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TIMELINE

The genetic consequences of our sweet tooth

Timothy M. Cox

First reported in 1956, hereditary fructose intolerance (HFI) illustrates vividly how interactions between genes and nutrients can influence taste preferences; the disease also reflects the ascendancy of sucrose and fructose as energy sources and as the world's principal sweeteners. However, HFI is not the only genetic ill to have emerged from our obsession with sugar: the slave trade, which had such a key part in the development of the sugar industry, also included major genetic consequences in its haunting legacy.

“Sweet, sweet, sweet poison for the age’s tooth”.
Shakespeare, *King John*, Act 1 Scene 1.

Hereditary fructose intolerance (HFI) is a potentially fatal nutritional disease that is caused by mutations in the liver isozyme of fructaldolase (**aldolase B**). The aldolase B gene, which maps to human chromosome 9q22.3, is required for the specific metabolism of exogenous fructose and its intermediates; a deficiency in aldolase B causes abdominal pain, nausea and vomiting, as well as HYPOGLYCAEMIA after ingestion of fructose^{1,2}. HFI was first documented in a young woman who is alive today³. During infancy, she learned to avoid symptoms of HFI by eschewing sweet-tasting foods and other dietary constituents that contain appreciable quantities of fructose and the related sugars, sorbitol and sucrose; as a result,

she has a complete set of teeth free of decay. Like many patients with HFI, this individual is homozygous for a point mutation (A149P) that interferes with the catalytic action of aldolase B on the specific metabolite of exogenous fructose, fructose-1-phosphate⁴ (FIG. 1a). Individuals that are heterozygous for mutations in aldolase B show no symptoms of disease; they have no resting biochemical phenotype and manifest no obvious advantage. The A149P mutation seems to have had an ancient common origin on an ancestral HAPLOTYPE⁵ and therefore spread, presumably by GENETIC DRIFT, in the absence of long-term selection, through the populations of Europe. Studies in Switzerland and the United Kingdom have shown that HFI occurs with an estimated birth frequency of ~1 in 20,000 — indeed, heterozygotes for the A149P allele alone occur at almost polymorphic frequency (>1 in 100) in the general population^{1,4–7}. Although HFI has a long history in the human population, the disease itself has only recently risen to prominence. As I describe below, changes in our lifestyle — specifically, our overconsumption of sugars — lie at the heart of this rise to prominence. A massive agro-industrial effort, based historically on former sugar colonies, now meets global demand for these commodities — but the consequences for human health extend well beyond HFI.

A disease of weaning

Unlike the milk of other mammals, human breast milk tastes sweet as a result of its content of ~70 g l⁻¹ (~0.2 M) of lactose — a disaccharide of glucose and galactose (FIG. 1b). Human breast milk is therefore innocuous to infants with aldolase B deficiency, and it is the period of weaning — particularly onto artificially sweetened milks, vegetable purées and other foods — that is the most perilous. Survival at this time is critically dependent on the ability of the parents to identify those foods that cause illness or that are rejected⁸. Continued ingestion of noxious sugars (mainly fructose and sucrose, but also sorbitol, which is often present in medicines and diabetic foods) injures those organs (the liver, intestine and proximal renal tubule) that metabolize dietary fructose. As a result, the infant or child with HFI develops renal tubular defects that lead to rickets and metabolic acidosis; chronic liver disease also occurs^{2,8,9}. The infant is distressed by abdominal symptoms and suffers from persistent vomiting, failure to thrive, jaundice and liver failure. No actuarial survival figures are available, but it has been reported that hundreds of patients and first-degree relatives with HFI have incurred life-threatening

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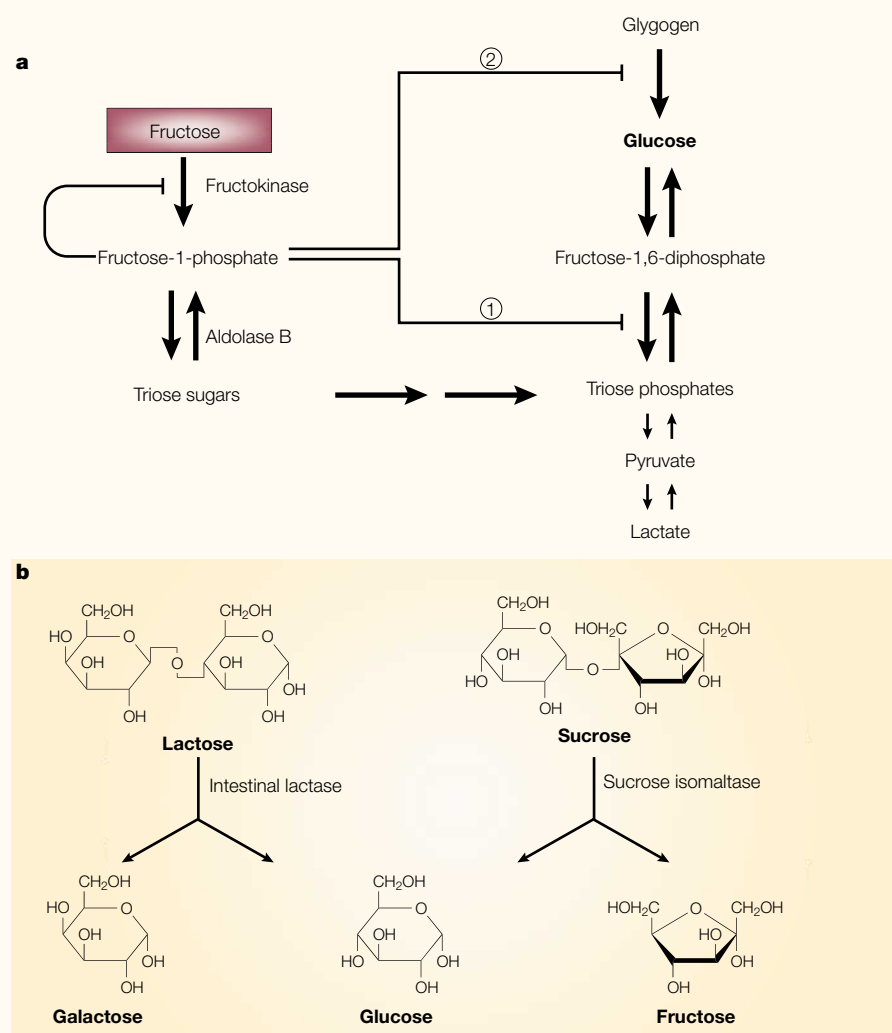


Figure 1 | Metabolic defect in hereditary fructose intolerance. a | Fructose from the diet is phosphorylated by fructokinase to form fructose-1-phosphate — the specific substrate of aldolase B. In individuals with hereditary fructose intolerance (HFI), who lack aldolase B, fructose challenge leads to the accumulation of fructose-1-phosphate and thereby to the sequestration of inorganic phosphate. In this environment, the activation of liver phosphorylase (which is required for glucose formation) is prevented, and purine nucleotide breakdown is initiated (not shown). Glucose formation is subsequently halted by inhibiting both gluconeogenesis (lower inhibitory line, 1) and glycogenolysis (upper inhibitory line, 2), and fructokinase activity is eventually inhibited. Hypoglycaemia, FRUCTOSAEMIA, HYPERURICAEMIA and ACIDOSIS result from the arrested metabolism^{2,4}. **b** | Structures of the principal dietary sugars. Lactose in milk is cleaved into D-glucose and D-galactose. D-Fructose occurs free in the diet but can be formed from sorbitol, a sugar alcohol (not shown), as well as from the cleavage of sucrose.

symptoms and even death through the consumption of contemporary sugar-rich foods^{2,4,7–13}.

A crucial feature of HFI is the ability of the fructose-metabolizing tissues to recover once the offending sugars are excluded^{9,10}. However, accidental exposure to very small quantities of harmful sugars in a single meal can precipitate symptoms and a severe metabolic disturbance at any age⁸. Deaths occur even in adult life, especially when infusions of fructose or sorbitol are used as intensive nutrients in hospital, as practised particularly

in Germany^{11,14}. At least 20 such avoidable deaths from HFI have been reported since 1956 (REFS 2,4,14).

Metabolic and molecular pathology

The aldolase B deficiency in HFI leads to a complex metabolic phenotype that occurs on challenge with fructose. Hypoglycaemia, which is resistant to the action of GLUCAGON, is the result of a combined metabolic arrest of glycogenolysis and gluconeogenesis (FIG. 1a). At the same time, there is lactic acidosis and a loss of cellular ATP in the liver and other

fructose-metabolizing tissues. Decreased cellular energy is associated with the degradation of purine nucleotides, which causes hyperuricaemia; transient HYPERMAGNEAEMIA also results from the breakdown of stored ATP–magnesium complexes^{2,4}. Indeed, large infused doses of fructose, which were formerly advocated in artificial feeding regimens, have been withdrawn from clinical use in most countries because hyperuricaemia and lactic acidosis might occur when fructose is metabolized rapidly — even in individuals without HFI^{2,14}.

Fructaldolases are widely distributed enzymes that catalyse the specific and reversible cleavage of the glycolytic hexose substrates — fructose-1,6-diphosphate and fructose-1-phosphate — into three-carbon sugars (FIG. 1a). Two methods of forming stable complexes with substrate are used in the aldolase reaction: in class I aldolases, such as aldolase B, a proton is transferred to the substrate from a conserved lysine residue at the active site; in class II aldolases, usually found in bacteria and plants, divalent metal cations participate in the proton-transfer reaction. The crystal structures of several tetrameric mammalian (class I) fructaldolases have been determined¹⁵, and the structural effects of the missense mutations that are responsible for HFI can be interpreted¹⁶. A class of mutations, which includes A149P, influences the stability of the active aldolase B holotetramer; other mutations directly affect its catalytic action. Mutations that affect the carboxy-terminal region, which confers specificity of the enzyme for fructose-1-phosphate rather than fructose-1,6-diphosphate, also cause HFI¹⁷.

Effects on eating behaviour

HFI patients who survive infancy and childhood have unusual eating behaviour as a result of their lifelong repugnance for sweet tastes. Typically, they have a predilection for savoury and spicy foods, as well as peppermint, and avoid social situations that require them to conform to universal acceptance of sugar-containing foods. Most alcoholic drinks (apart from spirits), as well as nuts, fruits, confectionery, sweetened drinks, vegetables and processed foods are rejected by those with HFI. However, such is the ubiquity of fructose in the modern diet and the extent to which contemporary flavours mask the taste of added sugars, that they are constantly at risk from symptomatic fructose toxicity — especially when nutrition is no longer under their personal control. Despite this, patients with HFI characteristically have caries-free teeth and generally consume only a few grams of fructose equivalents daily (about 10% of the mean daily

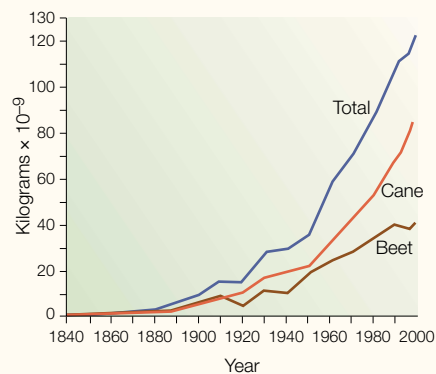


Figure 2 | World production of raw sugar. Industrial figures for so-called CENTRIFUGAL SUGAR. This does not include production of non-centrifugal sugars for local markets by numerous small-scale manufacturers, or of fructose syrup from hydrolysed starches. (Figure modified with permission from REF. 25 © (2002) Cambridge University Press).

consumption of their peers). Careful clinical studies, however, show that at least in children and adolescents, an insidious syndrome of chronic fructose toxicity can develop accompanied by rickets and delayed growth¹². Reducing the daily fructose consumption to <40 mg per kg of bodyweight is required to restore health.

In some respects, HFI can be seen as a sensitive genetic probe with which to explore contemporary eating behaviour in a population. It seems likely that its recognition in only the mid-1950s reflects post-war dietary changes, which included the introduction of free fructose and sucrose in foods and sweetened drinks, and as a carrier in medication. By contrast, in societies in which infants are weaned onto starchy root crops, such as cassava (manioc), there is little exposure to free sugars. Fruit and honey, which are rich in sucrose and fructose, have tended to be opportunistic rather than staple foods; moreover, as readily identifiable sources of noxious sugars, they can be more easily rejected than the pervasive sweeteners of modern diets. There has been an exponential rise in sugar production and consumption since the early nineteenth century^{13,18} (FIG. 2), and sucrose and fructose are the world's principal sweeteners, which satisfy the human craving for sweet flavours. The sugar industry — one of the oldest industries of the developed world — now manufactures ~150 million metric tonnes of sucrose per annum. Sugar is in a unique position in the cultural history of human food provision. At present, tropical (sugar cane) and temperate (beet) sugars are the principal sources but fructose crystals and syrup from other sources contribute increasingly to a massive global industrial effort.

Fructose itself is the most powerful sweetener of the naturally occurring sugars, and even sucrose (FIG. 1b) owes its taste to the fructose moiety. Fructose has an intensity of sweetness that is matched only by the brevity of its action, so lending it to successful blending with many other flavours and accounting for its burgeoning use in cordials and carbonated drinks. Fructose also has uniquely useful physico-chemical properties, including reducing power, which leads to browning after cooking. Highly purified fructose is now obtained by the enzymatic isomerization of glucose that is derived from the industrial hydrolysis of starch when it is extracted from maize, wheat, potatoes, tapioca and other crops¹⁹.

Interwoven history: sugar and slavery

The main natural source of sugar is honey from wild bees^{18,20}. Honey, which has been collected since Palaeolithic times (FIG. 3), contains glucose and fructose that are released from sucrose by the action of invertase in the stomach of the bee. Domestic sugar making has been known in India for ~5,000 years. In 325 BC, Nearchus, a general who accompanied Alexander the Great to the Indus Valley, noted the “the reeds that produce honey although there are no bees”¹⁸ and, presumably, so identified cultivated sugar cane (genus *Saccharum*) that is indigenous to the Far East (FIG. 3c). The extraction and manufacture of crystalline sugar from cane was introduced into the Mediterranean region by Arab agriculturalists but, because it was susceptible to frost, the crop was confined to the South and the Levant, later to be introduced to The Canaries and Madeira. These island colonies, together with the Portuguese-African territory of São Tomé, provided the *modus operandi* for colonial plantations across the Atlantic. After initial success by the Spanish in Hispaniola and the Portuguese in Brazil, the unlimited availability of land and timber for sugar mills in the New World led to the eclipse of the Mediterranean sugar-cane industry by the mid-seventeenth century. The other principal source of sucrose, sugar beet, was developed in France after the battle of Trafalgar in the nineteenth century. Beet is an important source of sugar in temperate countries, but was only introduced after the British blockade that prevented access by the French to their colonies in the Caribbean. To this day, sugar beet (*Beta vulgaris* var. *saccharifera*), which produces abundant sugar (up to 20% by weight in a single season), is grown in a regulated manner throughout Europe from French seed stocks.

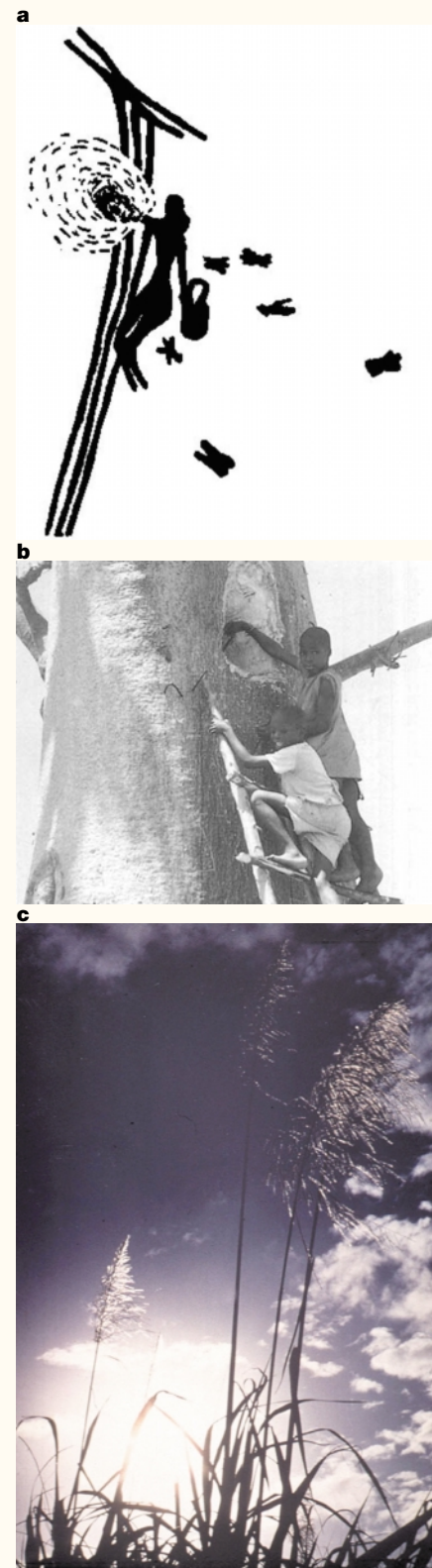


Figure 3 | Sources of sugar. a | Late Palaeolithic cave painting from Araña cave in South-eastern Spain. (Reproduced from REF. 18 © (1949) Chapman & Hall.) b | Collecting wild honey in Senegal © the Food and Agriculture Organization of the United Nations (from a document entitled ‘Insect providers — silk, honey and lac’.) c | Sugar cane.

Table 1 | **Sugar and slavery: slave importations**

Import route	Number of slaves*
Old World traffic [‡]	200,000
Spain	1,000,000
Portugal to Brazil	3,325,000
English island commerce [§]	1,900,000
English mainland traffic	1,500,000
American slave trade (1786–1808)	420,000
American illicit traffic	1,000,000
French New World importations	1,650,000
French slave trade to Mauritius and Réunion	450,000
Dutch slave trade to Guyana and islands	900,000
Danish slave trade	75,000
Total	12,420,000

For more information, see REF. 18. *The slaves counted on arrival — recorded losses on the journeys alone were between 3.6 and 23%. Noel Deerr estimated that the total toll of slaves taken would be as much as 20 million Africans, of whom two-thirds were intended for the production of sugar¹⁸. [‡]The slave trade to Spain, Portugal, Sicily and Italy, and recruitment of slave labour for the sugar industry in Madeira, The Azores, Cape Verde Islands, The Canaries and São Tomé. [§]The slaves taken to the West Indies during 1650–1808 and those taken to the mainland colonies until 1786.

The colonial history of sugar exploitation by European powers is one of the darker chapters of human history. It has been estimated that, after the discovery of the West Indies and other tropical colonies that were suitable for sugar-cane cultivation by the Spanish, Portuguese, French, British and Dutch, demands for labour led to the transportation of more than 12 million individuals who were taken or purchased as slaves, mainly from West Africa, to work principally in sugar plantations¹⁸ (TABLE 1). Even after the official abolition of the slave trade in the early to mid-nineteenth century, slaves of African ancestry were transported to South America and, in large numbers, to the Southern States of North America to grow cotton, tobacco and sugar in the plantations that were established gradually in Louisiana. In this way, the sugar industry has been the main impetus for enforced mass migrations of people, with all the historical consequences that threatened post-colonial democracy^{18,20}. On the eve of the US Civil War in 1860, the census recorded 4,441,830 North American slaves. Forty years later, the cultivation and manufacture of sugar had become one of the principal economic activities of the tropical world.

Nowadays, those countries that depended on the old colonial industries, such as sugar manufacture, face continuing economic difficulties — particularly because sugar from beet and fructose from starch crops can be obtained at competitive prices elsewhere. At present, an international sugar agreement, under the auspices of the United Nations Conference on Trade and Development, stabilizes free-market

prices and sugar manufacture by regulating export quotas. However, the socio-economic modernization of sugar-cane-growing regions remains a global priority, and economic dependency on sugar remains an unresolved challenge for many former colonies with populations that are descended from African slaves. It is a curious fact that the European Union now buys cane sugar at a preferential price from the past colonies of its member states, but is also a chief exporter of nearly three times this quantity of sugar manufactured from beet.

Genetic effects of sugar and slavery

The expansion of sugar production and consumption has influenced the genetics of human populations in the New World and in Europe in two main ways. First, the introduction of sugar as an important component of energy in the European diet has enhanced the incidence of HFI, which has come to light as a potentially fatal disease of infants and young children, particularly as a result of changes in maternal behaviour in rich nations. Dental studies of pre-historic and later societies indicate that widespread tooth decay is a relatively recent phenomenon, which correlates with the availability of soft foods in farming communities and the use of grindstones and pottery. Caries has increased markedly in the past few centuries with the introduction of refined foods and the use of sugar. In hunter-gatherer societies, it seems probable that the scarcity of soft foods and delayed weaning has protected infants and children with HFI from the deleterious effects of free sugar²¹.

Breastfeeding habits among women of all socio-economic groups have undergone striking changes during the past century. The introduction and widespread use of formula feeds and artificially sweetened ('condensed') milk will have accelerated the onset of symptoms of HFI in infants who are transferred from the breast at ever younger ages. Its appearance in newborn and very young infants reflects rapid changes in the social position of women, as well as the rise of working mothers, who dispense with the perceived inconvenience and unfashionable habit of breastfeeding soon after birth. HFI is, it seems, chiefly a disease of post-colonial affluence in Western-style civilizations.

The second genetic consequence of the rise of the sugar industry stems from the vast movement of people who, from the sixteenth century onwards, were made to work by sugar-consuming European countries in the West Indies and other colonies. With this movement of people, principally of African origin, came the introduction of genetic disorders, such as **sickle cell anaemia** and **glucose-6-phosphate dehydrogenase (G6PD) deficiency** (BOX 1). In regions such as Africa, individuals that are heterozygous for these variants have a well-documented selective advantage that confers decreased susceptibility to malaria; however, their introduction to largely non-malarial areas has had some profound consequences for the health of the immigrant communities.

Sickle cell anaemia is a disabling condition. In addition, acute sickle crises seem to be more frequent in overcrowded and impoverished communities that live in the cities of temperate climate zones, because of the infections and cold temperatures to which they are exposed²². Although the introduction of hydroxyurea therapy and, in rare cases, the use of bone marrow transplantation can improve the outcome of sickle cell disease in some patients, overall, those with sickling disorders have a greatly reduced quality and expectation of life. Unlike sickle cell anaemia, most individuals with G6PD deficiency do not need treatment, but life in the New World or any Western country renders individuals susceptible to near-fatal episodes of haemolysis induced by certain widely used oxidative drugs²³ (BOX 1). There is also a significant risk of neonatal jaundice and irreversible brain damage in some male infants. This is not the place to reiterate the numerous injustices that have continually been visited on descendants of African slaves in the Western world; the thesis here is that they have been compounded by genetic ills and

by a long-standing inability of health services in the adopted environment to tackle these diseases satisfactorily. Indeed, questions about the provision of adequate public health measures, hospital care and screening procedures for sickle cell anaemia are active issues²⁴.

Sugar and global nutritional disease

Global manufacture of at least 150 billion kg of sugar annually represents about 25 kg per capita — or sufficient to supply nearly 70 g daily to each member of the world's population. The consumption of sugar in developed European countries rose to a maximum in the mid- to late 1960s. Now, although global production and consumption continues to rise, and despite the International Sugar Agreement, the nations that consume most per capita are those that produce the most sugar, including Cuba, Brazil, Fiji and Australia. All of these countries have a historical colonial base for sugar production, the sugar-cane crops of which now greatly exceed average demand^{20,25} (TABLE 2). Sugar

cane is a labour-intensive crop with particular growth requirements; it is subject to numerous pests and diseases that threaten economic viability and, unlike sugar beet, sugar cane has a growth period that usually exceeds one year. Economic dependency on sugar cane has created a dilemma for the former colonies: they rely on special arrangements to sell their product to former rulers but, in the context of global oversupply, are unable to bargain for better investments to support or diversify their labour force²⁵.

Over the past few hundred years, the increasing desire for sweeteners has led to an astonishing domination of world trade by the sugar industry, along with some damaging consequences for human health. For example, the epidemic of obesity is due, in part, to the consumption and increased availability of refined carbohydrate, with its high density of energy and rapid satiation of appetite; this, perhaps, continues to reflect the desire for comfort that the intense sweetness of fructose and sucrose provide. The understanding of human

Table 2 | **Annual sugar consumption**

Region and date	Consumption in kg per capita
England 1700	1.7
England 1800	13.9
1990s	
Cuba	>80
Brazil	>50
Fiji	>50
Australia	>50
United States	30–40
Western Europe	30–40
China	6.5
Tropical Africa	<10

From Galloway²⁵ and other sources.

obesity and its effects on life expectancy represents an important challenge in social as well as clinical medicine. Obesity is associated with the contemporary pandemic of **non-insulin-dependent (type II) diabetes mellitus**, hypertension, hyperlipidaemia and premature coronary heart disease — all disorders with strong genetic contributions. The control of appetite and the downstream regulation of, and interplay between, dietary fructose and sucrose, insulin, lipids and energy metabolism are therefore areas of key importance for public health²⁶. There is evidence that, by elevating plasma lipids during fasting and specifically altering lipoprotein fractions, the ingestion of excess fructose and sucrose contributes to coronary heart disease in at least some individuals; fatty-acid metabolism is also disturbed by fructose^{27–29}.

Although more research is needed, increased availability of high-density energy in the form of refined carbohydrates, including high-fructose syrup and crystalline fructose³⁰, seems to be correlated globally with the high prevalence of obesity and will have an inevitable effect on the incidence of type II diabetes. Many social factors clearly operate to enhance the popularity of high-sugar drinks, but the influence of fads and fashion, which are typified by the powerful advertisements of the carbonated beverage industry, cannot be underestimated. As one of the main users of the high-fructose syrup in nutritional candy bars and other speciality food items³⁰, including so-called 'lite' energy supplements and sports drinks¹⁹, this industry has a good deal to answer for. High-calorie foods and drinks are widely promoted as a fashionably convenient and healthy means to promote enhanced physical performance.

Box 1 | **Diseases introduced into Europe and the New World by the slave trade**

β -globin abnormalities

About 8% of African Americans have the SICKLE CELL TRAIT, and the birth frequency of the homozygous state (HbSS) in this population is predicted to be ~1 in 650. African Americans also frequently carry the β -THALASSAEMIA trait, which can cause sickling disorder in compound heterozygotes with sickle thalassaemia (birth frequency, 1 in 5,000)³⁶. Haemoglobin C (HbSC) disease — a haemoglobinopathy caused by another missense mutation in the sixth amino acid of β -globin — is today found exclusively in populations of African ancestry: it reaches a peak incidence of ~15% in the West African countries of Ghana and Burkina Faso³⁶. Compound heterozygotes that carry sickle thalassaemia or those with HbSC disease also have a sickling disorder. Among African Americans, ~1 in 1,000 are predicted to have HbSC disease; in Jamaica, HbSC sickling disorder occurs in as many as 1 in 500 live births. Sickle cell anaemia has a variable phenotype, but in all cases is associated with a propensity to infection, which is the most common cause of death. Painful bone infarction crises, and major pulmonary and splenic sequestration crises and strokes, might occur at any time. The highest mortality occurs in the first five years of life but survival improves with age; it is estimated that 85% of homozygous HbSS patients now survive beyond 20 years of age^{36,37}. Haematology clinics and emergency services in cities throughout the Caribbean, United States and Europe are visited by thousands of patients with sickling disorders each year³⁶.

Glucose-6-phosphate dehydrogenase deficiency

This deficiency was discovered by the induction of haemolysis in American black soldiers who received the 8-aminoquinoline anti-malarial compound, primaquine, in the latter part of the Second World War³⁸. In glucose-6-phosphate dehydrogenase (G6PD)-deficient people, severe oxidative haemolysis occurs as a result of taking sulphonamides, analgesic and anti-pyretic drugs (as well as many other chemicals) after infection and, although not typically in black patients, after the ingestion of broad beans — not a traditional crop in tropical Africa. The human G6PD locus is one of the most polymorphic loci in the genome, with ~400 variants so far identified. In African and other black populations, different polymorphic mutations have been found to underlie G6PD deficiency. The highest prevalence rates for this X-linked condition are seen in Africa, closely followed by certain parts of the Mediterranean and Middle East. In African-Americans, the incidence of G6PD deficiency is 7–11%, and in Jamaica 15%; figures for South and West Africa are 1.3 and 21%, respectively, which presumably reflects differential evolutionary selection pressure due to the distribution of malaria.

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Much contemporary history has been determined by our appetite for sugar: the powerful interplay between human taste, macroeconomics and the commercial forces that are required to meet the ever-increasing demand for high-calorie convenience foods continues to drive world sugar production and sales²⁵. The importance of sugar in human affairs and in relationships between nations has long been recognized — Benjamin Disraeli, Prime Minister to Queen Victoria of England, summarized it as follows: “Strange that a manufacture which calms infancy and soothes old age should so frequently occasion political disaster”.

Countering sugar consumption

HFI probably occurs all over the world and it is certainly documented in the industrialized countries of North America, Scandinavia and Europe, as well as South America, Turkey and, probably, in the Middle East. Not surprisingly, European-type mutations in the aldolase B gene that cause HFI have also been detected in Australia and in New Zealand⁴. Unlike in **phenylketonuria** sufferers, the newer sweetener aspartame is harmless in HFI patients. Aspartame, although popular, is used more as a voluntary food additive than as a component of processed foods; aspartame is, moreover, unlikely to be selected by patients with HFI because of its sweet taste. Research into the significance of HFI in public health through simple mass population screening needs to be carried out using DNA obtained from blood spots that are widely collected at birth. In Britain, molecular analysis of neonatal DNA samples for the A149P allele of the aldolase B gene gave a predicted birth frequency of 1 in 18,000 for HFI⁶. This is comparable to the birth frequency of the other preventable nutritional disease, phenylketonuria (1 in 14,300 in Southern Britain), which has been the focus of neonatal screening in most countries for more than 30 years. As with phenylketonuria, the early introduction of an exclusion diet would be curative, and serious manifestations of this condition in the liver and kidneys would be prevented in the affected infant¹⁷. At least in Europe, DNA-based genetic testing for a few common widespread aldolase B alleles would allow detection of most affected homozygotes before tissue injury and illness ensues^{4,6}.

Identifying the individual that is uniquely maladapted to its nutritional environment and susceptible to HFI is a much more targeted strategy than any quixotic attempt to restrict the burgeoning global sugar industry;

after all, successive health campaigners have failed to reduce the domestic consumption of sugar, even in the most health-conscious and affluent societies. It seems that the ever-present need for gratification of our appetite for sweet food and drinks is irrepressible: most people believe that the consumption of concentrated fruit juice is an important component of a ‘healthy breakfast’, but do they realize that this contains many tens of grams of pure sucrose or fructose? Perhaps the introduction of water fluoridation programmes has also sufficiently reduced the frequency of dental caries to mask this public health aspect of excess sugar consumption.

With the increasing empowerment of the black population of the United States has come enhanced awareness of the need for an effective national programme to deal with the sickling disorders, which will include increased public awareness of the availability of rapid genetic tests. Continued medical education is needed to deal also with the legacy of G6PD deficiency. The introduction of testing programmes^{23,24}, and the use of bracelets that warn against the prescription of medications that provoke haemolysis, as well as the need for prompt treatment of infections in males and females at risk, are straightforward measures that would improve public health.

Perhaps the greatest challenges to the improvement of well-being and life expectancy in whole populations are in the effective delivery of health-promotion messages. Lifestyle advice to the over-nourished, whose health is threatened by excess sugar

consumption, has hitherto been singularly ineffective, despite much public trumpeting on the ‘healthy-eating’ theme. Clearly, a better understanding of the mechanisms that link taste and appetite would help to control the demand for sweet foods and drinks. Recently, molecular components of sweet-taste perception have been identified from genetic studies of the saccharin preference (*Sac*) locus in mouse strains that differ in their ability to discriminate sweet-tasting substances, including sucrose^{31,32}. A new G-protein-coupled receptor *Tas1r3* (taste receptor, type 1, member 3) was identified that is expressed selectively in taste buds; a human homologue (*TAS1R3*) that maps to chromosome 1pter–1p36.33 has also been identified³². Transgenic expression of the putative sweet-taste gene in mice of the non-taster strain restored their ability to detect sucrose and saccharin³³. Although more investigation is required, understanding the molecular basis of ligand–receptor binding and signalling by *TAS1R3* in humans might improve our ability to modify eating behaviour and taste preferences: specific agonists or antagonists might prove to be valuable tools for nutritional intervention and provide the means to explore the satiety that is induced by sugar. Ingestion of sucrose might release endorphins, and this sugar has even been used as an analgesic in newborn infants³⁴.

Ultimately, public intervention might be needed to moderate the provision of energy in common foods. It can only be hoped that the social pressures that operate to contain

Glossary

ACIDOSIS

An excess of acid in the body fluids as a primary disturbance of hydrogen ion metabolism.

CENTRIFUGAL SUGAR

An industrial term for the product of modern sugar factories; commercial sugar is described as raw sugar if it is >96% sucrose and further refining generates the pure product. The terms ‘centrifugal’ and ‘non-centrifugal’ distinguish between the products of modern and traditional methods of manufacture: they refer to the methods used to separate sucrose crystals from the molasses.

FRUCTOSAEMIA

The presence of fructose in the blood.

GENETIC DRIFT

The random changes in allele frequency that occur because genes that appear in offspring are not a perfectly representative sample of the parental genes (for example, as occurs in small populations).

GLUCAGON

A pancreatic hormone released from the islets of Langerhans. It stimulates the formation of glucose,

especially by activating liver phosphorylase, through the hormone-sensitive adenylyl cyclase signalling pathway. Phosphorylase is the rate-limiting enzyme for the breakdown of glycogen.

HAPLOTYPE

An experimentally determined profile of genetic markers that are present on a single chromosome of any given individual.

HYPERMAGNESAEMIA

A high plasma concentration of ionized magnesium.

HYPERURICAEMIA

A high plasma-urate concentration.

HYPOGLYCAEMIA

A low blood-glucose concentration.

SICKLE CELL TRAIT

Heterozygosity for the inherited β -globin variant, HbS; the individual does not have sickle cell disease.

β -THALASSAEMIA

A group of inherited blood diseases caused by reduced synthesis of β -globin polypeptide chains.

our other addictive pleasures will indeed be used to bear on our predilection for “the fruits of poison flowers — and all the measureless ill” that the Victorian poet Alfred, Lord Tennyson (1809–1892) perceived at the height of the British colonial period (*Maud*, stanza X, Part 1, Section 4)³⁵. Sigmund Freud might, after all, have been on the mark: an innate desire to return to the sweet consolations of infancy perhaps explains more than we realize about our behaviour.

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The following terms in this article are linked online to:

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Fructose metabolism disorders

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