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Age of Onset and Inheritance of Diabetes: The Importance of Examining Relatives

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Summary. Suggestions that diabetes of younger- and older-onset are inherited differently have been examined in a family study which compares the first-degree relatives of 735 diabetic patients with those of 514 'control' patients. Verbally reported histories from the propositi indicated an excess prevalence of known diabetes among the siblings of younger-onset diabetics; however, when the ostensibly normal, first-degree relatives were examined a high frequency of unsuspected glucose tolerance test abnormality was found. When the diabetes prevalence in relatives of diabetics was compared with that in relatives of controls (*K* ratio), a method at present widely used to determine the mode of inheritance, a number of problems arose suggesting that this means of genetic analysis may be misleading in diseases such as diabetes. It is concluded, for reasons which are discussed, that differences in prevalence ratios cannot be accepted as good evidence for different modes of inheritance of younger- and older-onset diabetes in man.

Age de l'apparition du diabète et sa transmission héréditaire. Importance de l'examen des membres de la famille

Résumé. La suggestion a été faite que le diabète commençant dans la première moitié de la vie est transmis d'une façon différente du diabète diagnostiqué plus tard. — Nous avons examiné cette hypothèse dans une étude qui compare les membres du premier degré des familles de 735 malades souffrant du diabète avec ceux des 514 sujets de contrôle. Les histoires familiales des malades, rapportées oralement, ont indiqué une prévalence excessive de diabète connu parmi les frères et les soeurs des diabétiques juvéniles. Toutefois, lorsque les membres — supposés normaux — furent examinés, une haute fréquence d'intolérance au glucose non-soupçonnée fut trouvée. Quand la prévalence de la maladie dans les familles des diabétiques fut comparée avec celle des sujets de contrôle (rapport *K*) — méthode souvent employée actuellement afin de déterminer le mode de transmission du diabète — nous nous sommes trouvés en face de certains problèmes qui sembleraient indiquer que cette méthode d'analyse génétique pourrait mener à certaines erreurs d'interprétation dans les maladies telles que le diabète. — Pour les raisons examinées, nous concluons que des différences dans les rapports de prévalence ne peuvent pas être acceptées comme preuves convaincantes d'un mode de transmission différent du diabète juvénile et du diabète d'apparition plus tardive.

Manifestationsalter und Vererbung des Diabetes: Die Wichtigkeit von Verwandten-Untersuchungen

Zusammenfassung. Die Hypothese eines unterschiedlichen Vererbungsmodus für den Diabetes mit frühzeitiger Krankheitsmanifestation und den Diabetes mit späterem Krankheitsausbruch wurde auf Grund von Familienuntersuchungen geprüft. Blutsverwandte 1. Grades von 735 Diabetikern wurden mit einer entsprechenden Kontrollgruppe von 514 Personen verglichen. Bei den Blutsverwandten der Patienten mit früher Diabetesmanifestation ist aus den Krankheitsanamnesen und mündlichen Berichten eine größere Diabeteshäufigkeit zu ermitteln. Wenn indessen die scheinbar normalen Verwandten ersten Grades untersucht wurden, fand man eine große Anzahl vorher unbekannter Fälle von Glucosetoleranzstörung. Bei einem Vergleich der Diabeteshäufigkeit unter den Verwandten der Zuckerkranken und den Verwandten der Kontrollfälle (*K* Vergleichszahl) einer Methode, die z. Zt. oft zur Bestimmung des Vererbungsmodus benutzt wird, ergaben sich einige Probleme, die andeuten, daß diese Art Vererbungsanalysen bei Erkrankungen, wie dem Diabetes, irreführend sein können. Aus den Ergebnissen der Untersuchungen wird gefolgert, daß die zahlenmäßigen Unterschiede, die sich bei dieser Methode des Vergleichs ergeben, keinen Beweis für einen unterschiedlichen Vererbungsmodus des früher oder später sich manifestierenden Diabetes darstellen.

Key-words: Genetics, glucose tolerance, family, heterogeneity, diabetes, juvenile, maturity.

Introduction

Are the clinical and biochemical differences between the two main types of diabetes in man (LAWRENCE, 1955) accompanied by differences in the mode of inheritance? Such differences have been asserted in the past from a consideration of diabetics' family histories alone (HARRIS, 1950). A more valid comparison may, however, be made using the prevalence in the general population (or a sample of it) as a base; thus there have been subsequent reports (SIMPSON, 1962; SIMPSON, 1964; Report of a working party appointed by the College of General Practitioners, 1965) that the excess prevalence of diabetes in the siblings of younger-onset patients over that in a like-aged general population sample is much greater than the excess prevalence in siblings of older-onset cases. There are, however, objections to drawing conclusions from such comparisons of diabetes prevalence, particularly when they are based upon verbal accounts of family history (STEINBERG, 1959; KLIMT, MEINERT, Ho and BRIESE, 1967). This paper re-examines the question of genetic heterogeneity in a group of diabetics. non-diabetics and the relatives of both with special reference to these and other objections.

Materials and *Methods*

The basis of the study was formed by 735 patients (diabetic propositi) attending the diabetic clinics at St. Mary's and King's College Hospitals London, England. The age and sex distribution of this sample is shown in Fig. 1, which also shows the composition of a

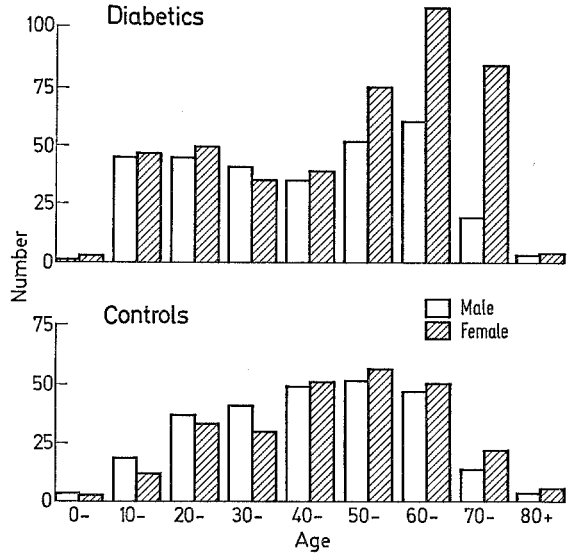

Fig. 1. Age and sex composition of 735 diabetic propositi (above) and 514 control propositi (below). The number of younger diabetics was specially augmented

control group of 514 randomly recruited outpatients attending St. Mary's Hospital. The only criterion of selection of the latter was that they were not known diabetics; in the main, they were attending for minor medical and surgical conditions. The age structure of the diabetic sample is not typical of the diabetic population in general for there was selective collection of younger patients to augment the numbers. The extra young patients were recruited without foreknowledge of their family history. A systematic enquiry for diabetes (the *reported* family history) in any member of the family was made of all diabetics and controls. Details were recorded of the status of all first-degree relatives (parents, siblings and offspring); and those who were reported to be free of diabetes and to live within the London area were invited to attend for examination. Significantly more relatives of diabetics responded than relatives of controls (Table 1). Each attender drank 50 g of glucose in 200 ml of water, answered a standardized verbal questionnaire and underwent a brief physical examination. The urine passed one hour after the glucose drink was tested for sugar with BENEDICT's solution. Of the 1149 relatives of diabetics tested, 26.4% had reducing activity in their post-glucose urine, significantly more than the 17.7% of the 609 relatives of controls similarly tested ($p < 0.002$). Relatives found to be glycosuric were asked to return for a glucose tolerance test (G.T.T.). Capillary blood samples were taken following an overnight fast, and then 30, 60, 90 and 120 minutes after 50 g of glucose by mouth. Samples were estimated in duplicate, using KING's modification of the FOLIN-WU method (KING and WOOTON, 1951).

Table 1. *The number of first-degree relatives of diabetic and control propositi who were reported to be non-diabetic and who were invited for examination is shown, along with the percentage that attended*

Relationship to Propositus	Diabetic Propositi		Control Propositi	
	Invited	Attended	Invited	Attended
Parents	368	72.6%	236	41.5%
Siblings	704	65.6%	613	46.6%
Offspring	549	77.1%	421	53.2%
Overall	1621	70.9%	1270	47.9%

The analysis which follows is divided into two parts. The first part deals with the *reported* family history as collected from diabetic and control propositi and is comparable, therefore, with most earlier studies. The second part re-assesses the pattern when the additional findings from the examination of the ostensibly normal, first-degree relatives are also embodied. In both cases, the ratios of frequency of diabetes in relatives of special classes of diabetics to relatives of corresponding controls (K ratios) have been calculated as suggested by PENROSE (1953).

Results

Analysis of Reported Family History

The proportions of diabetic and control propositi knowing of diabetes in either non-first-degree or first-degree relatives are shown in Table 2. The sexes are

Table 2. *The percentage of propositi reporting diabetes in non-first-degree and first-degree relatives (in each case whether the types of history were single or combined) is shown for propositi divided into twenty-year age groups. D/C, the ratio of percentage positive reporters in diabetics to controls, indicates the magnitude of excess family history given by diabetic propositi over controls*

Percentage of propositi reporting:						
Age of propositus	Non-first degree (± 1°) family history			First-degree (± non-1°) family history		
	Diabetic	Control	D/C	Diabetic	Control	D/C
0—19	40.7	17.6	2.3	8.2	—	—
20—39	27.5	12.9	2.1	13.8	2.2	6.3
40—59	17.6	7.2	2.4	31.2	6.3	4.9
60+	10.0	3.7	2.7	28.0	11.1	2.5

not separated as prior analysis had shown no clear differences between them. In successively rising age-groups of the diabetic propositi, successively more patients report first-degree relatives with diabetes. Though the absolute frequencies are higher in the

diabetics, the rise with age is faster in the controls and so the ratio of relative frequency (D/C) falls with increasing age. This contrasts with the ratios for the non-first-degree family history, which are similar in all age groups.

K ratios comparable with those published by Simpson (1962, 1964) and the College of General Practitioners (1965) may be calculated from the frequency of reported diabetes in the relatives themselves. These frequencies for parents and siblings of diabetics and controls, and the derived *K* ratios are shown in Table 3 for propositi with onset diabetes under 35 years of age and for those aged 35 years or more at onset. The *K* ratios all have values clearly exceeding unity, indicating familial aggregation of known cases. Only among the siblings is there an indication that familial aggregation, judged in this way, is more conspicuous in the families of younger-onset than of older-onset patients. Due to the absence of reported diabetes among the offspring of controls, it was not possible to calculate *K* ratios. However, Table 3 shows that diabetes is reported three times as frequently in the offspring of younger-onset diabetics than among those of older-onset patients.

Reported family history analysis, therefore, supports the view that inheritance plays a larger role in determining the appearance of diabetes in the families of younger-onset cases than among relatives of older-onset patients.

upper end of the blood sugar scale by comparison with relatives of controls. At all time points, older relatives tend to higher values. Although a number of the blood sugar values shown are obviously abnormally high, there is no clear division of the distributions into normal and abnormal groups. In order to make a comparison of the prevalence of abnormality in relatives of diabetics and controls, it is, therefore, necessary to make arbitrary definitions of abnormal responses. If a discriminating level is chosen high in the range, then the frequency of abnormality will be low and, due to the relative positions of the distributions, the calculated *K* ratio will be high. On the other hand, if the discriminating level is set low, although the frequency of abnormality will be higher, the *K* ratio will be lower. To compromise, we have made the division at the commonly accepted diagnostic levels shown as vertical lines on the frequency distributions (180 mg/100 ml at

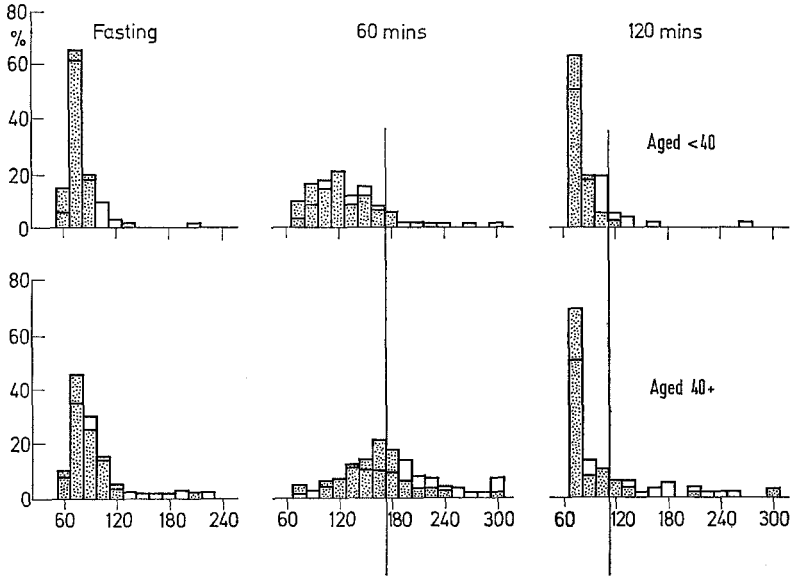

Fig. 2. Frequency distribution histograms of fasting, 60 min and 120 min blood sugar values (mg/100 ml on abscissa) from glucose tolerance tests on ostensibly normal, first-degree relatives of diabetics (white columns) and controls (dark columns) found to be glycosuric after oral glucose. Upper three blocks constructed from relatives aged less than 40 years; lower three represent relatives aged 40 years or more. Vertical lines indicate arbitrary dividing levels (see Table 4 and text)

Table 3. *The percentage of total parents, siblings and offspring reported diabetic is shown for histories taken from diabetic propositi aged less than 35 years and those aged 35 years and more at time of clinical diagnosis. Control propositi are similarly separated at 35 years of age. Total numbers of relatives in each class are shown in brackets. Parents and siblings of four diabetics and two controls who knew nothing of their family origins have been excluded. K ratios indicate the degree of excess of affected relatives of diabetics over those of controls*

	Diabetics Onset Age		Controls Age		*K* Ratio	
	< 35	35 +	< 35	35 +	< 35	35 +
Parents	4.0 (540)	9.7 (922)	1.1 (278)	2.9 (750)	3.6	3.3
Siblings	3.3 (596)	3.5 (2199)	0.5 (405)	0.8 (1797)	6.6	4.4
Offspring	2.7 (110)	0.9 (919)	0.0 (62)	0.0 (629)	—	—

Examination Findings in Relatives

G.T.T.'s were performed on 238 relatives of diabetics and 92 relatives of controls, all of whom were reported as normal by the propositi but found to be glycosuric at examination. The frequency distributions of their fasting, 1 h and 2 h blood sugar values are shown in Fig. 2., with results for younger and older relatives shown separately. In both age groups, the relatives of diabetics occupy positions towards the

60 min; 120 mg/100 ml at 120 min). In addition, a function of the area under the glucose tolerance curve has been calculated by summing the fasting and two hour blood sugars with twice the three intervening values. Division of areas into normal and abnormal groups was also made arbitrarily from a consideration of model curves. Four categories of abnormality so derived are defined in Table 4. Glucose tolerance curves which could not be assigned to these categories were classified as normal.

Table 4. *Criteria of abnormality of glucose tolerance test. Category 4 is a function of the area under the blood sugar curve and is calculated by adding to the sum of the fasting and two-hour blood sugar values (in mg/100 ml) twice the sum of the 30, 60 and 90 min values e.g. $a + 2b + 2c + 2d + e$*

1. Highest blood sugar 180 mg / 100 ml or more
2. Two hour blood sugar 120 mg / 100 ml or more
3. Abnormality 1 plus Abnormality 2
4. G.T.T. Area (2 h) 1200 or more

Table 6. *Relative prevalence (K) ratios calculated for each class of relative after adding to each, in turn, of the rates of newly found G.T.T. abnormality, the rates of known diabetes. The resulting estimates of total prevalence of glucose intolerance in relatives of diabetics were divided by the corresponding control estimates to give the K ratios*

Prop. Age Group	Relative Age	Abnormality 1	2	3	4
< 35	< 40	1.8	10.0	10.0	11.5
	40 +	1.3	3.3	7.2	1.9
35 +	< 40	6.4	13.2	9.4	5.6
	40 +	1.6	3.2	3.3	2.6

Table 5. *Rates of newly found G.T.T. abnormality (see Table 4) and of reported diabetes in the younger (under 40) and older (40 or more) relatives of younger (under 35) and older (35 or more) diabetic and control propositi; these rates are expressed as a percentage of all relatives seen in the particular group*

Relatives of Diabetics							Relatives of Controls						
Prop. Age of Onset	Relative Age	Newly Found Abnormality 1	2	3	4	Previously Known D.M.	Prop. Age	Relative Age	Newly Found Abnormality 1	2	3	4	Previously Known D.M.
< 35	< 40	2.7	0.7	0.7	1.3	3.3	< 35	< 40	3.0	0.0	0.0	0.0	0.4
	40 +	12.8	4.5	3.8	6.4	4.0		40 +	11.7	1.5	0.0	4.4	1.1
35 +	< 40	11.1	5.6	3.7	4.6	0.9	35 +	< 40	1.9	0.5	0.5	1.0	0.0
	40 +	17.3	8.1	7.0	13.3	5.2		40 +	12.9	2.9	2.4	5.9	1.3

Table 5 showns the rates of these newly-found G. T. T. abnormalities calculated after making allowance for the small number of glycosurics defaulting at G.T.T. The Table also shows the rates of *reported* known diabetes in the first-degree relatives. The relatives are divided by the onset age of the propositus contributing them to the study (< 35 or 35 +) and also by their own age at the time of examination (< 40 or 40 +). Abnormality rates have been calculated separately for each group. It is possible to make several different estimates of the total frequency of carbohydrate intolerance in the relatives by adding the rates of *reported* diabetes into each of the other rates in turn, for it is reasonable to assume that *reported* diabetics qualify for all of the G.T.T. abnormality categories.

K ratios calculated from these different total rates are shown in Table 6. The degree to which they exceed unity indicates the systematically higher rates of abnormality in relatives of diabetics compared with relatives of controls. Although the absolute frequency of abnormality is higher in older *relatives* (Table 5), the *K* ratios are higher for younger ones (Table 6). However, the values of *K* for relatives of younger- and older-onset *diabetics* do not show marked differences.

Analysis of *reported* family histories supplemented by examination of relatives, therefore, gives no clear indication of a larger inherited element in the families of younger-onset than older-onset diabetics.

Discussion

When estimates are based upon the analysis of verbal family histories, values of the *K* ratio for the relatives of diabetics of younger-onset are higher than those for the relatives of older-onset cases. However, when a fuller ascertainment of glucose tolerance status is made by submitting ostensibly normal relatives to examination and including abnormal responses to glucose in the calculation of the ratios, this difference between relative prevalence in the families of younger-onset and older-onset cases is found to be much less marked.

There are probably several reasons for the conflict between conclusions arising from family history study alone and from the history supplemented by examination of reported normal relatives. If diabetes breeds true symptomatically, younger-onset cases are more likely to know about affected relatives than the oligo or asymptomatic older-onset diabetics. This would lower the *K* ratio for relatives of older-onset cases.

A more serious objection to the use of the K ratio emerges when the prevalence of the condition in the general population shows a rise with age. To consider the extreme cases, if general population frequencies are extremely low or nil in youth, then a very few affected relatives of diabetic propositi will give a very, perhaps infinitely, high value for the K ratio ($X\%/0 = \infty$) as with the offspring in Table 3; at the other age extreme, the general population frequency may be so high that it is not possible to exceed it significantly ($X\%/100 < 1$). Fig. 3 depicts a hypothetical model where diabetes

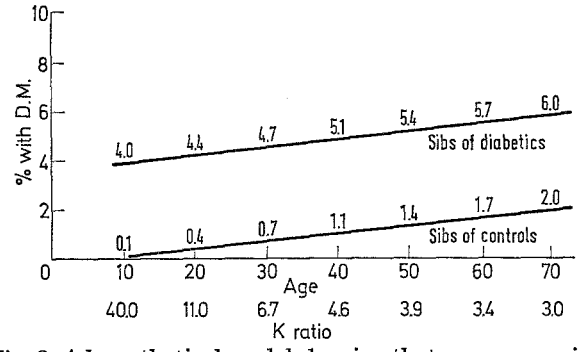

Fig. 3. A hypothetical model showing that, even assuming a constant genetic factor causing a fixed increase of 4% in the rate of affected siblings of diabetics at all ages, there is a considerable fall with age in calculated K ratios (see text for further explanation)

frequency in a population composed of siblings of diabetics is compared with that in a population composed of siblings of controls (or of the population at large). In its construction, two reasonable assumptions are made: (i) that the frequency of diabetes in the general population rises with age from zero to a total of 2%. (ii) that among siblings of diabetics a genetic factor, operating equally at all ages, causes diabetes in an extra 4% of them. The values of K ratios calculated on these assumptions are much higher at younger than at older ages. Thus, a result which has been proposed as evidence of different modes of inheritance can arise from a population which is, by definition, genetically homogeneous.

There are further difficulties in using the K ratio when the abnormality or disease in question represents an arbitrarily defined extreme of a continuously distributed variate, such as the blood sugar in this study. Not only will values for K depend upon the discriminating blood sugar level selected but, since it has been shown that there is a general rise in blood sugar with increasing age (Fig. 2), the K ratio will show a fall with age even though the blood sugar distributions, relative to each other, do not change!

Our findings suggest that the differences of K values published in support of the hypothesis that there are different modes of inheritance in the two clinical types of diabetes may arise in part from incomplete ascertainment of diabetes in the relatives, and that, in any case, the influence of age on diabetes prevalence introduces objections to the simple comparisons of relative prevalence.

It is clear that lesser grades of glucose intolerance occur with unsuspectedly high frequency among the relatives of patients (and in the population at large). Further, it appears that any choice of diagnostic criteria will represent an arbitrary division imposed for extraneous reasons upon a continuously varying series. EDWARDS (1960) has shown that even when 'thresholds' of recognition are arbitrarily imposed, it is still possible to demonstrate the mode of operation of a hereditary element. It would seem unwise, however, to apply his general argument to the question of different modes of inheritance of the two clinical types of diabetes for their 'thresholds' of recognition are entirely dissimilar.

The purpose of this paper is not so much to deny the existence of genetic heterogeneity in diabetes as to point out some of the objections to the use of the K ratio as evidence supporting it.

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