Risk of Diabetes in Offspring of Parents with Non-insulin-dependent Diabetes

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KEY WORDS Diabetes mellitus Families Hereditary diseases Risk factors Life-style Exercise Diet Primary prevention

Introduction

Diabetes mellitus affects about 2% of Western European populations and represents a lifetime risk of 10–15%. It is by far the commonest endocrine disorder and its incidence and prevalence are increasing.[1]

Current ideas about the pathogenesis of non-insulin dependent (type 2) diabetes (NIDDM) increasingly encourage calls for preventive action.[2–4] Such action inevitably requires an evaluation of risk status for the disease. There are two main primary preventive strategies: a 'general population' approach and a 'high risk' approach. The former consists of the non-selective application of preventive measures across the whole population to reduce the risk factors for NIDDM, for example, by avoiding obesity, promoting normal body weight and by encouraging more physically active lifestyles. The 'high risk' strategy concentrates preventive activity on people defined as being at particularly high risk. If this latter strategy is adopted, it is important to identify which people are specially vulnerable, and to have estimates of the magnitude of their enhanced risk.

This review concerns itself with one readily identifiable high-risk group: people with a positive parental history of NIDDM. A number of factors, both genetic and environmental, influence the offspring's risk of developing NIDDM. Factors affecting the individual's genetic endowment include family history, type of diabetes involved, whether one or both of the parents have diabetes, and race. Risk of disease expression is also related to lifestyle factors, the most important of which are probably obesity[5] and physical inactivity.[6] The roles of intrauterine and early life environment factors have been emphasized recently by the work of Hales, Barker and colleagues on the predictive relationship between low foetal and infant growth rates and impaired glucose tolerance in later life.[7]

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Genetic Factors

Family Studies

There has been a long tradition of family studies in the exploration of diabetes causation. The early studies treated diabetes mellitus as a single entity, failing to differentiate between the two major clinical types: distinguished as insulin-dependent mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) by WHO.[8,9] Some of the early studies of family history recognized differences in the mode of inheritance of diabetes diagnosed in early life and that diagnosed later in life.[10] A quarter of a century ago the consensus was that 'juvenile onset diabetes' (now called IDDM) showed a greater degree of 'hereditability' than 'maturity onset diabetes' (now called NIDDM).[11] Simpson[12] enquired into the diabetic status of first degree relatives of large numbers of diabetic patients in Canada. She calculated the empirical risk of diabetes in various classes of relatives of the diabetic probands and compared this with the risk of diabetes in the general population of a Canadian province calculated from available statistics. She found that when diabetes was diagnosed after 40 years of age in the proband, risk for siblings and children was increased by a factor of 2 or 3 but when diabetes was diagnosed before age 20, risk of diabetes was increased 12 fold in the siblings and more than 30 fold in the offspring of the proband.

Keen and Track[13] cautioned against drawing such conclusions from studies of the relative prevalence of diabetes in families of people with younger and older onset types of diabetes. Diabetes prevalence in the general population is so low at early ages that a very small number of affected relatives will give a very high excess prevalence. As the rates rise with increasing age in the general population that relative excess will inevitably fall, so it is therefore not valid to claim a difference in heritability simply on the basis of differential prevalence ratios.

Conclusions are also insecure when based only upon reported family histories. Submitting apparently non-

CCC 0742–3071/95/010006–08

diabetic relatives of NIDDM patients to formal glucose tolerance testing more than doubled reported known prevalence. Keen and Track identified 735 diabetic propositi and 514 outpatient controls not known to have diabetes and examined, respectively, 1149 and 609 of their first degree relatives. Analysis of family histories reported by the probands supported the view that inheritance plays a larger role in younger onset than older onset diabetes. However, when estimates of prevalence were based on the results of glucose tolerance tests in the relatives the excess prevalence in the younger onset cases was much less marked. In their study, using the prevailing diagnostic criteria, onset was about three times more common in the relatives of people with NIDDM than in similar aged controls.

Many of the older family studies of diabetes can now be seen to have one or more of the following flaws:

1. They did not distinguish between IDDM and NIDDM.
2. They largely relied on analysis of verbal reports from patient probands of known diabetes in their relatives.
3. When relatives received oral glucose tolerance tests, a wide variety of diagnostic criteria were used.
4. They dealt inadequately with the problems raised by increasing age being a major risk factor for NIDDM.
5. They did not allow for ascertainment biases for diabetes in the relatives.

More recent studies have tried to address these issues. The Whitehall Study in Great Britain[14] submitted a large population to a standard test of glucose tolerance and confirmed an excess of diabetes in the members of families of NIDDM patients. In 1976–80 the US National Health and Nutrition Examination Survey[15] found that among people aged 35–74 years, about 35% of those with a medical history of diabetes reported that one or both of their parents had diabetes. For people without a previous diagnosis of diabetes but who on testing met National Diabetes Data Group (NDDG) criteria for diabetes or Impaired Glucose Tolerance (IGT), 28% and 27%, respectively, reported that one or both of their parents had diabetes. These figures contrasted with a figure of 17% for those with normal glucose tolerance.[16] The CODIAB[17] study identified 218 subjects recruited from 10 geographically representative centres in France. Non-insulin-dependent diabetes in the proband was confirmed by a diabetologist. Sixty-six percent of these subjects reported at least one first degree relative with diabetes.

Ohlson *et al.*[18] reported on a cohort of 766 men free of diabetes at examination at age 54 in 1967. When re-examined by 100 g oral glucose tolerance tests (OGTT) in 1980, 47 (6.1%) were found to have diabetes. The risk for developing diabetes was 2.4-fold higher in those with a positive family history of diabetes at baseline compared with those with a negative family history.

Kobberling and Tillil[19] used data from Falconer *et al*[20] to calculate the age-dependent relative risk of developing NIDDM. They made estimates of risk based upon the increasing prevalence of NIDDM with age (Figure 1) Here it can be seen that, for example, of all those destined to develop diabetes by age 80, about 40% will have already developed it by age 60. Using a similar life table technique they calculated the cumulative prevalence of NIDDM. From this they estimated the hypothetical total risk of developing diabetes, assuming that all survive to 80 years, to be 38% for first degree relatives, compared with 11% for relatives of non-diabetic controls. The risk for a relative at a given age can be calculated by multiplying lifetime risk (38%) by the proportion shown by the figure to be affected by that age. For example, the risk of a first degree relative developing diabetes by 60 years of age is 40% of 38% (15.2%).

Family studies often fail to quantify the effects on risk of having varying numbers of parents and siblings with diabetes. Beaty *et al.*[21] examined 742 first degree relatives of white Americans with NIDDM. None of these relatives was known to have diabetes prior to the study. They performed a 3 h oral glucose tolerance test on them using a 1.7 g kg^{-1} load. Among the 434 females, the number affected sibs was found to be as important in influencing the probability of having diabetes as having a parental history of diabetes, but the number of affected parents was not. Similar results were found in the 308 males examined. They found greater concordance for diabetes between siblings than between parents and child, and suggested that this was attributable to environmental factors which are more likely to be common within a generation than across a generation.

Studies of the emergence of diabetes in parents and their children are likely to underestimate the degree of concordance. Typically NIDDM appears late in life and the offspring may not manifest the disease until after the

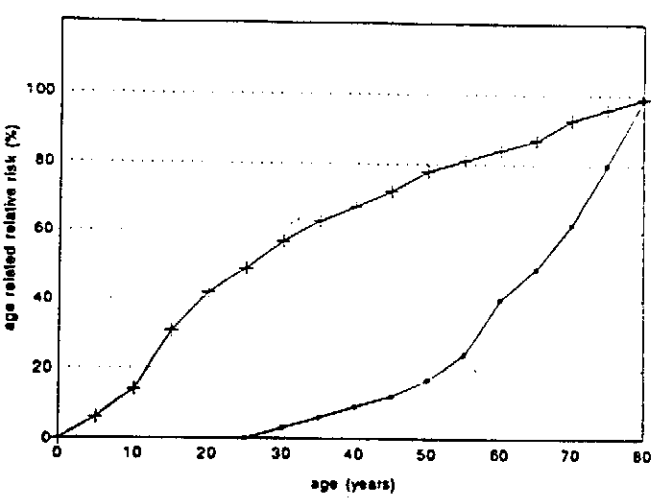

Figure 1. Relative risk of having developed NIDDM (□) and IDDM(+) at certain ages (Reproduced from The *Genetics of Diabetes Mellitus* by J Koberling and R Tattersall with kind permission of Academic Press (London) Ltd)

parent has died, perhaps prematurely because of their diabetes.

Impaired Glucose Tolerance in Family Studies

NIDDM may be preceded by demonstrable abnormalities of glucose tolerance and insulin release. If these features are also used in the parent–child analysis a rather different picture emerges.

Impared glucose tolerance (IGT) is defined by blood glucose value in the response to the standard oral glucose challenge (WHO) intermediate between normal and diabetic. It can therefore only be determined by an OGTT. Leslie *et al.*[22] studied non-diabetic offspring of a parent with NIDDM who also had at least one affected sibling. Offspring were relatively young (mean age 30 years). One 'child' was randomly selected from each of the 13 families, and each was matched for age, body mass index, sex, and social class with a control subject. In the standard OGTT, blood glucose, serum C peptide, and serum insulin rose to significantly higher levels 2 h after glucose load in the offspring than in the matched controls. Of all 32 offspring from the 13 families, 12 had impaired glucose tolerance (IGT).

Larger studies have suggested that 15–25% of the first degree relatives of people with NIDDM may develop IGT.[23] Several prospective studies have looked at rates of progression of IGT to diabetes. In Pima Indians, 5–6% per year of those with IGT progressed.[24] In other populations progression was as low as 1.5%–2%.[25,26] However the people with IGT in these studies did not necessarily have a relative with diabetes; the rates of progression to diabetes may differ in people with IGT, with and without a family history of diabetes.

Impaired glucose tolerance is both a heterogeneous and unstable category. On retesting, a large proportion of subjects will be found to have reverted to normal glucose tolerance, a much smaller number will give a diabetic response and the rest will remain in the IGT class. These three categories of IGT were interpreted by Yudkin *et al.*[27] as:

1. Those in the upper tail of the distribution of people with normal glucose tolerance (revert to normal on retest).
2. Those in the lower tail of the distribution of people with diabetes (display diabetes mellitus on retest).
3. Those truly positive for IGT (remain unchanged on retest).

Yudkin suggested that members of this third group may be in transition from normality to diabetes. An alternative view would be that the position of a given individual on the range of glucose tolerance/glucose intolerance is determined by many factors, genetic and environmental, which when acting in excess will result in the diabetic state, in deficit in normality, and at intermediate levels in IGT. Clearly such multiple factors could be quite labile with rapid variation in the resultant glycaemic response to the glucose load.

It is clear that caution must be exercised when interpreting the meaning of an IGT response in any one individual. It was precisely this uncertainty about the meaning of borderline results from OGTTs which led to the creation of the category of IGT. It has been suggested that the predictive interpretation of IGT can be improved by incorporating consideration of accompanying insulin values[28] or perhaps the split pro-insulin values[29] in the analysis.

Martin *et al.*[30] studied the mechanism of development of NIDDM. They followed up 155 normogylcaemic offspring of 86 families, where both parents had NIDDM, for a period of 6–25 years. They found that defects in both insulin-dependent and insulin-independent glucose uptake predicted the development of NIDDM. By contrast, measures of insulin secretion were not predictive. The presence of these defects more than a decade before the development of clinical disease suggests that they may be genetically determined characteristics of the prediabetic state. Other factors, such as excess calorie intake, obesity, and B cell failure add to or act synergistically with these primary defects ultimately leading to the development of NIDDM.

Type of Diabetes

Early family studies of diabetes were confounded by regarding diabetes mellitus as a single disease with varying clinical manifestations. The discovery of the HLA/IDDM association[31,32] and twin data[33] provided support for differing genetic bases for IDDM and NIDDM, at least in populations of European origin. Concordance for NIDDM was seen in 91% of monozygotic twins. Moreover the discordant non-diabetic twins had significant metabolic abnormalities.[34] It has been suggested that ascertainment bias may contribute to these high concordance rates but Newman *et al.*[35] met this problem by selecting twins from US military records. Although only 4 out of 25 pairs were concordant for NIDDM at first examination, within 10 years 20 of the 21 unaffected twins had developed diabetes. By contrast concordance for IDDM was shown in only 54% of monozygotic twin pairs ascertained from one with IDDM, although immunological changes associated with IDDM were found in many of the non-diabetic co-twins.

The separation of IDDM and NIDDM has major significance for genetic counselling. In general, the type of diabetes 'breeds true' within families. Insulin-dependent diabetes occurred no more often among the relatives of patients with NIDDM than among the general population.[19] However a proportion of NIDDM patients can be shown to have circulating islet cell antibodies and to carry HLA specificities characteristic of Caucasian IDDM patients. The pattern of inheritance in those patients is more likely to resemble that of IDDM.

The non-insulin-dependent state may result from a

number of causal mechanisms; and different patterns of inheritance may therefore be applicable in its different subtypes.

O'Rahilly *et al.*[36] described a type of NIDDM of early diagnosis, often requiring insulin to achieve adequate glycaemic control, not prone to ketosis and without evidence of islet autoimmunity, but associated with NIDDM in both parents. O'Rahilly suggested that this early onset form may be 'due to the inheritance of diabetogenic genes from both parents' and that 'the data are consistent with an autosomal genetic disorder which presents at an early age when homozygous, and when heterozygous leads either to late onset diabetes or remains as lifelong subclinical glucose intolerance'. This 'double-dose' model is supported by Viswanathan's[37] findings in Asian Indian families. In the affected offspring of 164 families where both parents had diabetes, 30% developed diabetes before the age of 40 years.

Maturity onset diabetes of the young (MODY)[38] was originally described as a familial type of diabetes in young people (under 25), not requiring insulin for survival, not prone to ketosis, and relatively spared the severe complications of the disease. Inherited in an autosomal dominant manner a patient with MODY confers a 50% risk for the disease to his or her offspring. Even MODY is clinically and genetically heterogeneous. Hattersely *et al.*[39] and Froguel *et al.*[40] described some MODY families with a defect in the gene for glucokinase linked with the presence of NIDDM.

Glucokinase and other potential candidate genes for NIDDM have been discussed by Randle.[41] In some families an abnormality in the mitochondrial DNA (mtDNA) has been found to be associated with the presence of NIDDM in the offspring. This is most commonly associated with the 'MELAS' syndrome or some features of it.[42] As an offspring inherits mtDNA only from the mother so the diabetes is maternally transmitted in these cases.

Although NIDDM itself is very common, the search for susceptibility genes is hampered by the paucity of suitable families. Large multiplex multigenerational pedigrees,[43] affected sib-pairs or nuclear families with both parents and offspring available, are necessary for these studies.[44] The late onset of the disease and the high mortality in affected subjects means that by the time diabetes has presented, one or both of the parents of the proband have died and the offspring are not yet old enough to manifest the disease. Cook *et al.*[45] interviewed 950 NIDDM patients about the availability of first degree relatives. During a 5-year period, 127 Caucasian families were identified and 589 first degree relatives characterized. This yielded three large pedigrees with MODY, and eight multiplex multi-generational NIDDM pedigrees. Twelve sib-pairs were identified in which both siblings had NIDDM but only seven of these had both parents alive, and two of these had both parents affected. Seventy-six complete nuclear families with both parents and offspring were available but only six of these were of optimal structure for linkage analysis.

The Effect of Conjugal Diabetes (Biparental NIDDM)

Reports of offspring when both parents have diabetes, have shown low diabetic prevalances of between 3 and 12% in European populations. However, the picture changes when the offspring are submitted to OGTT. Tattersall and Fajans[46] studied 199 offspring of 37 families where both of the parents had diabetes (the majority of whom had NIDDM). Twenty-three (11.5%) were known to have diabetes, and a further 28 had a positive OGTT, a total prevalence of 23% estimated to rise to 60% by 60 years of age. In the offspring of Asian Indian families where both parents had NIDDM, Viswanathan *et al.*[47] found diabetes in 50% and impaired glucose tolerance (using WHO criteria) in a further 12%.

In both series, small numbers of families had no offspring with diabetes and some in which all the offspring had diabetes. This variation may be due to the play of chance or an indication of genetic heterogeneity.

Race

The prevalence of NIDDM is very variable amongst different racial groups, from a low of 2% or less amongst Eskimos, some African peoples, and New Guinea Highlanders, to a high of 35% amongst the Pima Indians.[48] Certain racial groups like Micronesians (e.g. Nauruans), Native Americans (e.g. Pimas), Asian Indians, Mexican Americans, and Australian aborigines seem to be particularly prone to NIDDM. This susceptibility manifests itself when they move from a 'traditional' lifestyle to a more 'modern' one with the increased availability of food and reduction in the demand for physical exertion.[49]

This may represent the adverse expression of a genotype adapted to mere subsistence (Neel's[50] 'thrifty genotype') but the work of Barker and Hales has suggested that enhanced susceptibility to diabetes may result from deprivation in the intrauterine environment or early life producing what they have called a 'thrifty phenotype'.

In two populations with a high prevalence of NIDDM, the Nauruans[51] and the Pima Native Americans, an autosomal dominant mode of transmission has been suggested.[52] Several 'high prevalence' populations, Nauruans, Pimas, Polynesians, and Mexican Americans, demonstrate biomodality in the distribution of both fasting blood glucose levels and 2 h post-load glucose levels. Blood glucose levels in populations with lower prevalence of the disease (e.g. peoples of European origin) are unimodally distributed with marked positive skewness. It would be difficult to demonstrate biomodality in such populations with a low prevalence of diabetes even if it existed. The diabetes in these 'biomodal' and 'unimodal' populations may differ qualitatively. This

debate is reminiscent of the controversy over blood pressure distributions. Until this debate is resolved one should be cautious in extrapolating from findings from Nauruan and Pima populations to other ethnic groups.

Environmental Factors

The progression of lesser abnormalities of glucose metabolism to overt diabetes may be infuenced by environmental factors, particularly obesity and physical inactivity.

Obesity

The risk of development of NIDDM is positively associated with obesity. This association is strong, graded and consistent. It was the diabète gras of the last century further emphasized by Joslin early in this century,[53] and has since been demonstrated many times in many different populations. Westlund's data[54] nicely express the quantitative and prospective relationship between obesity and the development of diabetes. In 3751 Norwegian males aged 40–49, there was an accelerating increase in the rate of development of diabetes with increasing initial obesity.

The literature on obesity and diabetes has been comprehensively reviewed elsewhere.[55,56] Particularly pertinent are the studies which have explored the interaction of obesity and family history of diabetes. Baird[57] carried out 50 oral glucose tolerance tests on siblings of obese and non-obese people with diabetes. She defined obesity as more than 110% of the mean weight for people in the population of same sex, age, and height. Diabetes rates as high as 27.3% were found in the obese siblings of non-obese people with diabetes. This compared with the much lower rate of 4.8% in the non-obese siblings of obese people with diabetes. Her data suggested that obesity and family history independently, additively, and perhaps synergistically increased the risk of diabetes. Kobberling[58] found that rates of glucose intolerance were much lower in relatives of fat rather than lean individuals with maturity onset diabetes who did not require insulin. The underlying pathogenesis and genetic determinants of obese and non-obese NIDDM[9] may differ, however, and so may differentially influence heritability.

In a study of 32662 adult white women attending a Canadian Slimming group (TOPS), Morris *et al.*[59] also showed that family history and obesity were independent but positively interacting risk factors for NIDDM. However, this was an unusual population and analyses were based on reported family histories.

In Pima Native Americans, Knowler *et al.*[60] showed an accelerating increase in the age-adjusted incidence of diabetes with obesity in subjects with a positive parental history of diabetes in one or both parents, but obesity had little effect when neither parent had diabetes.

Vague[61] was the first to demonstrate that the distribution of obesity, central or peripheral, was at least as important as the degree of obesity in its metabolic associations. It has since repeatedly been shown that central obesity is a better predictor of NIDDM than total obesity.[62,63] We are not aware of any studies which have examined the interaction of the distribution of adiposity and family history of diabetes in determining the risk of diabetes.

Physical Activity

A few published epidemiological studies suggest that physical inactivity may be an important risk factor for NIDDM. In a cross-sectional study in Melanesian and Indian men in Fiji, diabetes was twice as prevalent in men classified as inactive or undertaking light activities as in men performing moderate or heavy exercise, even controlling for obesity and age.[64] Saltin *et al.*[65] showed that the frequency of IGT in middle aged non-diabetic men was significantly higher among those who were physically inactive during their leisure time. In a longitudinal though retrospective study the prevalence of diabetes in women who participated in college sport and remained physically active in later years was only half that of those who had not participated in college sport.[66] Helmrich *et al.*[67] studied 5990 men by questionnaire between 1962 and 1976, none having known diabetes prior to 1962. The degree of physical activity at baseline was inversely related to the incidence of diabetes during the 14 years to follow-up. Moreover the apparent protective effect of physical activity was most clearly seen in the subgroups with high risk characteristics for NIDDM, obesity, hypertension, and a positive family history of diabetes.

Eriksson and Lindegärde[68] studied the effect of regular physical exercise on rates of progression to diabetes. They encouraged 181 middle aged men with impaired glucose tolerance (IGT) to follow a healthy lifestyle including regular exercise. After 6 years the accumulated incidence of diabetes was 10.6% in the intervention group compared with 28.6% in the control group. The relative risk of diabetes in the two groups was 0.37 (95% confidence interval of 0.2–0.68; $p < .003$). Improvement in glucose tolerance was correlated to increased fitness ($r=0.22$; $p0.02$) and to weight loss ($r=0.19$;$p<0.02$).

Tuomilehto[69] examined 2149 people aged over 15 years in 1100 Maltese households. Diabetes was found in 7% (150) and IGT in 5.6% (121). The 271 with IGT or diabetes and a control group of 250 people with normal glucose tolerance were examined in detail and were followed up for 2 years. Among subjects with normal glucose tolerance at baseline those with low physical activity and a positive family history had approximately a 2 fold increase in age-standardized risk of diabetes compared with those with high physical activity and negative family history. It is difficult to distinguish the effects of physical exercise from those of family history in this study.

Sex of the Affected Parent

A number of studies have suggested that an offspring's risk of developing NIDDM is higher if the affected parent is the mother. Martin *et al.*[70] found a higher frequency of parental history of diabetes in women with gestational diabetes than in normoglycaemic pregnant controls, an excess largely accounted for by maternal diabetes. Analysing family histories of diabetic patients from an existing database of patients who had in the past 10 years attended hospital-based specialist clinics in the Cambridge area, Alcolado[71] found that 183 (56%) of 234 whie patients reported parental diabetes. Significantly more had an affected mother than an affected father (125 vs 48;$p<0.001$): 10 had both parents affected. The CODIAB study[17] recruited 536 NIDDM patients from 10 geographically representative centres in France. Two hundred and eighteen subjects were able to give complete information about the diabetic status of their first degree relatives. Of these 33% had a mother with diabetes and 17% had a father with diabetes ($p<.001$). Pettitt *et al.*[72] reported diabetes in 45% of 20–24-year-old offspring of Pima women with NIDDM during pregnancy compared with 8.6% when diabetes in the mother followed the pregnancy and 1.4% when the mother was non-diabetic. They proposed that, in addition to genetic factors, the diabetic intrauterine environment was an important determinant of diabetes in the offspring.

In animal models, Aerts and Van Assche[73] described the transmission of inadequate pancreatic beta cell responses during pregnancy starting with streptozotocin-induced diabetes with first generation. Gestational beta cell limitation persisted in the second (and third) generations of these rats. Similarly Gauguier *et al.*[74] found that the glucose intolerance was induced in the offspring of the female rats which were rendered hyperglycaemic by glucose infusion during the later stages of pregnancy. When glucose intolerant rats becaome pregnant the glucose intolerance was transmitted to the subsequent generation.

Hales *et al.*[7] have proposed an alternative explanation of the development of NIDDM, invoking fetal programming or adaptation to subnutrition during intrauterine development. Using the preserved records of birth weight and weight at 1 year of male infants born in Hertfordshire in 1920–1930, they were able to examine almost 400 of them at a mean age of 64 years. Those with the lowest birthweights and weights at 1 year were significantly more likely to develop glucose intolerance or diabetes in middle age than those in the upper range of birth weight for dates. The authors suggested that low birthweight may be a marker of inadequate intrauterine nutrition and that this fetal deprivaton is associated with failure of development of pancreatic beta cells. A reduced beta cell endowment may be appropriate to meet the reduced demands of a subsistence economy but may result in insulin deficiency and glucose intolerance in food is in surfeit. This hypothesis could offer an additional non-genetic explanation of family transmission of diabetes.

Conclusions and Implications

Familial clustering is a feature of NIDDM. Although published studies are not entirely consistent, concordance for diabetes between siblings appears to be stronger than that between parent and child. Published reports suggest that:

1. Having a parent with NIDDM increases an offspring's chance of developing that disease between two and four fold.
2. Having a parent with NIDDM does not affect an offspring's chance of developing IDDM.
3. The risk of NIDDM is increased:

   (a) if the affected parent is mother rather than father;
   (b) if both parents are affected (at least in some groups, e.g. Asian Indians);
   (c) if the parent had MODY;
   (d) in certain racial groups;
   (e) with increasing age.

4. Early developmental environment, particularly poor intrauterine and infant nutrition, may contribute to risk of later glucose intolerance. Obesity and physical inactivity also increase risk.

The interaction of genetic endowment and environmental conditions contributes powerfully to familial clustering of NIDDM.

In the increasing drive towards primary prevention of diabetes, the information reviewed in this paper could be a powerful motivation to adult family members of people with NIDDM. An evaluation of knowledge of and attitudes to risk factors for the disease among people with diabetes and their adult relatives is in progress and the effectiveness of sharing this knowledge is being assessed.[75]

References

1. King H, Zimmet P. Trends in the prevalence and incidence of non insulin dependent diabetes. *World Health Statistics Quarterly* 1988; **41**: 190–196.
2. Zimmet P. Type 2 (non-insulin-dependent) diabetes — an epidemiological overview. *Diabetologia* 1982; **22**: 399–411.
3. Tuomilehto J. Primary prevention of diabetes mellitus. *Diabetes Care* 1987; **10**: 238–248.
4. WHO Study Group. *Prevention of Diabetes Mellitus* (in press).
5. Zimmet P. Challenges in diabetes epidemiology — from west to east. *Diabetes Care* 1992; **15**: 232–252.
6. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS. Physical activity and reduced occurrence of non-insulin-

dependent diabetes mellitus. *N Engl J Med* 1991; **325**: 147–152.
7. Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, *et al.* Fetal and infant growth and impaired glucose tolerance at age 64. *Br Med J* 1991; **303**: 1019–1022.
8. WHO Expert Committee on Diabetes Mellitus; Technical Report Series 646, 2nd report. Geneva: WHO, 1980.
9. WHO - *Report of a WHO study group.* Technical Report Series 727. Geneva: WHO, 1985.
10. Harris H. The familial distribution of diabetes mellitus: A study of the relatives of 1241 diabetic propositi. *Ann Eugen* 1950; **15**: 1:95–117.
11. Report of a working party appointed by the College of General Practitioners. The family history of diabetes. *Br Med J* 1965; **1**: 960–962.
12. Simpson N. Diabetes in the families of diabetics. *Canad Med Assoc* 1969; **98**: 427–432.
13. Keen H, Track NS. Age of onset and inheritance of diabetes: the importance of examining relatives. *Diabetologia* 1968; **4**: 317–321.
14. Reid DD, Hamilton PJJ, Brett GZ, Jarret RJ, Keen H, Rose G. Cardiorespiratory disease and diabetes among middle aged male civil servants. *Lancet*. 1974; **1**: 469–473.
15. Harris MI. National Diabetes Data Group. Unpublished data from 1976-80. US National Health and Nutrition Survey, 1984. National Centre for Statistics.
16. Harris MI. National Diabetes Data Group. From data of 1976-80 US National Health and Nutrition Examination Survey, 1984. National Centre for Statistics.
17. Thomas F, Bulkau B, Vauzelle-Kervroedan, Papoz L, and the CODIAB-INSERM-ZENE CA study group. Maternal effect and familial aggregation in NIDDM. *Diabetes* 1994; **43**: 63–67.
18. Ohlson LO, Larson B, Bjorntorp P, Eriksson H, Svardsudd K, Welin L, *et al.* Risk factors for Type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one half years of the follow up of the participants of Swedish men born in 1913. *Diabetologia* 1988; **31**: 798–805.
19. Kobberling J, Tillil H. Empirical risk figures for first degree relatives of non insulin dependent diabetes. In: Kobberling J, Tattersall RB eds. *The Genetics of Diabetes Mellitus* London: Academic Press, 1982: 201–209.
20. Falconer DS, Duncan LJ, Smith C. A statistical and genetical study of diabetes. 1. Prevalence and morbidity. *Ann Hum Genet* 1971; **34**: 347–369.
21. Beaty TH, Neel JV, Fajans SS. Identifying risk factors for diabetes in first degree relatives of non insulin dependent diabetic patients. *Am J Epidemiol* 1982; **115**: 380–395.
22. Leslie RDG, Volkman HP, Poncher M, Hanning I, Orskov H, Alberti KGM. Metabolic abnormalities in children of non insulin dependent diabetics. *Br Med J* 1986; **293**: 840–842.
23. Tuomilehto J, Tuomilehto-Wolf E, Zimmet P, Alberti KGMM, Keen H. Primary prevention of diabetes mellitus. In: Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, eds. *International Textbook of Diabetes Mellitus.* Chichester, Wiley, 1992 pp. 1655–1673.
24. Saad MF, Knowler WC, Petit DJ, Nelson RG, Mott DM, Bennet PH. The natural history of impaired glucose tolerance in the Pima Indians. *N Engl J Med* 1988; **319**: 1500–1506.
25. Jarret RJ, Keen H, Fuller JH, McCartney P. Worsening to diabetes in men with impaired glucose tolerance ('borderline diabetes'). *Diabetologia* 1979; **16**: 25–30.
26. Keen H, Jarret RJ, McCartney P. Ten years follow up of the Bedford Survey (1962-1972): Glucose tolerance and diabetes. *Diabetologia* 1982; **22**: 73–78.
27. Yudkin JS, Alberti KGM, McLarty DG,Swai ABM. Impaired Glucose tolerance. Is it a risk factor for diabetes or a diagnostic rag bag? *Br Med J* 1990; **301**: 397–401.
28. Sasaki A,Suzuki T, Horiuchi N. Development of diabetes in Japanese subjects with impaired glucose tolerance: A seven year follow up study. *Diabetologia* 1982; **22**: 73–78.
29. Hales CN, Barker DJ. Non insulin dependent (Type II) diabetes mellitus thrifty phenotype hypothesis. *Diabetologia* 1992; **35**: 595–601.
30. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25 year follow up study. *Lancet* 1992; **340**: 925–929.
31. Nerup J, Platz P, Ortved-Andersen O. HLA Antigens and diabetes mellitus. *Lancet* 1974; **ii**: 864–866.
32. Cudworth AG, Woodrow JC. HLA system and diabetes mellitus. *Diabetes* 1975; **24**: 345–349.
33. Pyke D. Diabetes: the genetic connections. *Diabetologia* 1979; **17**: 333–334.
34. Barnett A, Spiliopoulos A, Pyke D. Metabolic studies in the unaffected cotwins of non insulin dependent diabetics. *Br Med J* 1981; **i**: 1656–1658.
35. Newman B, Selby V, King MC, Slemenda C, Fabsitz R, Friedman GD. Concordance for Type 2 (non-insulin dependent) diabetes mellitus in male twins. *Diabetologia* 1987; **30**: 763–768.
36. O'Rahilly S, Spivey RS, Holman RR, Nugent Z, Clark A, Turner RC. Type 2 Diabetes of Early Onset. A Distinct Clinical and Genetic Syndrome. *Br Med J* 1987; **294**: 923–928.
37. Viswanathan M, Mohan V, Snehalatha C, Ramachandran A. High Prevalence of Type 2 (non insulin dependent) diabetes among the offspring of conjugal type 2 diabetic parents in India. *Diabetologia* 1985; **28**: 907–910.
38. Tattersall RB, Fajans S. A difference between the inheritance of classic juvenile onset and maturity onset type of diabetes in young people. *Diabetes* 1975; **24**: 44–53.
39. Hattersley AT, Turner RC, Permult AA, Patel P, Tanizawa Y, Chiu KC, *et al.* Linkage of Type 2 diabetes to the glucokinase gene. *Lancet* 1992; **339**: 1307–1310.
40. Froguel P, Vaxillaire M, Sun F, Velho G, Zouali H, Butel MO, *et al.* Close linkage of glucokinase locus on chromosome 7p to early onset non-insulin dependent diabetes mellitus. *Nature* 1992; **356** 162–164.
41. Randle PJ. Glucokinase and candidate genes for Type 2 (non insulin dependent) diabetes mellitus. *Diabetologia* 1993; **36**: 269–275.
42. Reardon W, Ross R, Sweeney M, Luxon L, Pembury M, Harding A, *et al.* Diabetes mellitus associated with a pathological point mutation in mitochondrial DNA. *Lancet* 1992; **340**: 1376–1379.
43. Ott J. *Analysis of Human Genetic Linkage,* 1st edn. Baltimore, Maryland: John Hopkins University Press, 1985.
44. Suarez BK. A sib-pair strategy for the use of restriction cell fragments to study the mode of transmission of type II diabetes. *Am J Hum Genet* 1983; **35**: 34–48.
45. Cook JTE, Page RCL, O'Rahilly S, Levy J, Holman R, Barrow B, *et al.* Availability of Type II diabetic families for detection of diabetes susceptibility genes. *Diabetes* 1993; **42**: 1536–1543.
46. Tattersall RB, Fajans S, Arbor A. Prevalence of diabetes and glucose intolerance in 199 offspring of thirty seven conjugal diabetic parents. *Diabetes* 1975; 24: 452–462.
47. Viswanathan M, Mohan V,Snehalatha C, Ramachandran A. High prevalence of Type 2 (non insulin dependent) diabetes among the offspring of conjugal type 2 parents in India. *Diabetologia* 1985; **28**: 907–910.

48. Bennet P, Rushforth N, Miller M, Le Conte P. Epidemiological studies of diabetes mellitus in the Pima Indians. *Recent Progress in Hormone Research* 1976; **32**: 333–375.
49. Zimmet P, Dowse G, Finch C, Serjeantson S, King H. The Epidemiology and Natural History of NIDDM — Lessons from the South Pacific. *Diabetes Metab Rev* 1990; **6**: 91–124.
50. Neel JV. The thrifty genotype revisited. In: Kobberling J, Tattersall R. *The Genetics of Diabetes Mellitus*. London: Academic Press, 1982: 283–293.
51. Serjeantson S, Zimmet P. Diabetes in the Pacific: evidence for a major gene. In Baba S, Gould M, Zimmet P, eds. *Diabetes Mellitus: Recent Knowledge of Aetiology Complications and Treatment*. Sydney: Academic Press, 1984; 23–40.
52. Knowler W, Savage P, Nagulesparen M. Obesity insulin resistance and diabetes mellitus in the Pima Indians. In: Kobberling J, Tattersall RB, eds. *The Genetics of Diabetes*. London: Academic Press, 1982; 243–250.
53. Joslin EP. The prevention of diabetes mellitus. *J Am Med Assoc* 1921; **76**: 79–84.
54. Westlund K, Nicholaysen JM. Ten year mortality and morbidity related to serum cholesterol. *Scand J Clin Lab Invest* 1972; **30** (suppl): 3–24.
55. West KM. *Epidemiology of diabetes and its vascular lesions*. Amsterdam: Elsevier, 1978.
56. Felber JP, Acheson KJ, Tappy L. *From Obesity to Diabetes*. Chichester: Wiley, 1992.
57. Baird JD. *The role of obesity in the development of clinical Diabetes*. Edinburgh: Royal College of Physicians of Edinburgh, No. 42 (1973), pp. 83–99.
58. Kobberling J. Studies on the genetic heterogeneity of diabetes mellitus. *Diabetologia* 1971; **7**: 46–49.
59. Morris RD, Rimm DL, Hartz AJ, Kalkhoff RK, Rimm AA. Obesity and heredity in the etiology of non insulin dependent diabetes mellitus in 32,662 adult white women. *Am J Epidemiol* 1982; **1**: 112–121.
60. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: Contributions of obesity and parental diabetes. *Am J Epidemiol* 1981; **113**: 144–156.
61. Vague J. The degree of masculine differentiation of obesities; a factor determining predisposition to diabetes, asteriosclerosis, gout and uric calculus diseae. *Am J Clin Nutr* 1956; **4**: 20–34.
62. Feldman R, Sender AJ, Sieglaub AB. Differences in diabetic and non-diabetic fat distribution patterns by skinfold measurements. *Diabetes* 1969; **18**: 478–486.
63. Meuller WH, Joos SK, Hanis CL, Zavaleta AN, Eichner J, Schull WJ. The diabetes alert study: growth, fatness and fat patterning, adolescence through childhood in Mexican Americans. *Am J Phys Anthropol* 1984; **64**: 389–399.
64. Taylor R, Ram P, Zimmet P, Raper LR, Ringrose H. Physical activity and prevalence of diabetes in Melanesian and Indian men in Fiji. *Diabetologia* 1984; **27**: 578–582.
65. Saltin B, Lindegarde F, Houston M, Hurlin R, Nygaard E, Gad P. Physical training and glucose tolerance in middle aged men. *Diabetes* 1979; **28**: (suppl 1): 30.
66. Frisch RE, Wyshak G, Albright TE, Albright NL, Schiff I. Lower prevalence of diabetes. *Diabetes* 1986; **35**: 1101–1105.
67. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS. Physical activity and reduced occurrence of non Insulin dependent diabetes mellitus. *N Engl Med J* 1991; **325**: 147–152.
68. Eriksson KF, Lindegarde. Prevention of Type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. *Diabetologia* 1991; **34**: 891–898.
69. Tuomilehto J, Cacciottolo J, Vassallo A, Schrauz S, Nissinen A, Grech A. Trends in mortality from major non communicable diseases in the middle aged population of Malta. *Rev Epidem Sante* 1988; **36**: 216–225.
70. Martin AO, Simpson JL, Ober C, Freinkel N. Frequency of diabetes mellitus in mothers of probands with gestational diabetes. *Am Obstet Cynecol* 1985; **151**: 471–475.
71. Alcolado JC, Alcolado R. Importance of maternal history of insulin dependent diabetic patients. *Br Med J* 1991; **302**: 1178–1180.
72. Pettitt DJ, Aleck KA, Baird R. Congenital susceptibility to NIDDM. *Diabetes* 1988; **37**: 622–628.
73. Aerts L, Van Assche FA. Is gestational diabetes an acquired condition? *J Dev Physiol* 1979; **1**: 219–225.
74. Gauguier D, Bihoreau MT, Ktorza A, Berthault MF, Picon L. Inheritance of diabetes mellitus as consequences of gestational hyperglycemia in rats. *Diabetes* 1990; **39**: 734–739.
75. Pierce M, Hayworth J, Harding D, Morris R, Taub N, Keen H, *et al*. Prevention of non-insulin-dependent diabetes (NIDDM). Beliefs, perceptions and prospects for risk reduction. *Diabetic Med* 1993; **10** (suppl 1): S50.