studies.

The conjunctival changes which form characteristic patterns in the diabetic are found very early. In fact, in some cases glucose tolerance studies were done simultaneously with the conjunctival work, and Dr. Ditzel's description of vascular changes similar to those found in well-established diabetes coincided with the discovery of the borderline or prediabetic, indicating that there was some type of vascular change going on very early in the disease. Thus the question might be raised as to whether these changes are a genetic-related factor and

parallel the clinical course of diabetes mellitus. Certainly some of the recent work that he has done has indicated that these vascular changes may have increased in degree of severity as the clinical symptoms of retinopathy have appeared.

Also we have found that in diabetics with poor control, and with no evidence of vascular changes in the retina and the kidney, the serum protein patterns were similar to those of the diabetics with newly indicated clinical symptoms of vascular changes, even though the duration of the disease was less in the former group. The observation has been that protein changes follow both increased duration and poor control. However, in a group with good control, the longer the duration of the disease, the closer the serum protein pattern came to that abnormal pattern found in the diabetic with observable clinical changes of vascular lesions in the retina and the kidney.

This leads one to go along with Dr. Guest's idea as to the need for time and for study to gain an understanding of some of the background of this type of material.

ARNOLD LAZAROW, M.D., PH.D., (*Minneapolis*): In interpreting the data presented it is important to ascertain whether the poor control of the diabetes results from lack of patient cooperation or whether it is the result of the diabetic state, per se. If one were to assume that an unknown etiologic factor acts in two ways (1) it makes the diabetes more difficult to control, (2) it accelerates the development of the complications of diabetes, then in grouping the poorly controlled diabetics one would be selecting those individuals who are prone to develop the complications of diabetes. Do you have any specific information in the group of patients studied as to whether the poor control is a characteristic of the diabetic state, or whether it is due to lack of patient cooperation?

PRISCILLA WHITE, M.D., (*Boston*): I don't think I have expressed myself clearly. I think that right now our present tools, mixtures of insulin, regular and intermediate, in split doses, will give the next generation of diabetics a better chance for better chemical control than this group which I reported today.

ROBERT C. HARDIN, M.D., (*Iowa City, Iowa*): I think Dr. White has partially answered Dr. Dolger. I am not quite in agreement with Dr. Dolger, that this is an adynamic approach to diabetes. Perhaps we need a definition.

As I said, this paper described the people in whom degenerations appear, but does not say why they appear. Certainly one would not stop here but would go on to find out as much more as possible. Many who have spoken on this program have demonstrated this approach to the study of the production of degenerative lesions. It may be some of our observations when classified into those from controlled and those from uncontrolled diabetics will show differences of importance in the elucidation of this problem.

Dr. Guest, I think, talked on that very important subject, and I agree wholeheartedly with him. The people in this group who interest me most are those of whom he spoke, those who should have degenerative disease but do not, and those who shouldn't but do, and we have both.

These persons are of extreme interest, and we are carrying out studies on them.

Dr. Izzo asked about the degrees of correlation or rather the orders. I am sorry if they could not be seen at the back of the room. Those for duration were always of a lower order of magnitude. In the 1948 studies the values were 0.33 for duration and 0.74 for control. For the study of these people five years later, they were 0.17 for duration and 0.65 for control. In the next study the values were 0.31 for duration and 0.66 for control. The last study did not include control, but was for duration only. The values were 0.27 for the entire group and 0.07 for those above fifteen years.

Dr. Lazarow has brought up the question, I think, of whether there are two kinds of diabetes or more. Is there a kind of diabetes which is easily controlled, and which in its natural history does not go on to degenerative disease, and is there another which cannot be controlled, and which in natural history goes on to degeneration? The studies which we presented today do not answer this question. These were homogenous groups of patients and all were juvenile diabetics.