

STATISTICAL METHODS FOR EXAMINING RETINOPATHY IN RELATION TO THE CONTROL OF DIABETES AND OTHER FACTORS*†

BY

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THE introduction of insulin 40 years ago radically altered the expectation of life of diabetic patients. It is not always appreciated that this change will alone cause the population of diabetics to increase steadily at least until the 1970s, and that we may, therefore, expect that long-term diabetic complications, particularly retinopathy, will become more and more prevalent, as the population of diabetics with long histories continues to build up. So it is urgent that the causes of these complications and ways of avoiding them should be found.

At present it is far from clear to what extent control of diabetes affects the development of retinopathy. Some authors regard control as of the utmost importance if retinopathy is to be avoided, while others have suggested that control is of little consequence in this connexion. Some of the surveys that have been published are, however, open to the criticism that control is assessed subjectively in retrospect.

In our pilot survey we have attempted to overcome this difficulty by statistical analysis of the records. The survey is a pilot one in that the number of patients is small and the statistical approach is new. A preliminary survey of this type can only hope to try out methods, draw attention to difficulties, and provide a basis for further investigation.

Material

This survey started in 1958 when a record sheet was drawn up to enable the salient clinical features of patients attending the Addenbrooke's diabetic clinic to be transferred to Hollerith punched cards. The following particulars were included:

- (i) *Background Information:* Age, sex, marital status, duration of diabetes, type of disease, and details of mode of onset.

* Read at the combined meeting of the British Diabetic Association and the Irish Ophthalmological Society in Dublin on April 26, 1963.

- (ii) *Present Treatment*: Diet was assessed as free, intermediate, or strict. The dose, type, and number of injections of insulin per day were also recorded.
- (iii) *History of Treatment*: Duration of treatment with a single daily injection. Clinical assessment of whether the control maintained had been good (no symptoms, occasional glycosuria, and no ketonuria), intermediate, or poor (constant glycosuria, precoma or coma, and/or blood sugar generally above 250 mg. per cent.).
- (iv) *Diabetic Complications*: Grade of retinopathy:
- O = No retinopathy,
 - I = Occasional microaneurysms,
 - II = Conspicuous microaneurysms,
 - III = Haemorrhages + exudates,
 - IV = Vitreous haemorrhages.
- Presence or absence of cataract, iritis, renal complications, peripheral neuropathy, and dermatological complications
- (v) *Number of Pregnancies*.
- (vi) *Family History of Diabetes*.

In addition, all the blood sugar estimates, measured at each clinic attendance, together with the date the estimation was made, have been abstracted from the notes of each patient included in the survey. These series of observations are called the blood sugar histories.

Prof. A. L. Cochrane's surveys in South Wales have shown that about 50 per cent. of diabetics are unknown and untreated (personal communication), and this is now the view of many other workers. To make this investigation a survey of treated cases we have confined our attention to cases treated for at least 8 years. It was also necessary to exclude a few patients with a history of more than 8 years whose notes covered a period of less than 5 years. 81 patients were included in the survey.

Criticisms of the Material

A retrospective study is inevitably a survey of survivors, but the expectation of life of diabetics is now not much different from that of normal people. Also it can be argued that any selection due to mortality will probably tend to conceal differences between those with retinopathy and those without it.

It has been suggested that the blood sugar records are practically useless, as they are very sensitive to the time of day at which they are measured and to whether the patient is on a single dose of long-acting insulin or not. However, it would be very surprising if patients who have now got retinopathy have always tended to attend at a different time of day from those who have not got it, and an analysis of the relevant part of our material showed that the average blood sugar level is unrelated either to the dose or to the type of insulin being given at the time.

Summarizing the Blood Sugar Histories

Blood sugar levels are, in fact, part of a feed-back system, in that the blood sugar data is usually used as one of several guides to the treatment required, and so one

blood sugar estimate may affect the next. However, it is not unreasonable to suppose that the pattern of the disease, the success of the treatment, and the degree of control maintained will be reflected in the blood sugar history.

Fig. 1 shows a typical blood sugar history covering a period of 20 years. The blood sugar levels are plotted vertically, in milligrams per cent., against the time the observation was made on the horizontal axis. The problem is to summarize all this blood sugar material in terms of a few parameters which may be expected to preserve the most important features of the data.

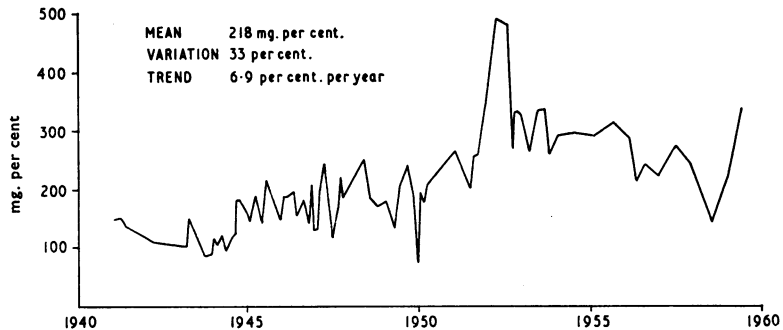


FIG. 1.—Typical blood sugar history, 1940–60.

Three such statistics are:

The mean, which for this subject is 218 mg. per cent.

The percentage variation about the mean, in this case 33 per cent.

The trend, or average rate at which the blood sugar level rises, expressed as per cent. per year, in this case 6.9 per cent. per annum.

The method of analysis used results in the last two figures coming out as percentages. The trend is highly significant in this case.

When these statistics had been calculated for each subject the results were added to the patient's Hollerith card, and the data were ready for analysis in relation to retinopathy. For this purpose the retinopathy grading has been treated as a linear scale.

Method of Analysis

The straightforward way of analysing this kind of data is to investigate the relation of retinopathy to each of the factors in turn. But there are two difficulties in this approach: one basic factor can show up in several ways, and real relationships can be concealed. To surmount these difficulties a simultaneous analysis of all the relevant factors is necessary.

The following is an example of the first obstacle:

Analysing our data factor by factor, we found retinopathy was associated with both duration of diabetes and age. The question arises; is the correlation of retinopathy grade with age merely a repeat of the correlation with duration, since the patients with long histories of diabetes will tend to be in the older age groups.

This kind of difficulty is fairly well known. What is less well known is that real associations can be concealed. Because of this, the following example, similar to the problem we are dealing with, has been cooked up to illustrate the point.

Fig. 2 shows the grade of retinopathy, vertically, plotted against dose of insulin for fourteen hypothetical patients. There is evidently *no* correlation between the two, which we indicate by saying the correlation coefficient, *r*, equals zero.

If, however, we now take account of the sex of the patients, the picture shown in Fig. 3 might emerge. Here, if either the female or the male patients are considered separately, the grade of retinopathy is clearly related to the insulin dose. These correlations did not appear in Fig. 2 because the women in this example have more retinopathy but less insulin than do the men. In this imaginary example the relation between retinopathy and dose only emerges when sex is also taken into account. In general this can only be done effectively by a fairly elaborate statistical analysis. In the present case, the appropriate method of analysis is multiple regression.

HYPOTHETICAL EXAMPLE OF A CONCEALED RELATIONSHIP

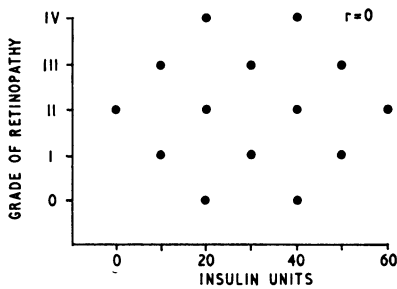


FIG. 2.

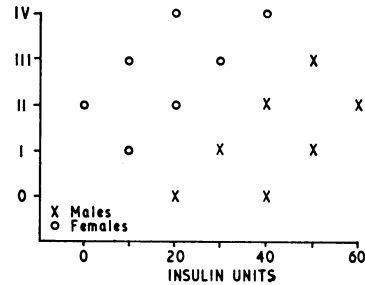


FIG. 3.

Results

When analysing our material 28 factors were included in the multiple regression analysis. The result may be expressed by means of the following equation:

$$\begin{aligned} \text{Predicted Retinopathy Grade} = & I + (\text{Duration of Diabetes} - 16 \text{ yrs}) \times 0.07 \\ & + (\text{Age at Onset of Diabetes} - 37 \text{ yrs}) \times 0.03 \\ & + (\text{Diet Rating} - 1) \times 0.7 \\ & + (\text{Daily No. of Injections} - 1) \times 0.6 \end{aligned}$$

This shows that only four factors, duration of diabetes, age at onset of diabetes, diet, and, surprisingly, the number of insulin injections per day, are statistically significant, all at the 1 per cent. level. The grade of retinopathy of any of our patients is best predicted from the clinical observations by means of this equation.

In each bracket, after the factor, the average is shown subtracted. Thus, the average duration is 16 years, the average age at onset of diabetes is 37

years, the average diet rating is 1 (which corresponds to intermediate—0 being free and 2 being strict), and the average number of injections per day is one. When all the factors are average, each of the brackets is zero and the grade of retinopathy is average, which is Grade I. Thus this equation predicts that after 16 years a patient who develops diabetes at 37, will have Grade I retinopathy, if *by then* his diet is only moderately restricted and he is on a single dose of insulin per day.

Other things being normal, this equation also predicts that the retinopathy grade will be about zero when the duration is zero, and will have reached Grade II after 30 years. The equation also shows that the earlier diabetes develops the longer retinopathy takes to develop from the age of onset. This could be due to there being less delay in diagnosing diabetes in the younger age groups.

The association with the diet rating is interesting. If the patient is considered to be on a strict diet, the value of the third line is -0.7 . Consequently such a patient is predicted to have a grade and a half less retinopathy than a patient on an unrestricted diet, other things being equal.

However, this diet rating relates to the time the retinopathy was assessed. Many of these long-term cases with retinopathy had an upward trend in the blood sugar levels, and in the multi-factor analysis this factor was nearly statistically significant. It gives rise to the question whether the development of retinopathy may be correlated with some psychological changes, which show up in an increasing unwillingness to diet.

The finding that patients on two insulin injections per day may be predicted to have more retinopathy than those on a single dose, or not on insulin at all, was very unexpected. It is a typical concealed relationship which only emerges when the other three factors are taken into account. Perhaps it reflects a tendency to put patients on a double dose of insulin if they begin to develop retinopathy.

If this equation is used to predict the retinopathy grade of the patients included in this survey, the correlation between the observed and predicted grade is only 0.57, but this is statistically very highly significant indeed.

In conclusion it should be stressed that these results are tentative, and refer to one group of diabetic patients in a particular geographical area, but that further studies along these lines might be worthwhile, especially to investigate:

- (1) The suggestion that the grade of retinopathy is associated with an upward trend in the blood sugars.
- (2) The history of treatment.
- (3) The history of adherence to diet.

Summary

A pilot retrospective investigation has been carried out on 81 patients with a diabetic history of at least 8 years. The investigation was planned to

study relationships between the degree of retinopathy, the control maintained as measured by the blood sugar history, and other clinical observations.

The validity of such an investigation is discussed, and the statistics used to summarize the blood sugar histories described. The analysis of these statistics and the clinical observations in relation to the grade of retinopathy poses some difficulties owing to inter-relationships between the factors. A multiple regression analysis has been used to overcome these difficulties, and some results are presented.

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