

The double puzzle of diabetes

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Why is the prevalence of type 2 diabetes mellitus exploding in most populations, but not in Europeans? The genetic and evolutionary consequences of geographical differences in food history may provide the answer.

Type 2 diabetes mellitus exacts a huge toll in money and human suffering. For instance, it accounts for more than 100 billion dollars of healthcare costs annually in the United States, or 15% of costs due to all diseases combined. The number of cases worldwide is estimated at 150 million. But this is a minimum number because, for each diagnosed case, there is thought to be one undiagnosed case in First World countries and eight in the Third World¹. Despite its other name of adult-onset diabetes, the disease is becoming more common in young people^{1,3}. At its present rate of increase, within a few decades it will be one of the world's commonest diseases and biggest public-health problems^{2,4}, with an estimated minimum of half-a-billion cases⁵. This explosion in prevalence is occurring especially in the Third World, at about 50% per decade; and because the epidemic is just beginning in the world's two most populous countries, India and China, by the year 2010 more than half of the world's diabetics will be Asians^{2,3,5}.

There are two main forms of diabetes mellitus, and the principal characteristics are outlined in Box 1. But this is the story of type 2, not only because it is much more common and rising steeply in prevalence, but because that rise is doubly puzzling. Not only would the disease seem to be highly disadvantageous in terms of natural selection, but some human populations are much more affected than others.

The geographical variations are shown in Fig. 1 (overleaf). The lowest prevalences, of practically zero, are in rural Third World areas, whereas the highest, 37–50%, are among Nauru Islanders of the tropical Pacific^{6,7}, Pima Indians in Arizona⁸ and urban Wanigela people in Papua New Guinea⁹. Most of the world's broad geographical groupings of people include populations of both very low and very high prevalence — for instance, Mapuche Indians versus Arizona Pima Indians, and rural New Guineans versus the urban Wanigela. Populations undergoing increases in the incidence of type 2 diabetes include not only Asian Indians and Chinese, but also Japanese, Aboriginal Australians, Hispanic Americans and Afro-Americans^{2,4,10}. A conspicuous exception is the absence of any comparable explosion, or very-high-prevalence population, among people of European ancestry. Thus, the puzzling aberrations are not Nauruans and

Pimas, as usually assumed; they are merely the extreme examples. Instead, the aberration demanding explanation is Europe.

As an evolutionary biologist, I have long been puzzled by these differences. In this article I shall suggest a hypothesis for why we are not seeing nearly as much of an explosion among Europeans as among other populations. The evidence comes initially from food history, and tests of it may come from medicine, medical history and molecular biology.

Genetics and lifestyle

Genetics The high prevalence of type 2 diabetes in any large population poses a further evolutionary question. Why is the disease so common, when it should disappear as those genetically susceptible to it are removed by natural selection? (Readers who answer, "Because it kills only older individuals whose child-bearing or child-rearing years are behind them" will find this objection answered below.) The disease certainly has a genetic component^{11,12}, as is evident from the following.

- There is a concordance in diagnosis of nearly 100% for monozygotic twins (those that develop from the same fertilized egg, and so have identical genetic constitutions), but only 20% for dizygotic twins. The latter figure is comparable to that for non-twin siblings, suggesting that factors in the uterus

play a quantitatively minor role (without denying the existence of such factors^{3,13}).

- The prevalence of diabetes among Hispanic Americans varies according to their proportion of Native American genetic ancestry¹⁰.

- Many specific genetic susceptibility factors have been identified^{11,12}. Because the highest mutation rates for any human gene are only around 10^{-5} per generation, the expectation is that only deleterious genes with prevalences below 10^{-5} could be sustained within a population by recurrent mutations alone. The actual incidence of type 2 diabetes is up to 50,000 times higher. And the high prevalence of the disease in many large, ancient, well-mixed populations rules out explanations in terms of the founder effect or genetic drift. These, respectively, are instances where there was only a very limited initial genetic variability, or where random processes such as selective extinction operated, and they tend to affect only small populations. Hence, the high prevalences of type 2 diabetes, like the prevalence of sickle-cell anaemia in certain groups, must be sustained by some compensating advantage that offsets the obvious morbidity and mortality (in the case of sickle-cell disease, the compensating advantage is a certain resistance to malaria).

Lifestyle In addition to that genetic component, type 2 diabetes also involves environmental and lifestyle risk factors —

Box 1 The diversity of diabetes mellitus

The term 'diabetes mellitus' covers a wide variety of conditions that are linked only by shared symptoms arising from high levels of blood sugar. That diversity may be crudely partitioned^{2,3,11,12} into type 2 (adult-onset) and the less-common type 1 (juvenile-onset). The respective prevalences among diabetics in the United States are 90–95% and 5–10%. Both diseases centre on the hormone insulin, which is responsible for mediating the uptake by cells of glucose from the blood.

Type 1 diabetes (insulin-dependent diabetes mellitus) is an autoimmune disease in which autoantibodies destroy the pancreatic-islet cells that synthesize insulin. Patients are thin, produce little or no insulin, and are prone to ketosis, a particular metabolic imbalance. They carry certain gene types — the HLA alleles *DR3*, *DR4* or both — that encode particular components of the immune system. Type 2 diabetes (non-insulin-dependent diabetes mellitus) involves altered insulin secretion and insulin resistance. Patients are often obese and are not subject to ketosis. They do produce insulin but become insulin-resistant — that is, unable to respond effectively to it.

Distinguishing the two forms can be complicated, however, because there is early-onset type 2 and late-onset type 1. Type 2 diabetes is itself very heterogeneous, both genetically and in the associated pathological and physiological symptoms. The disease arises from at least 60 identified genetic disorders, united only by the common feature of high blood-glucose levels due to insulin resistance. This heterogeneity reinforces the evolutionary puzzle: genes that predispose the bearer to type 2 diabetes must really convey some advantage, because they have evidently been preserved independently many times by natural selection. The 'thrifty gene' hypothesis, according to which such genes allow efficient food utilization in times of plenty, in preparation for famine, provides a possible explanation.

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especially, high calorie intake and low exercise^{2,11,12,14}. For example:

- Disease prevalence is 5–10 times higher in obese people than in those of normal weight.
- The metabolic abnormalities and symptoms of diabetes can often be reversed by dieting and exercise.

- The symptoms decline or disappear in populations under starvation conditions — as, for instance, they did in French diabetics under the food rationing imposed during the 1870–71 siege of Paris³.

- Prevalence of diabetes increases within about two decades^{1,15} in populations that have adopted a high-calorie, low-exercise lifestyle as a result of emigration: for instance, when Yemenite Jews were airlifted to Israel, and when there was a burst of Japanese emigration to the United States. Other examples are groups of emigrant Asian Indians in Fiji, Mauritius, Singapore, Tanzania, the United States and Britain^{3,4,16}, and of emigrant Chinese in Hong Kong, Mauritius, Singapore and Taiwan^{2,3,17}.

- Prevalence similarly rises rapidly in a population that remains in the same geographical area but in which calorie intake increases and exercise decreases. Examples include the Nauru Islanders, Arizona Pima Indians, white Australians, urban Aboriginal Australians, urban black Africans in Cape Town¹, urban Samoans, Chinese, Asian Indians and Japanese.

- In Japan, graphs against time of the incidence of type 2 diabetes and of economic indicators are parallel — down to details of year-to-year wiggles. *That's because people eat more, and so risk developing diabetic symptoms, when they have more money³.*

- As I learned while serving on the Animal Regulation Committee of the Los Angeles Zoo, there is now a diabetes epidemic among captive populations of many primate species whose zoo lifestyle approximates the high-calorie, low-exercise lifestyle of urban humans in the First World. It will be instructive to see whether or not our primate relatives share genes conferring susceptibility to diabetes with us.

All in all, the basis of type 2 diabetes can be summarized as follows³: it “is a lifestyle disorder with the highest prevalence seen in populations that have a heightened genetic susceptibility; environmental factors associated with lifestyle unmask the disease”.

Nauru

Nauru is a remote island in the Pacific that was colonized by the Micronesians in prehistoric times. It was annexed by Germany in 1888, occupied by Australia in 1914 and eventually achieved independence in 1968. It is the world's smallest republic, but it also has a less welcome distinction. The island is the site of a grimly instructive epidemic of diabetes, which illustrates a rarely documented

phenomenon — an epidemic of a genetic disease^{5,7}. Epidemics of infectious diseases wax when transmission of the infectious agent increases; they then wane when the number of susceptible potential victims falls, due both to acquired immunity of the survivors and to differential mortality of those who are genetically susceptible. An epidemic of a genetic disease waxes because of a rise in environmental risk factors, and then wanes when the number of susceptible potential victims falls (but only because of the preferential deaths of those who are genetically more susceptible).

The traditional lifestyle of Nauruans was based on agriculture and fishing, and involved frequent episodes of starvation because of droughts and the island's poor soil. Early European visitors nevertheless noted that Nauruans were plump, and that they admired big, fat people and put girls on a diet to fatten them and so make them more attractive. In 1906 it was discovered that most of Nauru consists of high-quality phosphate rock that could be used for fertilizer, and in 1922 the mining company extracting the rock began to pay royalties to the islanders. As a result of this new wealth, average sugar consumption by Nauruans reached a pound per day by 1927, and labourers were imported because Nauruans disliked working as miners.

During the Second World War the island was occupied by Japanese military forces, who imposed forced labour, reduced food rations to half-a-pound of pumpkin per day, and then deported most of the population to Truk, where half of them died of starvation. When the survivors returned, they regained their phosphate royalties, and resumed eating sugar and other store-bought food. They abandoned agriculture almost completely, became sedentary, and came to rely on motor vehicles to travel around their 20-km² island. Following independence in 1968, per capita phosphate royalties rose to A\$37,500 (US\$22,500) annually, making Nauruans among the world's richest people. Today they are the most obese and have the highest blood pressure of all peoples in the Pacific; their average body weight is half as much again as that of Australians of European origin.

Although colonial European physicians on Nauru knew how to recognize type 2 diabetes, and diagnosed it there in non-Nauruan labourers, the first case in Nauruans was not noted until 1925. The second was recorded in 1934. After 1954, however, the prevalence of the disease rose steeply and it became the commonest cause of non-accidental death. One-third of all Nauruans over the age of 20, two-thirds of those over age 55, and 70% of those few who survive to the age of 70, are diabetics. Within the past decade, prevalence of the disease has begun to fall, not because of mitigation of environmental risk factors

(obesity and the sedentary lifestyle are as common as ever), but presumably because those who are genetically most susceptible have died. If this interpretation is correct, then Nauru provides the most rapid instance known to me of natural selection in a human population — an occurrence of detectable population-wide selection within less than 40 years.

The case of Nauru also illustrates why, earlier in this article, I dismissed the usual objection that type 2 diabetes lacks selective impact because it supposedly affects people only when their reproductive years are behind them. In fact, although the disease appears mainly after age 50 in Europeans, in Nauruans and other non-Europeans it affects people of reproductive age in their twenties and thirties, especially pregnant women, whose fetuses and newborn babies are also at increased risk. For instance, in Japan today, more children suffer from type 2 than type 1 diabetes, despite the latter's popular name of juvenile-onset diabetes. Moreover, in traditional human societies, unlike modern First World societies, no old person is truly 'post-reproductive' and selectively unimportant, because grandparents contribute crucially to the food supply, social status and survival of their children and grandchildren¹⁸.

Thrifty genes

The leading evolutionary theory for the possible benefits of genes predisposing to type 2 diabetes is James Neel's 'thrifty gene' hypothesis^{3,14,19,20}. Neel postulated the existence of metabolically thrifty genes: these permit more efficient food utilization, fat deposition and rapid weight gain at occasional times of food abundance, thereby making the gene-bearer better able to survive a subsequent famine. Examples of thrifty genes would include those resulting in high levels of insulin or of leptin (a hormone released by fat cells that regulates appetite), or in hair-triggered insulin release. Such genes would be advantageous under the conditions of unpredictably alternating feast and famine that characterized the traditional human lifestyle, but they would lead to obesity and diabetes in the modern world when the same individuals stop exercising, begin foraging for food only in supermarkets, and consume three high-calorie meals day in, day out. Following Arthur Koestler, Zimmet refers to the spread of this lifestyle to the Third World as “coca-colonization”^{3,4}.

So accustomed are we in the First World to regular meals that we find it hard to imagine the fluctuating food availability that was formerly the norm and remains so in some parts of the world. I often encountered such fluctuations during my fieldwork among New Guinea mountaineers still subsisting by farming and hunting. For example,

some years ago, in a memorable incident, I hired a dozen men to carry heavy equipment all day over a steep trail up to a mountain campsite. We arrived just before sunset, expecting to meet another group of porters with food, and instead found that they had not arrived because of a misunderstanding. Faced with hungry, exhausted men and no food, I expected to be lynched. Instead, my carriers just laughed and said, "*Orait, i samting nating, yumi slip nating, enap yumi kaikai tumora*" ("OK, it's no big deal, we'll sleep on empty stomachs tonight and wait till tomorrow to eat"). Conversely, on other occasions when pigs were slaughtered for a feast, the New Guineans would consume prodigious amounts of food. This anecdote illustrates an accommodation to the pendulum of feast and famine that was very necessary in times when that pendulum swung often but irregularly — a situation that was much more typical of our evolutionary history than the state of plenty to which we are accustomed.

Two lines of human evidence and two animal models support the plausibility of Neel's thrifty gene hypothesis. Non-diabetic Nauruans and Arizona Pima Indians have postprandial levels of plasma insulin (in response to an oral glucose load) that are triple those of Europeans¹⁴. And given ample food, diabetes-prone populations of Pacific Islanders, Native Americans and Aboriginal Australians do exhibit more propensity to obesity than Europeans: first they gain weight, then they develop diabetes. As to the animal examples, laboratory rats carrying genes predisposing them to type 2 diabetes and obesity survive starvation better than do normal rats, illustrating the advantage of these genes under occasional conditions of famine¹⁶. And the Israeli sand rat, which is adapted to a desert environment with frequent scarcities of food, develops high levels of leptin and insulin, and insulin resistance, obesity and diabetes, when maintained in the laboratory on a 'westernized rat diet' with abundant food. But those symptoms reverse when its food is restricted²¹.

Natural selection

The thrifty gene hypothesis provides an explanation for why humans in general become prone to diabetes under a westernized lifestyle. But why, in light of this hypothesis, are Nauruans and Arizona Pima Indians experiencing especially severe epidemics of type 2 diabetes while European populations — in Europe and elsewhere — have uniquely low prevalences?

Nauru Nauruans suffered two extreme bouts of natural selection for thrifty genes, followed by an extreme bout of coca-colonization⁷. First, like other Pacific Islanders — but unlike the inhabitants of continental regions — their population was

Population grouping	Region	Percentage prevalence
Europeans	Britain	2
	Germany	2
	Australia (1981)	2
	Australia (2002)	8
	United States	8
Native Americans	Chile Mapuche	1
	US Hispanic	17
	US Pima	50
Pacific Islanders	Nauru (1952)	0
	Nauru (2002)	41
New Guineans	Rural	0
	Urban	37
Aboriginal Australians	Traditional	0
	Westernized	23
Middle East	Yemen, traditional	4
	Yemenite Jews in Israel	13
	Lebanon, westernized	14
Black Africans	Rural Tanzania	1
	Urban South Africa	8
	United States	13
Chinese	Rural China	0
	Urban Singapore	9
	Urban Taiwan	12
	Urban Mauritius	13
Asian Indians	Rural India	0
	Urban Tanzania	11
	Urban India	12
	Urban Singapore	17
	Urban Mauritius	17
	Urban Fiji	22

Figure 1 Age-standardized prevalence of type 2 diabetes mellitus. Among the main features are the low prevalence among groups of European origin, especially those remaining in Europe; the high prevalence among Pima Indians and urban New Guineans, and among Nauruans today; and the higher prevalence in urban or westernized groups, compared with their rural or traditional counterparts. Because type 2 prevalence in a given population increases with age, it would be misleading to compare raw values of prevalence between two populations that differ in their age distribution; the raw values would be expected to differ merely as a result of the different age distributions, even if prevalences at a given age were identical between the two populations. Instead, one measures the prevalence in a population as a function of age, then calculates what the prevalence would be for that whole population if it had a certain standardized age distribution³⁰. (From refs 5, 30 and other sources.)

founded by people who undertook inter-island canoe voyages lasting several weeks. In numerous attested examples of such lengthy voyages, many or most of the canoe occupants died of starvation, and only those who were originally the fattest survived. That is why Pacific Islanders in general tend to be heavy people. Second, the Nauruans

were then set apart from most other Pacific Islanders by their extreme starvation and mortality during the Second World War, leaving the population presumably even more enriched in diabetes susceptibility genes. After the war, their new-found wealth, superabundant food and diminished need for physical activity led to exceptional obesity.

The Pimas Like other Native Americans, Arizona Pima Indians were formerly peasant farmers and hunter-gatherers who had a physically vigorous lifestyle and were at periodic risk of starvation. Their extra bout of natural selection possibly came during the late nineteenth century, when European immigrants diverted the headwaters of the rivers on which the Pimas depended for irrigation water. The result was crop failures, widespread starvation and the likely enrichment of the surviving population in thrifty genes^{8,22}.

Europe Europeans are unique among the modern world's populations in the relatively low prevalence of type 2 diabetes. Although prevalence of the disease is increasing, it is still lower than in any non-European population matched for lifestyle, even though Europeans — in Europe itself, and throughout the world — are the richest and best-fed people in the world, and the originators of the Western lifestyle. As Fig. 1 shows, even compared with the European population with the highest prevalence (white Australians, 8%), almost all other major population groupings (Native Americans, Pacific Islanders, Aboriginal Australians, East Asians and South Asians of the Indian subcontinent) include populations with much higher prevalences of 15–50%.

This uniquely low occurrence of type 2 diabetes among Europeans is curious. Several experts in the study of the disease have suggested to me informally that perhaps Europeans traditionally had little exposure to famine, so that they would have undergone little selection for a thrifty genotype. But this is not the case — there is abundant documentation of famines that have caused widespread and severe mortality in medieval and Renaissance Europe^{23–27}. So lack of exposure to famine seems unlikely to be an answer.

Instead, a more promising hypothesis is based on Europe's recent food history (see also ref. 28 for another view). The periodic widespread and prolonged famines that used to wrack Europe, like the rest of the world, disappeared between about 1650 and 1900 at different times in different parts of Europe — the late 1600s in Britain and the Netherlands, for example, and the late 1800s in southern France and southern Italy^{23–27}. With one famous exception, Europe's famines were ended by a combination of three or four factors: increasingly

efficient state intervention that rapidly redistributed any surplus grain to famine areas; increasingly efficient food transport by land and especially by sea; increasingly diversified agriculture after AD 1492, a consequence of the advent of crops, such as potatoes and corn (maize), which were brought back by European voyagers and broadened the base of European agriculture, thereby reducing the risk of starvation from failure of a single crop; and finally perhaps, Europe's reliance on 'rain agriculture', which reduced the risk of a crop failure that was too widespread to be solved by food transport within Europe, rather than (as in many populous areas outside Europe) 'irrigation agriculture'. The famous exception is, of course, the Irish potato famine of the 1840s. But this may be the exception that proves the rule. The potato famine was due to a disease of one crop in an economy that was unusual in Europe in its reliance on that single crop, and it occurred on an island governed by a state centred on another island.

A cryptic epidemic in Europe? A corollary of this view based on Europe's food history is that, several centuries before the advent of modern medicine, Europeans, like modern Nauruans, should have undergone an epidemic in type 2 diabetes that resulted from the new reliability of adequate food supplies and eliminated most diabetes-prone bearers of the thrifty genotype. However, there would have been big differences between that postulated earlier European epidemic and the well-documented modern epidemics among Nauruans and among so many other peoples today. In the modern epidemics, abundant and continually reliable food arrived suddenly, within a decade for the Nauruans and within just a month for the Yemenite Jews. The result was a sharply peaked surge in prevalence to 20–50% that occurred right under the eyes of modern diabetologists. That increase will probably wane quickly, as individuals with the thrifty genotype become eliminated by natural selection within a mere generation or two. In contrast, Europe's food abundance would have increased gradually over the course of several centuries, and the result, between the 1400s and 1700s, would have been a slow rise in type 2 prevalence long before there were diabetologists to take note.

A possible victim of this postulated cryptic epidemic of diabetes was the composer Johann Sebastian Bach (1685–1750). Bach's medical history is too poorly documented to permit certainty as to the cause of his death. Nonetheless, the corpulence of his face and hands in the sole authenticated portrait of him, the accounts of deteriorating vision in his later years, and the evident deterioration of his handwriting, possibly secondary to his failing vision, are consistent with a diagnosis of type 2 diabetes. The

disease certainly occurred in Germany during Bach's lifetime, being known as "*honigsüsse Harnruhr*" (honey-sweet urine disease)²⁹.

Tests of the hypotheses

These ideas about the evolution of type 2 diabetes can be tested. Here are some of the questions that can be asked, and predictions that can be tested.

● How much evidence is there for the postulated epidemic of diabetes in late medieval and Renaissance Europe, either in individual biographies (as that of Bach) or in contemporary medical treatises? Did the timing of the epidemic vary locally with the different times for the disappearance of famines in different parts of Europe? Was a diabetes epidemic evident after the Black Death, when human population declined much more rapidly than did food availability?

● The prevalence of type 2 diabetes in European immigrants of British and German ancestry to the United States and Australia is reported as 7–8%, much higher than the 2% for British and German people still living in Europe today under similar lifestyles. This difference is consistent with the socially stratified emigration often discussed by historians. The Europeans who stayed at home tended to be richer than those who emigrated; in the former group, the genotype predisposing the bearer to type 2 diabetes may have already been selected out by centuries of abundant food, whereas those who emigrated may have been the starvation-prone poor who still carried the thrifty genotype³. This possibility could be tested by controlled comparison of modern Europeans still living in Europe with overseas Europeans whose ancestors' country of origin and date of emigration are known. As a specific example, are overseas descendants of Irish emigrants in the 1840s more susceptible to diabetes than are Ireland's inhabitants today?

● In pre-modern times, the risk of famine was higher in the drought- and flood-prone northern areas of China than in the south. Is there a corresponding difference in predisposition to diabetes? And did China's famines during the Great Leap Forward of the late 1950s produce additional selection for thrifty genes?

● Were the risks of famine, and so selection for thrifty genes, higher in societies that depended heavily on fishing and hunting-and-gathering (Nauruans, Pimas and Aboriginal Australians, for instance) than in farming societies in which food storage had become the norm (Europe and China)?

● Are genetic susceptibility factors for type 2 diabetes especially evident in Nauruans, Yemenite Jews and other populations showing recent surges of the disease?

● Anecdotal accounts suggesting that there were other modern epidemics of diabetes deserve investigation. For instance, a colleague whose grandfather was from northern

Iran recounts that improved food transport there in the early 1900s reduced the frequency of starvation and triggered a diabetes epidemic, especially among rich people — hence the local term 'the rich man's disease'.

● Medical geneticists seek to identify and preemptively counsel people carrying susceptibility factors for specific diseases. Can Third World populations, whose history of marked swings between food and starvation puts them at risk of diabetes with the spread of colonialization, be likewise identified and preemptively counselled by public-health officials? That might spare them the fate of the Nauruans, Arizona Pima Indians and Wani-gela. The evolutionary history and geography of type 2 diabetes would then have provided us not only with a double puzzle, but also with insights that could potentially help save millions of people from premature death.

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