*For debate***Strategies for reduction in the prevalence of NIDDM; the case for a population-based approach to the development of policies to deal with environmental factors in its aetiology****B. J. Boucher**

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The debate on Nature vs Nurture in the causation of human diabetes mellitus has been greatly enlivened by the work of Hales and Barker and others [1–4] on the relationship of adult non-insulin-dependent diabetes (NIDDM) and associated disorders to low birth weight. Though low birth weight could reflect rather than cause syndrome X, the prevalence of NIDDM and its associated hypertension and lipid disorders, indeed most of the features of syndrome X, may be increased in adults who had a low weight and a small head circumference at birth as a result of fetal deprivation rather than as a result of genetic factors alone. This concept is attractive since it supports the idea that there may be easier ways to reduce the growing burden of diabetes than identification of the genetically 'high-risk' individual.

Epidemiological evidence suggests that environmental factors are active in the aetiology of insulin-dependent diabetes (IDDM) [5]. Critical evaluation of the evidence suggests that 60–90 % of diabetes prevalence is environmentally determined within affected populations, an appraisal that has not been challenged [6]. Many studies have been made on the environmental factors associated with an increased prevalence of NIDDM and one study in twins has suggested an increased role for environmental agents when compared to IDDM [7]. The possible significance of such findings continues to be discussed [8]. The criteria used in these studies are those accepted by the World Health Organisation to evaluate environmental contributions to cancer [9]. Their use in the examination of the evidence for envi-

ronmental 'triggering' of NIDDM is of interest since they should introduce order into the disparate information that is now available and facilitate analysis of its significance. Determination of the relative contributions made by the various factors under debate could provide direction for effective health education and health promotion. This could be useful in communities with an increasing prevalence of diabetes in the same way as exercise, dietary adjustments and avoidance of smoking are in the reduction of heart disease [10] and lung cancer [11]. Significant burdens on health care services as well as much misery for individuals might thereby be reduced. We show here examples of the available evidence for environmental causation, or 'triggering' of NIDDM:

It should be possible to produce NIDDM in laboratory animals by exposure to certain environmental agents. Food itself in excess is an inducer of NIDDM in some strains of mice [12], and variations in diet induce different incidences of NIDDM in susceptible rodents [13]. Vitamin D deficiency impairs insulin release followed, if prolonged, by impairment of insulin secretion and reduction of glucose tolerance which progresses to irreversible diabetes [14–16]. Protein deficiency during pregnancy in the rat causes failure to grow, reduced glucose utilisation and increased insulin resistance in the conceptus [17, 18]. The influence of parental diabetes, especially in the mother, in producing subsequent diabetes in offspring can be considered to reflect genetic transmission [19], but, whilst maternal hyperglycaemia protects offspring against IDDM [20], it appears to be a potent agent in the induction of NIDDM [21]. Many naturally occurring nitrosated compounds damage islets with subsequent reduction in insulin production, abnormally large regenerative islets, and diabetes without insulin dependence [22–24]. Neonatal exposure to streptozotocin induces a non-insulin-dependent type

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Abbreviations: NIDDM, Non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus.

of diabetes in the adult rodent [24]. Similar changes have been found in 8.3 % of CD-1 mice given 20 % betel-nut (Areca-nut) feed for 5 days, and in 25.6 % of non-betel-fed F1 and in 12.9 % of F2, 3.0 % of F3 and 22 % of F4 offspring [25, J.M. Stowers, personal communication]. The diabetes produced is non-insulin-dependent and though the mechanisms involved are unknown, maternal hyperglycaemia is not a factor. It may be due to specific Arecal nitrosamines [25] in much the same way as is seen in F1 offspring after comparable feeding of adult CD1 mice with Icelandic smoked cured mutton or with the specific nitrosamines it contains [26, 27].

There should be considerable geographical differences in the incidence of NIDDM. This is certainly true for the prevalence of NIDDM with, for example, 3 % of Caucasians and 10–15 % of various Asian groups having the condition in the United Kingdom, whilst forty percent of Nauruans and 66 % of older Pima Indians have NIDDM [28–31].

In some populations there should be rapid temporal changes in incidence in less than a generation which could not be accounted for by genetic change. There are examples from various parts of the world where observations on the prevalence of NIDDM show that this does occur, and is not due to differences in ascertainment. For example, NIDDM increased in parts of Western Samoa from 0.1 to 5.3 % between 1978 and 1991 and from 8.2 to 13.5 % in women in urban areas [32]. In Nauru the prevalence rose by 40 % between 1965 and 1975; whilst its incidence remained constant the prevalence of impaired glucose tolerance fell from 21.1 % in 1975/1976 to 8.7 % in 1987 [33]. Similar trends have been seen in Hispanic Americans [34, 35].

The risk to immigrants of developing NIDDM should rapidly rise to that of the host country. NIDDM has been found to increase in prevalence in Asians who migrate to more affluent communities, often in the western world, and also in members of rural communities who move to cities and assume an urban life style [36, 37]. Whilst it may be underestimated in some studies, prevalence may be rising in rural areas [38].

There should be strong epidemiological evidence that certain environmental agents cause NIDDM in man. Affluence, obesity and lack of exercise are associated with increased prevalence of human diabetes [39], and the value of increased exercise and weight control in reducing the risk of diabetes has already been demonstrated [40]. The rat poison Vacor leads to diabetes in survivors of accidental poisoning in man, and whilst poisoning in the United States where packets contain 760 mg of active agent pro-

duced IDDM in survivors, in Korea only 20 % of survivors developed IDDM, 80 % developing the non-insulin-dependent type; the packets sold there containing only 360 mg of active agent [41].

Malnutrition is associated with fibrocalculous pancreatic damage with diabetes in man [42]. The findings of Hales and Barker [1] that small babies in the United Kingdom have an increased risk of later developing NIDDM and associated markers of diabetes and vascular disease, have now been confirmed by similar findings in the United States [43]. If the suggestion that this reflects gestational nutrition rather than simply inherent genetic factors is substantiated, such data will need to be evaluated under this heading. Cigarette smoking has now been shown to be associated with increased prevalence of NIDDM in a study on American women [44]. Insulin resistance, which contributes to the development of NIDDM, has been suggested to be genetic in origin in some racial groups [45] but is acquired with obesity and reduction in physical activity and as a result of certain drugs and situations with increased lipolysis and circulating non-esterified fatty acids [46–48].

Discussion

Genetic factors are likely to contribute significantly to susceptibility to development of NIDDM in man [49, 50]. However, it is also clear that there are environmental agents or situations which cause its appearance in susceptible individuals which provide a basis upon which policies for reduction of its prevalence could be developed. The fact that tuberculosis was generally thought to be hereditary until the work of Koch in 1882 [51], despite observations such as those made by Smollet [52] many years earlier on the value of reducing cross-contamination, should not be forgotten. Simple observations often point the way to preventing disease despite the lack of understanding of its pathogenesis, as in the use of inoculation with cowpox for the prevention of smallpox [53]. The diabetogenicity of many of the factors mentioned may itself depend on various genetic factors, as for example in the feeding of genetically susceptible mice [54] and in the diabetogenicity of low-dose administration of streptozotocin which is MHC-type dependent in mice [55]. The finding that various agents can induce significant levels of diabetes in subsequent generations [25–27], and that offspring of rats rendered diabetic with low-dose streptozotocin are insulin resistant and can develop diabetes [56, J.M. Stowers, personal communication], suggests that there may be complex interactions between the susceptibility genes and the environmental agents precipitating diabetes. Such interactions make work in this field more difficult than might at first be apparent.

As Rose pointed out [57], when considering any given disease the answer to "Why did this particular individual in this population get this disease?" is not necessarily the same as the answer to "Why does this population have so much disease?". Whilst prevention of IDDM is developing along the 'high-risk' approach which seeks to identify and protect susceptible individuals, and a similar approach has been suggested for NIDDM [58], it may well be that the 'population' approach which seeks to identify and control environmental causes of high incidence [59] may prove more effective for NIDDM. These approaches should not conflict, but the priority with a common disorder should be 'to discover and control the causes of incidence' [59]. The report on diabetes to the United States Congress in 1976 [60] described increases in prevalence in diabetes from which one could extrapolate a predicted prevalence of 100% by the year 2040. The need for action to reduce overall incidence is clear. The possibility of effecting a reduction in NIDDM by improving nutrition or removal of dietary toxins appears to be realistic [61]. If evaluation of the available epidemiological data for NIDDM indicated an environmental contribution to prevalence approaching the 60–90% suggested for IDDM, then the considerable body of knowledge in this field [62] could be applied with vigour. Trials of simple measures known to reduce insulin resistance, to improve maternal nutrition, to protect islet beta cells from toxins such as nitroso-compounds (e.g., administration of nicotinamide) and the correction of relevant vitamin deficiencies could be carried out [63–65]. Health professionals, governments and individuals alike could then be advised on ways to reduce the burden of diabetes on communities, individuals and the state. Appreciation of the dangers of smoking and of the value of exercise for the heart is already altering corporate, public and individual life styles in many affluent communities. Guidelines could be developed [66] and contribute to the formulation of regulations affecting the food industry, in designing core curricula for physical and health education in schools and in town and country planning of recreational facilities. Those in a position to work together on quantitative evaluation of the relevant epidemiological evidence on the induction of NIDDM, as is in progress for environmental agents in the causation of human cancer [67–70], should be supported. The World Health Organization, the European Association for the Study of Diabetes, with Eurodiab, are ideally placed to organise, host and support such international initiatives.

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