X

Susceptibility and Resistance

The Capitoline Museum in Rome contains an extensive collection of busts of Roman Emperors, carved during their lifetimes. These sculptures constitute a veritable portrait gallery of the Imperial Era and the depiction of their subjects reflects the pursuit of realism rather than idealism by Roman artists. The busts of three of the Emperors, Tiberius, Vespasian and Trajan (Illustration 10), depict earlobe clefts, now known to be an epiphenomenon that marks a predisposition to the development of coronary heart disease.[1] None of the three Emperors suffered or died from anything that could be interpreted as a direct manifestation of heart disease. Vespasian reputedly passed away after suffering from a stomach chill and Trajan after a paralytic stroke.[2] Gaius Suetonius recorded a belief that at the age of seventy-seven Tiberius was the victim of a debilitating poison administered by his designated successor Caligula and finally smothered.[3] Whilst therefore something of a curiosity, the earlobe clefts portrayed in three sculptures suggest that many centuries before William Heberden made his historic presentation to the Royal College of Physicians of London, an inborn predisposition to coronary heart disease may have existed, awaiting the impact of the risk factors to which people were subsequently to become exposed for the first time. It is consequently worth considering whether, by analogy with infectious diseases, populations newly exposed to lifestyle changes and the associated risk factors could initially have had a heightened susceptibility to coronary heart disease that was innate. Would this susceptibility have lessened subsequently as a result of natural selection during continued exposure to lifestyle risk factors over many generations? Specifically, could vulnerability to the changed diets and their consequences have been greater among eighteenth-century Englishmen than among their twentieth-century descendants? It is necessary, therefore, to examine relationships between some genetic factors predisposing to coronary heart disease and their interplay with lifestyle changes. Finally, consideration must be given to possible evolution of these relationships over many generations.

There is epidemiological evidence to indicate that some communities of recent migrants from the developing to the western world have an incidence of CHD that is not just equal to but greater than that of the indigenous populations, South Asian migrants to the UK constituting an example. R Balarajan and colleagues calculated the 1975–77 circulatory mortality ratios of Indian immigrants from the subcontinent

[1] Edgar Lichtstein *et al.*, 'Diagonal ear-lobe crease and coronary artery sclerosis', letter in *Ann Intern Med*, 1976, **85**: 337–8.

[2] M Grant, *History of Rome*, New York, Charles Scribner and Sons, 1978, pp. 291, 297.

[3] Gaius Suetonius Tranquillus, *Lives of the Caesars*, transl. C Edwards, New York, Oxford University Press, 2000, pp. 133–4.

Illustration 10: Emperor Trajan (*c.* 53–117), from a sculpture in the Museum of Anatolian Civilisation, Ankara, Turkey. The earlobe cleft is clearly visible. (Photograph by Professor James Russell, reproduced with permission.)

using overall 1975–77 deaths in England and Wales as a basis for comparison. The South Asians suffered an excess of circulatory (notably ischaemic heart disease) deaths of 20 and 17 per cent among men and women respectively. The excess was evident among both Hindus and Moslems, as well involving groups with differing places of origin within the subcontinent.[4] P M McKeigue and M G Marmot's findings revealed even greater differences. They reported that among South Asian immigrant residents in various parts of London the 1979–83 coronary heart disease death rate excess was 50 per cent. Whether the Asians were located in areas of affluence or deprivation made no difference and the findings constituted a worsening over the previous decade.[5] The blood pressures of the Asians were on average slightly lower than those of the whites. The Asian mortality cannot be explained by changing living patterns and adoption to excess of the undesirable health practices of the western world, specifically limited physical activity, excessive consumption of animal fats, energy intake in excess of needs and cigarette smoking. Immigrants do indeed adopt these lifestyles, but comprehensive reviews by Jatinder Dhawan and co-workers

[4] R Balarajan *et al.*, 'Patterns of mortality among migrants to England and Wales from the Indian subcontinent', *Br Med J*, 1984, **289**: 1185–7.

[5] P M McKeigue and J G M Marmot, 'Mortality from coronary heart disease in Asian communities in London', *Br Med J*, 1988, **297**: 903.

Table X.1
Risk factors: British white and Asian patients. Mean SD ( ) or confidence limits [ ]

Risk factor		White (n = 87)	Asian (n = 83)
Age (years)		56.7 (8.7)	51.9 (7.1)
Social Class	I	11	12
	II	38	34
	III	44	47
	IV	7	7
BMI (kg/m^2)		25.7 (3.2)	25.5 (9.9)
Waist/hip ratio		0.97 (0.06)	1.02 (0.05)
% Physically Active		37	23
Mean lifetime cigarette consumption (1000s)			
Ex and current smokers		212 [164–267]	159 [121–203]
BP (mmHg)	Systolic	137.8 (24.4)	130.2 (20.6)
	Diastolic	81.8 (10.5)	79.1 (8.3)

Adapted from Jatinder Dhawan *et al.*, 'Insulin resistance, high prevalence of diabetes and cardiovascular risk in immigrant Asians. Genetic or environmental effect?', *Br Heart J*, 1994, **72**: 413–21, p. 415. (With permission from the BMJ Publishing Group.)

(Table X.1) and by McKeigue and colleagues (Table X.2) suggest that, in the case of South Asian immigrants to the United Kingdom, this adoption is not excessive by overall English standards. Compared to the general population, the immigrants' energy intake was not excessive, and their mean body mass index virtually the same. Their consumption of animal fats was low, their fibre intake high, and their carbohydrate consumption only marginally greater. They were less active physically, but on the other hand they smoked less.[6] It is therefore possible that these immigrants had an innately high degree of vulnerability to the coronary risk factors to which they had become exposed for the first time. These considerations also raise the possibility that the heightened susceptibility to coronary heart disease among recent migrants to the western world could have had a parallel in the population of late eighteenth-century England. In both groups this vulnerability would have become manifest with their first exposure to the same unhealthy lifestyles, the one with change of location, the other with passage of time. Twentieth-century geographical and eighteenth-century historical developments would have been obverse and reverse sides of the same coin. Evolutionary adaptation to the new risk factors over the course of many generations might therefore account for twentieth-century native English having gradually become less vulnerable and consequently having a lower incidence of CHD than the recent unadapted immigrants to the UK. The evidence for this will be discussed later in some detail.

[6] Jatinder Dhawan *et al.*, 'Insulin resistance, high prevalence of diabetes, and cardiovascular risk in immigrant Asians. Genetic or environmental effect?', *Br Heart J*, 1994, **72**: 413–21, pp. 415–16; P M McKeigue *et al.*, 'Diet and risk factors for coronary heart disease in Asians in northwest London', *Lancet*, 1985, **ii**: 1086–90, p. 1087.

Table X.2
Nutrient intakes in Asian households compared with national food survey

	Asian (184 households) Mean ± SE	UK national food survey
Consumption per person per day		
Energy (Kcal)	2415 ± 83	2210
Fat (g)	106.1 ± 4.4	104
Fatty Acids:		
Saturated (g)	36.8 ± 1.8	45.6
Monosaturated (g)	38.8 ± 1.4	38.9
Polyunsaturated (g)	27.2 ± 1.2	11.4
Linoleic Acid (g)	25.6 ± 1.2	9.8
Cholesterol (mg)	200 ± 15	405.0
Carbohydrate (g)	284 ± 9	264.0
Dietary fibre		
Cereal fibre (g)	10.4 ± 0.4	8.7
Vegetable fibre (g)	18.7 ± 1.1	9.2
Source of energy (per cent of total)		
Fat	38.8 ± 0.6	42.2
Carbohydrate	48.6 ± 0.6	44.9
P/S ratio	0.85 ± 0.04	0.28

Source: P M McKeigue *et al.*, 'Diet and risk factors for coronary heart disease in Asians in northwest London', *Lancet*, 1985, **ii**: 1086–90, p. 1087. (Permission granted by The *Lancet* Ltd.)

A suggestion of such adaptation is provided by comparative studies of the relationship between fat intake and serum lipid levels among males of Japanese ancestry resident in either Japan or the USA. Not surprisingly, it was found that the higher intake of fat among people of Japanese origin living in California was reflected in abnormal lipid profiles (Table X.3). Particularly noteworthy, however, was a finding that the degree of significance of the positive correlations between saturated fat intake and serum cholesterol levels was greater among the residents in Japan whose intake of animal fats was customarily low, and weaker in the Japanese men who were living in either Hawaii or the Continental United States and habituated to a higher intake (Table X.4). An apparent ability to compensate biochemically for the changes in dietary practices that followed emigration had become evident within a generation or two.[7]

As noted earlier, the incidence of coronary heart disease mortality among Asian immigrants to the United Kingdom exceeds the national rates, and differing exposure to lifestyle risk factors could not explain the excess.[8] When patients from both

[7] Hiroo Kato *et al.*, 'Epidemiological studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Serum lipids and diet', *Am J Epidemiol*, 1973, **97**: 372–85, pp. 375, 378.

[8] Dhawan *et al.*, op. cit, note 6 above, pp. 415–16.

Table X.3
Nutrient intake (24 hour recall) and serum lipid levels of Japanese resident in Japan or California

Intake/day	Japan		California	
	Mean	SD	Mean	SD
Total calories	2164	619	2262	695
Total fat (g)	36.6	20.4	94.8	36.4
Saturated fat (g)	16.0	13.3	66.3	30.5
Unsaturated fat (g)	20.6	13.7	28.5	20.4
Cholesterol (mg)	464.1	324.4	533.2	297.8
Weight (kg)	55.2	9.0	65.9	9.2
Serum cholesterol (mg/dl)	181.1	38.5	228.2	42.2
Serum triglycerides (mg/dl)	133.8	87.1	233.7	144.4

Source: Hiroo Kato *et al.*, 'Epidemiological studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Serum lipids and diet', *Am J Epidemiol*, 1973, **97**: 372–85, p. 375. (By permission of Oxford University Press and Dr J L Tillotson (co-author)).

Table X.4
Regression coefficient between saturated fat intake and serum cholesterol.* Subjects of Japanese origin

Place of residence	Number of subjects	Regression coefficient
Japan	1717	0.434**
Hawaii	7949	0.0766**
California	178	0.0965

* Adjusted for age and relative body weight.
** Significant at 1% level.

Source: Hiroo Kato *et al.*, 'Epidemiological studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California. Serum lipids and diet', *Am J Epidemiol*, 1973, **97**: 372–85, p. 378. (By permission of Oxford University Press and Dr J L Tillotson (co-author)).

populations who had angiographically proven coronary arterial disease were compared, their lipid profiles were almost identical, but the South Asian patients had somewhat higher blood sugar levels when fasting and significantly higher levels after a glucose load. Their insulin levels were significantly and strikingly higher (Table X.5), and their incidence of diabetes mellitus greater. These findings indicate that the South Asians were characterized by differences in carbohydrate metabolism and above all by greatly heightened insulin resistance. Comparisons of subgroups of white and Asian patients who exercised regularly yielded similar differences in glucose/insulin metabolism (Table X.6) despite nearly identical mean body mass indices (24.55 and 24.32 respectively). The serum insulin, both fasting and after a glucose load, was significantly higher in the exercising Asian group and indicative

Table X.5

Biochemical risk factor profile: British Asian and white patients* (SD 95% confidence limits otherwise)

		British Asian	White
No. of patients		83	87
Total cholesterol (mmol/L)		6.16 (1.09)	6.32 (1.14)
HDL cholesterol (mmol/L)		1.02 (0.97–1.07)	1.08 (1.20–1.14)
Glucose (mmol/L)	fasting	5.34 (4.97–5.74)	4.77 (4.5–5.0)
	2 hr after glucose	7.37 (6.64–8.19)**	6.13 (5.61–6.70)**
Insulin (μU/ml)	fasting	122.0 (104.8–142.0)	12.7 (10.8–14.9)**
	2 hr after glucose	90.0 (79.3–102.3)**	43.5 (36.5–51.9)**

* Angiographically proven CHD ** P<0.05

Adapted from Jatinder Dhawan *et al.*, 'Insulin resistance, high prevalence of diabetes and cardiovascular risk in immigrant Asians. Genetic or environmental effect?', *Br Heart J*, 1994, **72**: 413–21, pp. 416–17. (With permission from the BMJ Publishing Group.)

Table X.6

Comparison of aspects of risk factor profile. Exercising British Asian and white coronary heart disease patients

	British Asian	White
Body mass index	24.32 (0.71)*	24.55 (0.52)**
Total serum cholesterol (mmol/L)	5.96 (1.8)*	6.56 (0.23)**
Log insulin (μU/ml) fasting	18.9 (15.1–21.7)	8.41 (7.1–9.8)**
1 hr after glucose	125.2 (77.4–135.6)	54.9 (43.8–68.1)**
2 hr after glucose	50.9 (37.7–68.7)	27.66 (22.1–34.4)**

SD singly starred. Numbers in brackets are confidence limits. ** P<0.05

Adapted from Jatinder Dhawan *et al.*, 'Insulin resistance, high prevalence of diabetes and cardiovascular risk in immigrant Asians. Genetic or environmental effect?', *Br Heart J*, 1994, **72**: 413–21, p. 417. (With permission from the BMJ Publishing Group.)

of their greater insulin resistance.[9] As the differences between the white and Asian patients could not be explained by differences in diet, physical activity or incidence of obesity, a possible genetic basis suggests itself.

N Shaukat, D P de Bono and D R Jones compared the biochemical profiles of eighty-nine healthy sons of South Asian cardiac patients and eighty-two healthy sons of comparable North European cardiac patients. The two parent groups were matched for age and symptom duration, and all had been investigated by coronary

[9] Ibid., pp. 416–17.

Table X.7
Biochemical physical features. South Asian and North European patients and their sons free of CHD. Means and 95% probability intervals ( )

	Patients		Sons	
	Asian	N. European	Asian	N. European
Total cholesterol (mmol/L)	6.0 (5.8–6.2)	5.9 (5.7–6.2)	4.2 (4.0–4.4)	4.1 (4.0–4.2)
HDL cholesterol	1.1 (1.0–1.1)	1.1 (1.0–1.3)	1.2 (1.2–1.3)	1.3 (1.2–1.3)
Lp(a) (mg/dl)	27.2 (25.8–28.5)	19.5 (18.3–20.4)	19.1 (16.8–21.8)	10.5 (8.3–12.8)
Fasting glucose (mmol/L)	4.6 (4.2–5.1)	4.1 (3.7–4.6)	4.4 (4.1–4.6)	4.2 (3.9–4.5)
Insulin (fasting) (μmol/L)	17.6 (16.4–19.0)	13.5 (12.4–14.8)	14.3 (12.9–15.8)	8.43 (7.29–9.60)
Waist/hip ratio	0.94 (0.92–0.96)	0.89 (0.87–0.91)	0.87 (0.85–0.89)	0.83 (0.81–0.85)
Body mass index (kg/m^2)	25.4 (24.5–26.3)	26.3 (25.7–26.9)	24.1 (23.6–24.6)	24.0 (23.6–24.8)

Adapted from N Shaukat, D P de Bono and D R Jones, 'Like father like son? Sons of patients of European or Indian origin with coronary heart disease reflect their parents' risk factor patterns', *Br Heart J*, 1995, **72**: 318–23, pp. 320, 322. (With permission from the BMJ Publishing Group.)

angiography. The sons ranged in age from fifteen to thirty years (Table X.7). Comparison of the two groups showed that the European and Asian sons had almost identical fasting blood sugars but the latter had significantly higher serum insulin levels, indicating that the young overtly healthy Asians already had greater insulin resistance.[10] This is a recognized risk factor for arteriosclerosis, which could account in some measure at least for the excess South Asian incidence of coronary heart disease.[11] As it manifested itself early in life and in the absence of either higher young Asian energy intake or reduced energy needs, a genetic basis is here too a distinct possibility.

Finally, N Shaukat and colleagues compared cardiac patients of South Asian and North European origin and their sons with respect to serum Lp(a) levels, elevations of which are associated with heightened susceptibility to CHD. All the diagnoses of ischaemic heart disease had been confirmed by coronary angiography. The Lp(a) levels were almost 50 per cent higher among the Asian patients, 27.2 as opposed to 19.5 mg/dl, a highly significant difference. When the biochemical profiles of the healthy sons of these two patient groups were studied, there was found to be a very high correlation between fathers and sons with respect to Lp(a) concentrations, the sons of Asian patients having serum Lp(a) levels significantly higher than those of

[10] N Shaukat, D P de Bono and D R Jones, 'Like father like son? Sons of patients of European or Indian origin with coronary artery disease reflect their parents' risk factor patterns', *Br Heart J*, 1995, **74**: 318–23, p. 321.

[11] P J Savage and M F Saad, 'Insulin and atherosclerosis: villain, accomplice, or innocent by-stander?', *Br Heart J*, 1993, **69**: 473–5.

their North European counterparts.[12] As Lp(a) levels are largely independent of diet, the combination of the differences between the two communities and the similarities between the two generations of each suggests a genetic basis for Lp(a) abnormalities and their cardiac consequences.

The South Asian groups in the various studies were made up almost exclusively of Punjabis or Gujeratis whose ancestors had originated in Central Asia in the distant past and subsequently migrated to North West India. They therefore had the same remote prehistoric Indo-European ethnic origins as the white English subjects. However, the forebears of the South Asian patients had not been exposed to high animal fat and energy intake until their migration to Britain in the mid-twentieth century. The differences between the two populations that have been described are therefore compatible with the white English population alone of the two groups having undergone some favourable evolutionary adaptive changes. These would have occurred during the two centuries and more during which their forefathers had been eating a diet changed permanently by the Agricultural Revolution and high in its animal fat content.

Any favourable influences of natural selection on vulnerability to CHD risk factors may be diminished but are certainly not nullified by the tendency for the disease to become manifest late in male reproductive life. Reasons for this conclusion have their bases in the demographics of eighteenth-century England. E Anthony Wrigley and Roger Schofield's early studies have shown that, in general, marriage in the eighteenth century took place when men were in their late twenties. Marriage tended to be later still among the middle and upper classes as it was commonly delayed until a man had the means to support a wife, and it may even have had to wait upon an inheritance.[13] Thomas H Hollingsworth reported that throughout the eighteenth century the age of marriage of 35 to 40 per cent of male members of the nobility was above thirty years.[14] The tendency for men to father some children relatively late in life was increased by the large numbers of their progeny and also by the high maternal mortality rates, with subsequent second marriages of men, often to younger women. The average age of widowers marrying spinsters in the late eighteenth century was estimated by the Cambridge Group to be between thirty-nine and forty years.[15] This frequently brought the age of a second round of fathering into the fifth decade of life, if not later still. William Heberden himself was a typical example. Of the three sons by his second marriage who survived to adult life, the oldest was born when their father was fifty-six, the second three years and the youngest five years later.[16] Before the late twentieth-century adoption of risk factor control measures, symptoms of ischaemic heart disease not infrequently became

[12] Shaukat, de Bono and Jones, op. cit., note 10 above, p. 320.

[13] E Anthony Wrigley and R S Schofield, *The population history of England 1541–1871: a reconstruction*, Cambridge, MA, Harvard University Press, 1981, p. 255.

[14] T H Hollingsworth, *Demography of the British peerage*, *Population studies*, **18**: Supplement No. 2, London, Population Investigation Committee, London School of Economics, 1964, pp. i–iv, 3–108.

[15] E Anthony Wrigley *et al.*, *English population history from family reconstitution, 1580–1837*, Cambridge University Press, 1997, p. 149.

[16] Ernest Heberden, *William Heberden: physician of the age of reason*, London, Royal Society of Medicine Services, 1989, p. 80.

manifest as early as the fifth decade of life. They were so reported by Heberden and subsequent eighteenth-century English medical writers. One of John Fothergill's two documented patients with angina pectoris was only thirty years old.[17] John Ryle and W T Russell, writing in 1949, reported that 39 of their 149 male patients developed angina pectoris below the age of fifty and in 16 it was below forty years.[18] It follows that despite a tendency for ischaemic heart disease to occur somewhat late in male reproductive life, there was an opportunity for the forces of natural selection to effect evolutionary changes in the successive generations born in England after the mid-eighteenth century.

In conclusion, there are possible genetic factors that predispose to development of coronary heart disease and manifest themselves, *inter alia*, as abnormalities in the serum cholesterol response to dietary fats, glucose/insulin metabolism and serum Lp(a) levels. Evidence has been adduced to suggest that, because of these presumed genetic factors, a population first exposed to a diet high in animal fats and to other lifestyle risk factors may be particularly vulnerable to the cardiovascular consequences. The population of England was thus exposed during the course of the eighteenth century, when heightened susceptibility could have then contributed to the emergence and subsequent increasing prevalence of coronary heart disease with natural selection playing some part in lessening predisposition during the subsequent two centuries.

[17] John Fothergill, 'Case of an angina pectoris with remarks', *Medical Observations and Inquiries*, 1776, **5**: 233–51, p. 241.

[18] John A Ryle and W T Russell, 'The natural history of coronary heart disease', *Br Heart J*, 1949, **11**: 370–89, p. 381.