GENETICS AND THE NATAL INDIAN DIABETIC*

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The genetics of diabetes has recently been referred to as a geneticists' nightmare[1]—a state of affairs which is hardly surprising, considering the heterogeneous nature of the condition and the probability that many investigators are dealing with different 'types' of the disease. Racial differences and environmental factors such as dietary peculiarities add to the complexity of the problems.

The present study was designed to measure the response of the non-pregnant Natal Indian woman to an oral dose of 100 G of glucose. Consequently it may be more correct to refer to this study as the hereditary nature of abnormal carbohydrate metabolism.

MATERIAL AND METHODS

The subjects studied were healthy, ambulatory, Natal Indian women who had usually accompanied patients to my consulting rooms. They were selected purely on the basis of a family history of diabetes, but were themselves asymptomatic at the time of investigation. Modifying factors such as environment and diet were excluded, since the socio-economic background and dietary habits of the subjects were similar. They were also equal as regards age and parity.

Of the 241 patients studied, 141 had a positive family history of diabetes, and were divided into 3 groups according to their likelihood of developing diabetes (Table I). Unfortunately, the limited scope of this study precluded the investigation of the diabetic relatives. When both parents of the subject are diabetics, they are defined as conjugal diabetic relatives; a first-degree relative is a person whose father, mother, brother or sister is diabetic; and second- and third-degree relatives are subjects with affected grandparents, uncles, aunts or cousins.

TABLE I. PREVALENCE OF ABNORMAL GLUCOSE TOLERANCE IN RELATIVES OF DIABETICS

Relationship	*Total No. tested*	*Abnormal GTT*	%
Conjugal diabetic relatives	43	12	27·9
First-degree relative	57	7	12·3
2nd- or 3rd-degree relatives	41	4	9·7
No diabetic relatives	100	6	6·0

To serve as a control, carbohydrate tolerance was studied in 100 patients without a family history of diabetes, but who were comparable in all other respects.

After an unrestricted diet for at least 3 days, the subjects were instructed to fast overnight. Samples of venous blood and urine were collected in the fasting state and 2 hours after the ingestion of 100 G of glucose. Postglucose blood-sugar values of 140 mg./100 ml. or higher (Folin and Wu) were regarded as being abnormal.

RESULTS

The results of this investigation may be considered under the headings: (*a*) the correlation between the genetic predisposition to diabetes and abnormal carbohydrate tolerance, and (*b*) the mode of genetic transmission.

Family History and Abnormal Carbohydrate Tolerance

Of the 141 subjects with positive family histories of diabetes, the parents of 43 were both diabetics; 57 had an affected mother, father or sister; and the remaining 41 had diabetic grandparents, aunts, uncles or cousins. The respective frequency of abnormal glucose-tolerance tests in these groups was 27·9%, 12·3% and 9·75%.

Of the 100 control females without a family history of diabetes, six had abnormal 2-hour postglucose blood-sugar levels (Table I).

Mode of Genetic Transmission

Whereas many modes of inheritance have been postulated, the most favoured view is probably the 'recessive gene with incomplete penetrance hypothesis'.[2-5] According to this theory, the ratios of affected children with no, one or both parents diabetic should be 1:2:4, provided that the non-affected parents of each mating class are carriers of the recessive gene. As all the parents in the control group could not be expected to be carriers, the second- and third-degree relatives were used for comparison. Thus, 9·7% of the Natal Indian females without diabetic parents but with some diabetic relatives were found to have abnormal glucose-tolerance tests, compared with 10·4% and 27·9% when one or both parents were affected. The ratio of 1:1·07:2·8 is therefore not consistent with the recessive gene theory (Table II). Since only a quarter—and not all—of the offspring of connubial diabetics were found to have abnormal tolerance it is possible that the degree of 'penetrance' was reduced to 25%, a figure which correlates closely with that obtained by Pincus and White.[6] It should be noted, however, that the age distribution of the study group comprised young subjects between the ages of 16 and 48 years, and that the degree of penetrance might therefore be appreciably higher if persons of advanced years were included.

TABLE II. MODE OF GENETIC TRANSMISSION: THE RECESSIVE HYPOTHESIS

	Both affected	*One affected*	*Nil*
Expected ratio of affected offspring	4	2	1
Present series % offspring with abnormal GTT	27·9%	10·4%	9·75%
Ratio	2·84	1·07	1·00

To test the validity of the above results, a histogram of the 2-hour postprandial blood-sugar values of the conjugal relative group was constructed. If environmental factors are completely excluded, a single hypothesis should result in a bimodality in the distribution of the blood-sugar values, whereas a continuous distribution from normal to

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abnormal values would suggest a multifactorial control of the blood sugar.[7,8] It is suggested from the histogram in Fig. 1 that a cut-off point occurs at 180 mg. and possibly at the 140 mg./100 ml. level. More data will be needed, however, to document this with confidence.

DISCUSSION

Genetic Transmission

The hereditary transmission of diabetes is generally accepted but there is as yet little agreement as to the mechanisms of inheritance. When abnormal glucose tolerance (a 2-hour postglucose blood-sugar value of 140 mg./100 ml. or more) is used as a biological marker, Natal Indian females with positive family histories of diabetes were found to be more prone to abnormal carbohydrate tolerance when compared with control groups without such histories. Thus, abnormal glucose tolerance was 2 or 4 times more common among the offspring of diabetics, depending upon the number of parents affected. In a similar study, Thompson[8] concluded that relatives of known diabetic patients had more labile blood-sugar levels than those of controls, suggesting an impairment of normal homoeostasis in subjects with a family history of diabetes.

The mode of genetic transmission in the Natal Indian female is less clearly defined. When the transmission of abnormal glucose tolerance is studied in relationship to the parentage of the subjects, a ratio of 1·00 : 1·07 : 2·84 is obtained. However, the distribution curve of blood-sugar levels in the subjects with conjugal diabetic relatives suggests a bimodal pattern which is compatible with the single-gene hypothesis (Fig. 1).

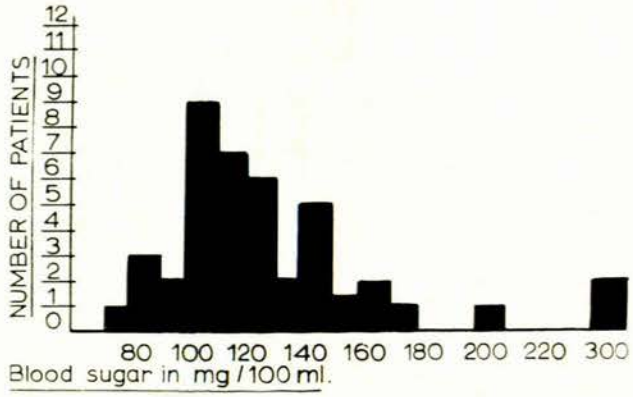

Fig. 1. Distribution of the 2-hour postprandial glucose level in 41 patients with first-degree diabetic relatives.

The concept of bimodality is dependent upon the phenotypic feature measured. Thus, Penrose[9] illustrated the alteration in the frequency distribution of some characteristics of phenylketonuria in affected patients and control populations, from a uniform curve when hair colour is used as the 'biological marker' to a typical bimodal graph when phenylalamine in blood plasma is studied. It is possible that the genetic transmission of diabetes fits into a similar model.

Rimoin[10] has suggested that ethnic variability in clinical disease, unrelated to significant environmental factors, is indicative of genetic heterogeneity. When two persons are homozygous for a recessive gene at the same locus, all the resulting offspring will be affected. If the two persons are homozygous at different loci, however, the offspring will be heterozygous at each of the individual loci and clinically normal. This method of genetic transmission may well explain the paradox that although the diets of the

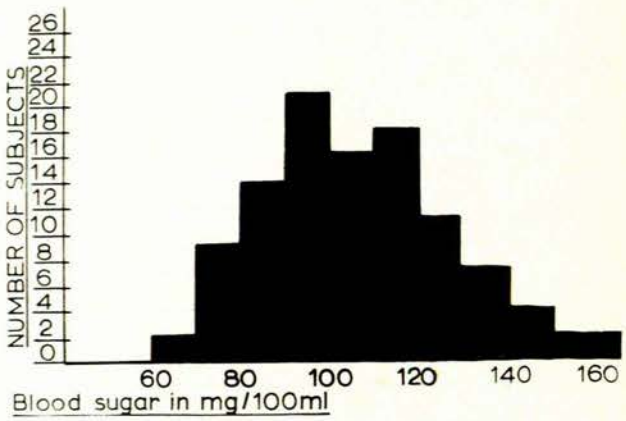

Fig. 2. Distribution of the 2-hour postprandial glucose value in 101 controls.

Natal Indian and South African Bantu are similar as regards total fat and carbohydrate intake, the clinical presentation of diabetes differs markedly, for ketosis is rare and vascular disease common in the Natal Indian, while the reverse is true of the South African Bantu.[11] It is therefore not possible to conclude which method of genetic transmission applies to the Natal Indian female. The main problem is the inability to pin-point the basic defect in diabetes, for the mode of transmission varies with the 'biological marker' employed—e.g. autosomal recessive or multifactorial[1-5,7,8] if the results are based on blood-sugar analysis and autosomal dominant when synalbumin antagonism is studied.[12] Therefore conclusive genetic studies will not be possible until reliable and accurate markers for the detection of prediabetes are made available and the basic defect in diabetes is established.

Environmental Factors

A recent editorial on the inheritance of diabetes mellitus stated: 'it has perhaps been insufficiently appreciated that environmental factors as well as genes can produce a positive family history'.[13] This view is supported by the animal experiments of Okamoto,[14] in which he was able to demonstrate the inheritance of 'spontaneous' diabetes from an acquired diabetes in the parents. It is also well known that environmental factors such as age, parity, obesity, race and diet may influence glucose tolerance and should therefore be taken into account when assessing the significance of inheritance of diabetes. For example, the prevalence of diabetes among the Yemenite Jews has increased significantly since their arrival in Israel, probably due to the inclusion of refined carbohydrate in their diet, a foodstuff rarely indulged in before their immigration.[15]

Campbell[16] believes that the importance of the genetic component in the emergence of diabetes in the Natal

Indian is secondary to that of environmental factors. While not agreeing with this view entirely, we must concede that, although only 3 generations have elapsed since the Indians arrived in South Africa,[17] the incidence of diabetes is very much greater in the Natal Indian as opposed to the native-born Indian, the main environmental difference being the amount of sugar in the daily diet.[18] The over-all *per capita* consumption of sugar in India is 5·4 kg. *per annum*, whereas in the Natal Indian working class it rises to 35 kg. *per annum* and to 50 kg. in the upper classes.[16] Campbell[16] states that the increased incidence of diabetes is the result of overindulgence in sugar by the Natal Indian, and has linked these observations to Neel's[19] concept of the 'thrifty' genotype—a hypothesis which suggests that diabetes is characterized by an excess availability of insulin in the early stages of the disease, followed by the over-production of insulin antagonists.

The initial overproduction of insulin is thought to have an important energy-conserving mechanism during periods of low calorie intake.

The influence of environment is further evident in the South African Bantu, since the incidence of diabetes in the urban Bantu is similar to that of the White South African, whereas diabetes rarely occurs in the rural Bantu.[17]

CONCLUSION

To arrive at a satisfactory conclusion it is of vital importance to know how close the blood sugar is to the primary action of the gene producing diabetes. All that can be concluded from the present study is that disturbed carbohydrate metabolism has a familial tendency. Since the use of different 'biological' markers will reveal different modes of genetic transmission, it is essential to define the 'diabetic syndrome' and to base one's results on the supposed aetiological factors.

Because of the obvious heterogeneous nature of clinical diabetes it is suggested that all future studies on the genetics of diabetes be conducted on carefully selected patients of a similar racial, socio-economic and environmental background; and to base the conclusions on the evaluation in each subject of the genetic transmission of all known prediabetic biological markers.

SUMMARY

To determine the genetic transmission of diabetes in the Natal Indian female, glucose tolerance was studied in 240 subjects, 140 of whom had positive family histories of diabetes. Whereas conflicting results were obtained as to the exact mode of genetic transmission, it can be concluded that abnormal carbohydrate tolerance has a definite familial tendency.

The importance of environmental factors in the production of positive family histories is discussed and the specific role it plays in the Natal Indian is stressed. To elucidate the genetic transmission of diabetes it is necessary to define the disease and to employ appropriate and accurate biological markers. Because of the heterogeneous nature of the syndrome it is suggested that the genetic transmission of all known prediabetic factors be studied in future surveys.

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REFERENCES

1. Neel, J. V., Fajans, S. S., Conn, J. W. and Davidson, R. T. *in* Neel, J. V., Shaw, M. and Schull, W., eds. (1965): *Genetics and Epidemiology of Chronic Disease*, p. 105. Washington, DC: US Dept of Health, Education and Welfare, Public Health Service.
2. Pincus, G. and White, P. (1933): Amer. J. Med. Sci., **186**, 1.
3. Post, R. H. (1962): Diabetes, **11**, 56.
4. Steinberg, A. G. (1965): *The Nature and Treatment of Diabetes*, p. 601. Amsterdam: Excerpta Medica Foundation.
5. Simpson, N. E. (1962): Ann. Hum. Genet., **26**, 1.
6. Pincus, G. and White, P. (1934): Amer. J. Med. Sci., **188**, 782.
7. Clarke, C. A. (1961): Diabetes, **10**, 175.
8. Thompson, G. S. (1965): J. Med. Genet., **2**, 221.
9. Penrose, L. S. (1951): Ann. Eugen. (Lond.), **16**, 134.
10. Rimoin, D. L. (1967): Diabetes, **16**, 346.
11. Walker, A. R. P., Richardson, B. D. and Mistry, S. D. (1964): Brit. Med. J., **2**, 1394.
12. Vallance-Owen, J. and Lilly, M. D. (1961): Lancet, **1**, 806.
13. Leading Article (1965): Brit. Med. J., **1**, 940.
14. Okamoto, K. (1965): *Proceedings of the 2nd International Congress on Endocrinology*, part 2, p. 1018. Amsterdam: Excerpta Medica Foundation.
15. Cohen, A. M., Boaly, S. and Poznzski, R. (1961): Lancet, **2**, 1399.
16. Campbell, G. D. (1963): S. Afr. Med. J., **37**, 1195.
17. Bernstein, R. E. (1965): Med. Proc., **11**, 625.
18. International Sugar Council (1961): *Sugar Year Book*, p. 259. London: Brown, Knight & Truscott.
19. Neel, J. V. (1962): Amer. J. Hum. Genet., **14**, 353.