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ORIGINALS

Observations on Heredity and Obesity in the Emergence of Diabetes

W.P.U. Jackson, G.D. Campbell, M.D. Goldberg and N.Marine
Endocrine Research Group, University of Cape Town and Medical Research Council, and the Diabetes Clinic, King Edward VIII Hospital and University of Natal, South Africa

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Summary. The 899 offspring of Natal Indian diabetic couples are compared with the general Indian population. Diabetes was present in 25% of offspring aged 40–49 as against 14.7% of the general population. The ratio of offspring diabetics to population diabetics diminished with age, suggesting that the genetic influence affects mainly age of onset of diabetes. "Old" and "young" diabetic couples had a similar proportion of diabetic children. Another similar comparison could be made between an inbred Tamil Indian family in Cape Town and the general population of Cape Hindus. More young diabetics were obese than old diabetics, in 3 different racial groups and in both "clinic" and "survey" diabetics, whereas in the general population obesity is more common over age 40. Overweight may be a more important diabetes risk factor in young than in old people.

Observations sur l'hérédité et l'obésité dans l'apparition du diabète

Résumé. 899 enfants nés de couples Indiens diabétiques (province du Natal) ont été comparés à l'ensemble de la population indienne. Le diabète était présent chez 25% des descendants âgés entre 40 et 49 ans contre 14.7% pour la population générale. La différence de prévalence du diabète entre les descendants des couples diabétiques et la population générale diminuait avec l'âge, ce qui semble indiquer que le facteur génétique affecte surtout l'âge d'apparition du diabète. La proportion d'enfants diabétiques était identique pour les couples diabétiques jeunes ou vieux. Cette même comparaison a pu se faire entre une famille indienne Tamil dont les membres s'épousent entre eux et vivant au Cap et l'ensemble de la population indienne du Cap. La prévalence d'obésité était plus grande chez les diabétiques jeunes que chez les diabétiques âgés dans trois groupes raciaux différents et ceci aussi bien pour le diabète symptomatique qu' asymptomatique; par contre l'obésité est plus fréquente pour la population générale dépassant l'âge de 40 ans. L'obésité semble jouer un rôle plus important comme facteur diabétogène chez les jeunes que chez les personnes âgées.

Beobachtungen über Erblichkeit und Fettleibigkeit beim Auftreten des Diabetes.

Zusammenfassung. Eine Gruppe von 899 Indern aus Natal, Nachkommen diabetischer Elternpaare, wurde mit der indischen Gesamtbevölkerung in Natal verglichen. Diabetes wurde in 25% der Nachkommen im Alter zwischen 40 und 49 Jahren beobachtet, verglichen mit 14.7% in der Gesamtbevölkerung. Die Verhältniszahl: Diabetiker unter den Nachkommen zu den Diabetikern in der Gesamtbevölkerung verringerte sich mit ansteigendem Alter; dieser Befund scheint anzudeuten, daß ein möglicher genetischer Faktor einen besonderen Einfluß auf das Alter ausübt, in dem der Diabetes sich manifestiert. „Alte" und „junge" Elternpaare hatten eine ähnliche zahlenmäßige Verteilung diabetischer Kinder. Ein ähnlicher Vergleich konnte zwischen einer Familiengruppe indischer Tamilen in Kapstadt und der gesamten Hindu-Bevölkerung von Kapstadt angestellt werden. Bei drei rassisch verschiedenen Bevölkerungsgruppen und bei „klinischen" wie bei „neuentdeckten" Diabetikern wurde festgestellt, daß Fettleibigkeit häufiger bei jungen als bei alten Diabetikern auftrat, während in der Gesamtbevölkerung die Fettleibigkeit im Alter von über 40 Jahren häufiger war. Übergewicht ist als Risikofaktor für den Diabetes vielleicht wichtiger bei jüngeren als bei älteren Personen.

Key words: Offspring of diabetic couples, age and heredity in diabetes, obesity, population studies, diabetes prevalence.

Diabetes mellitus causes floundering among geneticists. We clinicians cannot tell them whether hyperglycaemia *per se* means diabetes, whether "idiopathic diabetes" is one or more diseases, whether all or only a fraction of diabetes is hereditary, whether it is the same disease in different races and which of the different manifestations of the diabetic syndrome are inherited. Furthermore, we believe that people may inherit the diabetic genetic predisposition yet never develop diabetes, either because they die too young or because environmental factors prevent its expression.

This paper attempts to provide a little more data that may be of some interest.

The findings

Connubial Offspring. Among the many diabetic Indians in Durban we had traced 152 husband and wife diabetic pairs and 899 of their offspring up to 1966 [5]. Ascertainment was through one or other parent, and the term "diabetic" here means the overt, clinical disease. For various reasons we were unable to confirm the presence of diabetes in both members of all the pairs by actual measurement of blood glucose, and the same applies to the diabetics among their children ("connubial offspring"). The diabetes is thus "reputed" rather than "proven" in some cases.

During the same period of time, a diabetes prevalence study involving 2427 Indians in the Durban area was performed, providing us with knowledge concerning already known diabetes and previously unrecognized diabetes, diagnosed at our survey[2].[1] Table 1 compares the prevalence of reputed diabetes among the connubial offspring with *known* diabetes among the Indian community.

Table 1. *Known diabetes among connubial offspring (899) and Indian survey population (2427) (in percentages)*

Age group	Offspring	Indian population
10–19	0.7	0.0
20–29	3.5	0.3
30–39	10.5	1.4
40–49	14.5	4.8
50–59	41[a]	7.0
60–69	—	10.0
All ages	6.5	1.8

[a] Less than 10 subjects.

In Table 2 the diabetic couples are divided into "old" and "young" after the criteria of Cooke and co-workers [1] — "young" when at least one parent was under age 40 at the time of diagnosis of diabetes. The "old" and "young" couples appear equally fertile. Offspring of the "old" couples had more diabetes than offspring of the "young" couples, but were themselves older. Age correction indicates a slightly, but insignificantly, lower frequency of diabetes among the offspring of the "old" couples (see last 2 columns of Table 2).

We then went further and accepted only those families in whom the presence of diabetes in the parents could be verified by the demonstration of diagnostic hyperglycaemia. The great majority of their offspring underwent oral glucose tolerance tests — 332 in all. In Table 3 we compare the *total* prevalence of diabetes (known plus discovered) in the offspring with the total prevalence among the Indian population on survey. (Methods and interpretations as previously described [4, 6]). It may be observed that the *ratio* of diabetes prevalence among offspring to prevalence among population diminishes with age, as diagrammatically shown in Fig. 1.

Table 3. *Total diabetes (known + discovered) among connubial offspring (332) and Indian survey population (2427) (in percentages)*

Age group	Offspring	Indian population
10–19	7.1	0.7
20–29	5.6	0.9
30–39	19.4	7.2
40–49	25.0	14.7
50–59	—	20.6
60–69	—	24.5
70+	—	31.3
All ages	13.3	6.0

Table 2. *Offspring of diabetic couples (Natal Indians)*

	couples			offspring		
	No.	No. fertile	No. with diabetic offspring	total No.	actual No. diabetic	expected No. diabetic
old	101	100	31 (31%)	621	47 (7.6%)	—
young[a]	51	49	9 (18.4%)	278	12 (4.6%)	10.4[b] (3.7%)

[a] At least one parent under 40 at diagnosis (criterion of Cooke *et al.*, 1966).

[b] Calculated using offspring of old parents as the standard and correcting for differences in age distribution.

A Tamil "Family". During studies among Indians living in Cape Town (of whom the total is only around 9000 as against half a million in Natal) we found a

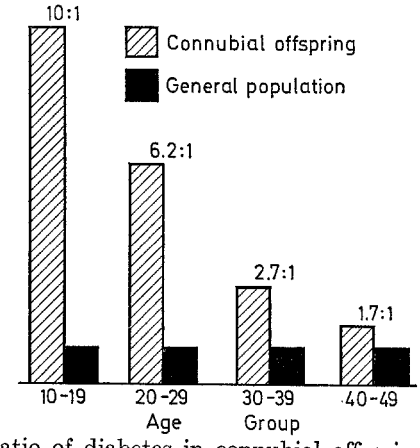

Fig. 1. Ratio of diabetes in connubial offspring to diabetes in Indian population with age

1 90% of all subjects over 10 years of age living in one village were screened by blood and urine glucose estimation two hours after 50 g of oral glucose. Those who showed glycosuria or whose blood glucose exceeded 109 mg per 100 ml had full glucose tolerance tests. A final diagnosis of "discovered diabetes" was made if 2 of the 3 estimations on blood taken while fasting, at 1 h and 2 h exceeded 120, 185 and 140 mg per 100 ml respectively (venous plasma, Autoanalyzer, Hoffman method).

high prevalence of diabetes in one area (Rylands Estate). Thirty-eight per cent over age 25 were diabetic; one third of these already under treatment. It then transpired that all the inhabitants in this area could be considered as one big family of Tamilian Hindus, with several first and second cousin marriages and uncle-niece marriages.

At the same time we were investigating other Hindu Indian populations [6], and Fig. 2 shows a comparison between known, discovered and total diabetes among the Tamil family and the Indian population.

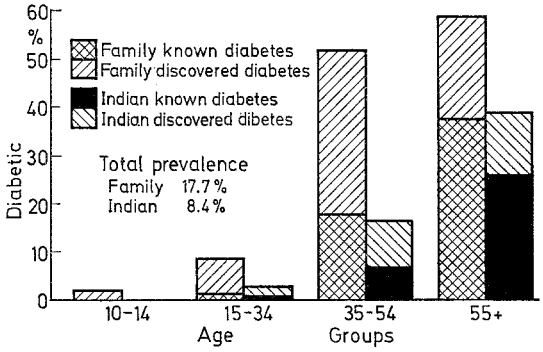

Fig. 2. Diabetes prevalence in Tamil family (311) and Cape Indian population (830)

Body Weight. In none of our population studies have we found any positive correlation between screening values of blood glucose and body weight, yet in all of them diabetes itself appeared to be closely related to weight [2, 6, 3]. Among the Natal Indians the prevalence of diabetes was 1.9% among those less than 85% of their standard weight,[2] rising to 17.8% in those more than 25% overweight [3]. The difference was less among Cape Bantu; and Bantu women, who were enormously more fat than men, had less diabetes [6].

On analysis of our Indian studies we observed that more young (under age 40) diabetics were obese (over 15% above standard weight) than old diabetics. We analysed our figures further, and found that the same applied to Indian established diabetics attending a clinic, to white clinic diabetics in Cape Town and to Cape-coloured diabetics discovered at survey. On the other hand, in all three races in the non-diabetic population, more people over 40 were obese than under 40. These findings are briefly shown in Table 4. In this Table only women are included (because of the small number of males) except in the coloured group which includes both sexes. Only non-diabetic Indians are shown, but a similar ratio between the two age groups is present among the non-diabetics of all races examined. The difference between obesity rates in "old" and "young" diabetics is statistically significant.

Discussion

Several previous reports on the children of diabetic couples have appeared [1, 9, 11, 8, 10], and the prevalence of diabetes in these children has been around 5% in most of them. In the largest series known to us, from Roumania, 28% of 1173 offspring were diabetic [7]. Among our 899 *Indian* offspring the frequency of *clinical diabetes* (6.6%) was in keeping with most reports in white communities, but from our data we could go further and report the *total* diabetes prevalence among 332 offspring (13.3%), in comparison with that of the general Indian population (6.0%). The difference between the connubial offspring and the general population was really greater than these figures indicate because of the youth of the offspring, and comparisons are best made between matched age groups. Incidentally, the offspring were no more overweight than the population.

With increasing age the difference in diabetes prevalence between offspring and population diminishes from 10 : 1 to 1.7 : 1 (Fig. 1). This change in ratio with age is again seen when the large, consanguineous Tamil family is compared with a similar Indian population in Cape Town (Fig. 2), and has been noted by Cooke *et al.* from British data [1]. It would seem then that the total *potential* for diabetes is little different between connubial offspring and the general population, but that the main effect of inheritance is to influence its *age of onset*. Such observations would seem to fit most readily with the theory of multifactorial genetic influence.

Table 4. *Obesity in "young" and "old" diabetics (showing percentage obese)*

Age	*Diabetic*								*Non-diabetic*	
	Indian Clinic		Survey		White Clinic		Coloured[a] Survey		Indian	
Under 40	63%	(11)	39%	(36)	38%	(23)	57%	(14)	13%	(720)
Over 40	42%	(72)	22%	(63)	27%	(165)	24%	(57)	23%	(130)

Figures in brackets indicate total number in each group.
[a] Both sexes included, only women in other groups. Difference between percentage obesity in all diabetics under 40 and all diabetics over 40 = 45% − 28.5% = 16.5. Standard error of difference = 5.75; $p < 0.01$.

2 On Documenta Geigy tables.

Cooke and co-workers [1] divided their diabetic couples into "young" (at least one parent under age 40 at time of diagnosis of diabetes) and "old". They found no difference in fertility between young and old couples, but their young couples had a significantly higher proportion of offspring who were diabetic. Our own considerably larger figures do not show any difference and do not support the suggestion that inheritance is of greater importance in diabetes of earlier onset. It should, however, be noted that diabetes among the Indian is in some ways different from that among white people — especially in the virtual absence of insulin-dependence, even in adolescents.

The frequency of diabetes among the inbred Tamil family indicates the importance of genetic influence, but does not help to distinguish the type of inheritance concerned. It must make one cautious of accepting prevalence rates of small communities as indicating more than the effects of isolation and inbreeding, assuming that there was a high concentration of the diabetic genes in the few progenitors of the group under consideration.

That obesity was more common among diabetics under 40 than over 40 was surprising to us, but was found in all groups analyzed (Table 4), whereas among each corresponding general population obesity was more frequent *over* the age of 40. This suggests that overweight may be a more important environmental factor in producing hyperglycaemia and diabetes in young people than in older people. In the past we may have missed this because of our tendency to be preoccupied with the ketosis-prone type of diabetes in younger people.

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W.P.U. Jackson, M.D.
University of Cape Town
Dept. of Medicine
Medical School
Cape Town, South Africa