HYPOTHESIS

Diabetes epidemic in newly westernized populations: is it due to thrifty genes or to genetically unknown foods?

Riccardo Baschetti MD

J R Soc Med 1998;91:622–625

SUMMARY

Until a few decades ago, certain 'new-world' populations that kept to traditional dietary habits were virtually free from diabetes; then, after they began eating some foods that are common in Europe, the disease reached epidemic proportions. Europeans, by contrast, have a low rate of diabetes. To account for this paradox, it has been suggested that those new-world populations have a thrifty genotype, which would have conferred a selective advantage during the frequent famines of the past, while today it would be detrimental because the recently adopted foods are constantly available. Here it is proposed that thrifty genes are unlikely to exist. Both the diabetes epidemics that occur in newly westernized populations and the low rate of diabetes in Europeans can be explained by the hypothesis that Europeans, through millenary natural selection, have become adapted, albeit incompletely, to some diabetogenic foods for which humankind is genetically unequipped.

INTRODUCTION

In 1978, Zimmet and colleagues[1] reported that the prevalence of non-insulin-dependent diabetes mellitus (NIDDM) in Nauru, a Central Pacific island, was 44% in people aged 20 years and over, and pointed out that in a 1933 medical survey in Nauru no cases of diabetes had been reported. Similarly, Knowler and colleagues[2] found that the prevalence rate of NIDDM in Pima Indians, who live in Arizona, was 50% in people aged at least 35 years, and commented that Hrdlicka, when making physical and medical observations in Pima Indians, had noted only one case of diabetes in 1908. It is not only in Nauruans and Pima Indians that there has been an explosion of NIDDM. In many other 'new-world' populations the disease, virtually non-existent until a few decades ago, has reached epidemic proportions[3–5]. Invariably, this phenomenon is associated with the drastic change in dietary habits that accompanies either the westernization of these traditional societies[1–5] or migration to developed countries[5] where diets are of western type.

Why should NIDDM so ravage traditional populations after a switch to western diets when Europeans themselves have a low rate of NIDDM? The medical community welcomed an explanation advanced by Neel[6] in 1962. His hypothesis 'envisions diabetes mellitus as an untoward aspect of a "thriftiness" genotype which is less of an asset now than in the feast-or-famine days of hunting and gathering cultures'[6]. The hypothesis proposes that populations highly prone to NIDDM have genes[7–9] that would have been selectively advantageous in the past, during frequent periods of prolonged starvation (because such genes allowed their carriers to utilize and conserve food energy most efficiently), whereas they would be detrimental now, because the newly adopted western diets are steadily abundant. The thrifty genotype hypothesis, however, has lately been challenged[10,11] on several grounds. One objection is that Pacific populations would in many cases have avoided frequent and prolonged starvation: their tropical-equatorial islands had luxuriant vegetation all year round and were surrounded by lukewarm waters full of fish. Rather we might expect thrifty genes to be more common in Europe, with its less abundant vegetation due to long harsh winters and its almost continuous devastation by wars (a notorious cause of famine and starvation). Nevertheless, Europeans have a low rate of NIDDM[8–10]. Thus, the search for a second hypothesis seems justifiable.

Cues for a new hypothesis come from Eaton and colleagues[12–15]. Their underpinning concept suggests that 'the range of diets available to preagricultural human beings determines the range that still exists for men and women living in the 20th century—the nutrition for which human beings are in essence genetically programmed'[15]. Accordingly, it can be said that humankind is still genetically unequipped for some foods that were unavailable to hunter–gatherers. Those foods, therefore, are genetically unknown and, as such, they may be responsible for chronic degenerative diseases such as atherosclerosis, hypertension, and diabetes[14]. Here I propose that some genetically unknown foods, commonly available in western diets,

Via Savonarola 144, 35137 Padua, Italy

account for the epidemic of NIDDM in newly westernized populations. I also postulate that the low rate of NIDDM in Europeans reflects their moderate, albeit insufficient, adaptation to those foods, which has been achieved through millenary natural selection.

DIETARY SUCROSE IN GENETICALLY UNKNOWN FORMS

There is evidence suggesting that sucrose is genetically known, and therefore innocuous, only if it is consumed in solutions containing $\leqslant 4.18$ MJ/L and about 40 mmol/L potassium[16], because this form mimics the solutions present in fresh fruit, which largely moulded our metabolic physiology (our ancestors lived mainly on fresh fruit for millions of years[16]). Potassium is essential in carbohydrate metabolism[16,17]. The importance of taking into account the form in which sucrose is consumed is demonstrated by the observation that diabetes was absent in cane cutters who ate large amounts of sucrose by chewing cane (which provides a juice containing <4.18 MJ/L and potassium) but common in their employers who ate large amounts as refined sucrose[18]. Unfortunately, the researchers' failure to realize that the mode of consumption is important in determining its metabolic effects[19] has led, for many decades, to conflicting findings[16,18,19] that have diverted attention from sucrose as a possible cause of NIDDM. As a consequence, current dietary recommendations, based on the results of misleading research[19] performed essentially on western volunteers, claim that diabetics can safely consume sucrose[20]. While this advice may harm only moderately diabetic westerners, because they have some adaptation to sucrose and their disease is far less severe than that seen in recently modernized countries[2,3], it may be highly detrimental in newly westernized populations who lack even the slightest adaptation to concentrated sucrose.

Concentrated sucrose consumed by healthy Americans, who have some adaptation through their European ancestry, produces undesirable changes in several of the indices associated with glucose tolerance[16]. In view of this, we should not be surprised if concentrated sucrose triggers NIDDM in populations for which it is a novelty. In fact, as West[4] emphasized, 'sugar consumption has been increasing in most, if not all, of the United States tribes in whom diabetes rates have recently increased precipitously. This same association has been observed in Eskimos of Alaska, Canada, and Greenland as well as in Polynesians'. Unlike in the past[21], cakes, sweet rolls, gelatine desserts, and soft drinks make now large energy contributions to the Pima diet[22]. In Nauru, biscuits, tea sweetened with both sucrose and sweetened condensed milk, lemonade, and coke are popular[23]. Australian Aborigines consume extremely sweet tea (estimated to contain 20–30% added sugar[24]), sweet biscuits, and sweetened condensed milk[24]. Additionally, ice creams, cold desserts, soft drinks, and confectioneries are popular among Australian Aborigines[25].

One could object that in Europe large consumption of sucrose began rather abruptly in the early 1700s[26] and, despite this, no epidemic of diabetes was recorded. Europeans, however, had already achieved some indirect adaptation to concentrated sucrose because they previously consumed large quantities of honey[26], which nutritionally is little different from sucrose, being basically a concentrated solution of fructose and glucose[26]. Among Europeans' ancestors there were the Romans whose consumption of honey was prodigious. In fact, half of the 468-odd recipes in a Roman cookery book call for honey as an ingredient[26]. It is not surprising, therefore, that diabetes was described 2000 years ago[14]. With reference to Eaton and colleagues' concept[15], it should be observed that, despite the possible availability of honey to preagricultural human beings, its actual consumption was not abundant, frequent, regular, and common enough to modify the genetic moulding produced by fresh fruit[27].

DIETARY FAT IN GENETICALLY UNKNOWN QUANTITIES

Before the diabetes epidemic, the traditional Pima diet provided 8–12% fat and ~70–80% carbohydrate[21]. Dietary fat then reached 50% with the shift to western diet[28]. The adverse effects of increased dietary fat upon carbohydrate metabolism have been repeatedly demonstrated[29,30]. The lipid metabolism of preagricultural humans was shaped by a low-fat nutritional environment, because the meat from wild game was very lean, and oils, butter, and dairy products did not exist[31]. No wonder, therefore, that dietary fat consumed in genetically unknown quantities causes harmful metabolic consequences[32], including obesity[33] and NIDDM[28–30]. Both of these conditions improved dramatically in a group of Australian Aborigines in just 5 weeks, after reversion to their traditional low-fat diet[34]. Likewise, in just three weeks a group of obese Hawaiians lost on average 7.8 kg thanks to the *ad libitum* feeding of their traditional low-fat diet[35]. These findings, besides lending support to the evolutionary view that human beings are genetically unsuited to high-fat diets[32], clearly show that even unlimited quantities of traditional foods are unlikely to cause obesity. Thus, to explain both the epidemic of NIDDM[1–5] and the widespread obesity[1,2] seen in recently westernized people, we should not focus on the quantity of foods (contrary to the feast-or-famine tenet that underlies Neel's hypothesis[6]) but rather on their energy density, which is substantially greater in the western foods than in the traditional ones.

NATURAL SELECTION

The epidemic of NIDDM in newly westernized countries provokes lethal effects because, unlike in Europe, natural selection is at the beginning of its action. As a consequence, the disease is not only far more frequent[3] but also more serious (accompanied by retinopathy, nephropathy, and coronary heart disease[2]). Additionally, unlike in Europe, where NIDDM occurs in post-reproductive ages[3,10], in recently westernized people it affects even teenagers[1,3]. This clearly indicates, as stressed earlier, that current dietary recommendations[20] may be dangerously inadequate for affected individuals of newly modernized countries. The remarkable differences in both prevalence and severity of NIDDM between Europe and 'new-world' countries mirror differences in the length of natural selection. In fact, as Diamond[36] pointed out '[b]efore modern medicine made NIDDM more manageable, genetically susceptible Europeans would have been gradually eliminated, bringing NIDDM to its present low frequency'. An incipient process of elimination through natural selection can already be observed in Nauru, where there has been a decline in incidence of epidemic glucose intolerance, despite little evidence for beneficial dietary changes[37].

IMPLICATIONS OF THE 'GENETICALLY UNKNOWN FOODS' HYPOTHESIS

While evolutionary concepts largely underpin all biological science, they are still paradoxically overlooked by most nutritionists[32]. This is a pity, because evolutionary thoughts explain otherwise puzzling findings[16,38], rectify misleading study designs[19], and can even foresee the results of clinical investigations[39]: 'nothing in medicine makes sense except in the light of evolution'[40]. The time is ripe, therefore, not only for a *theoretical* evolutionary approach to diseases, but also for a *practical* one.

The 'genetically unknown foods' hypothesis has eminently practical implications. It suggests that diabetic individuals from newly westernized populations can safely consume even western quantities of sucrose, as long as it is ingested only in the form of solutions not exceeding the physiological limit imposed by evolution, i.e., 4.18 MJ/L[16,18,19]. Those solutions should also contain about 40 mmol/L potassium[16–18], the addition of which in soft drinks may be far more important for the health of newly westernized people than for the westerners' one, because the latter populations are part protected by some adaptation to sucrose solutions without potassium. Those who sell sweetened beverages such as Coca-Cola and Sprite[41] in newly westernized countries should consider adding that metabolically essential mineral[16–18] to those drinks; luckily their energy content does not exceed 4.18 MJ/L[41]. Evolutionary thoughts, moreover—in view of the fact that any sugared beverages should mimic as much as possible the sugar solutions present in fruit[16], which contains potassium in non-chloride salts[42]—suggest that this potassium should be added as citrate, not chloride. It is also noteworthy that potassium citrate is more effective than potassium chloride in protecting against nephron loss from nephrosclerosis during severe sodium-chloride-induced hypertension[43]; this reduced effectiveness of potassium chloride is probably due to the hypertensive effect of chloride[44]. Alternatively, and perhaps more cheaply, the manufacturers could simply replace the refined sucrose with wholly unrefined sucrose, which will obviously contain adequate potassium.

Both scientific evidence[45] and evolutionary thoughts[27] also suggest that the fruit-mimicking sucrose solutions should not be ingested shortly after starch intake, to lessen the hazard that the fructose moiety of sucrose will cause hypertriglyceridaemia[45]. Furthermore, diabetic individuals from newly westernized countries should revert to the habit of low fat intake, which was typical of both preagricultural human beings[31] and pre-westernized societies[21,31,34,35].

CONCLUSION

As lately emphasized by Sharma, 'most investigators are attempting to find the ''mutations'' or genetic defects responsible for obesity, hypertension, or NIDDM'[46]. However, 'the genetic basis for these diseases is not to be found in recent mutations or genetic defects but rather lies in the conservation of the ancestral version of the relevant genes'[46]. This means that the extensive yet inconsistent research aimed at identifying the genetic 'defects' responsible for the epidemic of NIDDM[47], besides unavoidably stigmatizing populations with the label of genetic predisposition[48], is meaningless because those populations simply have the original version of man's genotype. In conclusion, therefore, to paraphrase Sharma's enlightening message[46], rather than continuing to look for putative disease-causing 'mutations' common to the majority of individuals with NIDDM in newly westernized populations, it might be more rewarding to look for mutations that cause 'resistance' to NIDDM in westerners despite exposure to the same detrimental environment represented by foods that are unknown to the original genotype of humankind.

REFERENCES

1 Zimmet P, Arblaster M, Thoma K. The effect of westernization on native populations. Studies on a Micronesian community with a high diabetes prevalence. *Aust NZ J Med* 1978;**8**:141–6

2 Knowler WC, Pettitt DJ, Savage PJ, Bennett PH. Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 1981;**113**:144–56

3 O'Dea K. Diabetes in Australian Aborigines: impact of the western diet and life style. *J Intern Med* 1992;**232**:103–17

4 West KM. Diabetes in American Indians and other native populations of the New World. *Diabetes* 1974;**23**:841–55

5 Coughlan A, McCarty DJ, Jorgensen LN, Zimmet P. The epidemic of NIDDM in Asian and Pacific island populations: prevalence and risk factors. *Horm Metab Res* 1997;**29**:323–31

6 Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 1962;**14**:353–62

7 Groop LC, Tuomi T. Non-insulin-dependent diabetes mellitus—a collision between thrifty genes and an affluent society. *Ann Med* 1997;**29**:37–53

8 Swinburn BA. The thrifty genotype hypothesis: how does it look after 30 years? *Diabetic Med* 1996;**13**:695–9

9 Dowse G, Zimmet P. The thrifty genotype in non-insulin dependent diabetes. The hypothesis survives. *BMJ* 1993;**306**:532–3

10 Ozanne SE, Hales CN. Thrifty yes, genetic no. *Diabetologia* 1998;**41**:485–7

11 Bradley PJ. Re: "Decline in incidence of epidemic glucose intolerance in Nauruans: implications for the 'thrifty genotype'". *Am J Epidemiol* 1992;**136**:499–500

12 Eaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited: A twelve-year retrospective on its nature and implications. *Eur J Clin Nutr* 1997;**51**:207–16

13 Eaton SB, Eaton SB III, Konner MJ, Shostak M. An evolutionary perspective enhances understanding of human nutritional requirements. *J Nutr* 1996;**126**:1732–40

14 Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am J Med* 1988;**84**: 739–49

15 Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med* 1985;**312**:283–9

16 Baschetti R. Sucrose metabolism. *NZ Med J* 1997;**110**:43

17 Anderson JW, Herman RH, Newcomer KL. Improvement in glucose tolerance of fasting obese patients given oral potassium. *Am J Clin Nutr* 1969;**22**:1589–96

18 Campbell GD, Batchelor EL, Goldberg MD. Sugar intake and diabetes. *Diabetes* 1967;**16**:62–3

19 Baschetti R. Sucrose in weight-loss regimens. *Am J Clin Nutr* 1998;**67**: 150–1

20 American Diabetes Association. Nutrition recommendations and principles for people with diabetes mellitus. *Diabetes Care* 1997; **20**(Suppl 1):S14–7

21 Boyce VL, Swinburn BA. The traditional Pima Indian diet. *Diabetes Care* 1993;**16**:369–71

22 Reid JM, Fullmer SD, Pettigrew KD, Burch TA, Bennett PH, Miller M, Whedon GD. Nutrient intake of Pima Indian women: relationship to diabetes mellitus and gallbladder disease. *Am J Clin Nutr* 1971;**24**:1281–9

23 Ringrose H, Zimmet P. Nutrient intakes in an urbanized Micronesian population with a high diabetes prevalence. *Am J Clin Nutr* 1979;**32**: 1334–41

24 O'Dea K, Spargo RM, Nestel PJ. Impact of westernization on carbohydrate and lipid metabolism in Australian Aborigines. *Diabetologia* 1982;**22**:148–53

25 O'Dea K, Traianedes K, Hopper JL, Larkins RG. Impaired glucose tolerance, hyperinsulinemia, and hypertriglyceridemia in Australian Aborigines from the desert. *Diabetes Care* 1988;**11**:23–9

26 Allsop KA, Brand Miller J. Honey revisited: a reappraisal of honey in pre-industrial diets. *Br J Nutr* 1996;**75**:513–20

27 Baschetti R. Paleolithic nutrition. *Eur J Clin Nutr* 1997;**51**:715–6

28 Swinburn BA, Boyce VL, Bergman RN, Howard BV, Bogardus C. Deterioration in carbohydrate metabolism and lipoprotein changes induced by modern, high fat diet in Pima Indians and Caucasians. *J Clin Endocrinol Metab* 1991;**73**:156–65

29 Marshall JA, Hoag S, Shetterly S, Hamman RF. Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. The San Luis Valley Diabetes Study. *Diabetes Care* 1994;**17**:50–6

30 Howard BV, Hannah JS. Dietary fat and diabetes. *Curr Opin Endocrinol Diabetes* 1995;**2**:530–7

31 Baschetti R. The low fat/low cholesterol diet. *Eur Heart J* 1997;**18**:1514–15

32 Baschetti R. Low-fat diets and HDL cholesterol. *Am J Clin Nutr* 1998;**68**:1143–4

33 Schutz Y, Flatt JP, Jéquier E. Failure of dietary fat intake to promote fat oxidation: a factor favoring the development of obesity. *Am J Clin Nutr* 1989;**50**:307–14

34 O'Dea K. Marked improvement in carbohydrate and lipid metabolism, in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. *Diabetes* 1984;**33**:596–603

35 Shintani TT, Hughes CK, Beckham S, O'Connor HK. Obesity and cardiovascular risk intervention through the ad libitum feeding of traditional Hawaiian diet. *Am J Clin Nutr* 1991;**53**:1647S–51S

36 Diamond JM. Diabetes running wild. *Nature* 1992;**357**:362–3

37 Dowse GK, Zimmet PZ, Finch CF, Collins VR. Decline in incidence of epidemic glucose intolerance in Nauruans: implications for the "thrifty genotype". *Am J Epidemiol* 1991;**133**:1093–104

38 Baschetti R. Gastric emptying: gender differences. *NZ Med J* 1997; **110**:238

39 Baschetti R. Evolution, cholesterol, and low-fat diets. *Circulation* 1998 (in press)

40 Lee M. Evolution and healing. *Lancet* 1995;**346**:686

41 Gisolfi CV, Duchman SM. Guidelines for optimal replacement beverages for different athletic events. *Med Sci Sports Exerc* 1992; **24**:679–87

42 Kopyt N, Dalal F, Narins RG. Renal retention of potassium in fruit. *N Engl J Med* 1985;**313**:582–3

43 Tobian L, MacNeill D, Johnson MA, Ganguli MC, Iwai J. Potassium protection against lesions of the renal tubules, arteries, and glomeruli and nephron loss in salt-loaded hypertensive Dahl S rats. *Hypertension* 1984;**6**(Suppl I):I-170-6

44 Kurtz TW, Al-Bander HA, Morris RC, Jr. "Salt-sensitive" essential hypertension in men. Is the sodium ion alone important? *N Engl J Med* 1987;**317**:1043–8

45 Baschetti R. Eating fruit and hypertriglyceridaemia. *NZ Med J* 1996;**109**:128–9

46 Sharma AM. The thrifty-genotype hypothesis and its implications for the study of complex genetic disorders in man. *J Mol Med* 1998;**76**:568–71

47 Elbein SC. An update of the genetic basis of type 2 diabetes. *Curr Opin Endocrinol Diabetes* 1998;**5**:116–25

48 Cooper R. Diabetes and the thrifty gene. *Lancet* 1994;**344**:1648