The metabolic basis of increased coronary risk attributed to people from the Indian subcontinent

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People originating from the Indian subcontinent living abroad are reported to have a higher prevalence of coronary heart disease (CHD) compared to indigenous populations in the countries they reside. Recently there have been reports of increases in prevalence of CHD from India also. Initial reports indicate that people of Indo-origin may be more prone to CHD due to a metabolic syndrome which comprises of resistance to insulin-mediated glucose uptake, serum triglycerides that are at the upper end of normal, a low level of high density lipoprotein (HDL) cholesterol and blood glucose values in the pre-diabetic range. In addition, people of Indo-origin have increased concentrations of lipoprotein (a), a particle that is associated with increased propensity to CHD. Both insulin resistance and lipoprotein (a) are genetically determined, but the increased CHD risk related to them seems to come into play when environmental factors such as diet and physical inactivity lead to obesity and/or increases in serum cholesterol. Alterations in traditional lifestyles due to migration from rural areas to urban areas in India and or on migration abroad to more prosperous conditions may explain why people of Indo-origin are at an increased risk of CHD. There is a need for more studies in India and cross-country studies of Indians abroad to clarify some of these issues. The results of these studies will help put into place health promotion strategies to prevent CHD which often affects people when they are most productive.

The burden of CHD in Indians living overseas

There are several reports which indicate that the people of Indian origin living outside India have a greater prevalence of CHD than co-existing indigenous populations. Most of these initial data arose from studies carried out in the West Indies, UK and South-East Asia[1–4]. More reports have emerged from Mauritius and the United States recently[5,6], but there are no large studies on the incidence of CHD. The data on prevalence are further confounded by problems such as reluctance or delays in access to medical care in Indian immigrant populations[7]. A further issue relates to the heterogeneity of people from the Indian subcontinent. Many of the older studies have been carried out on Gujaratis or Punjabis, and on people from different countries of the subcontinent such as India, Pakistan and Bangladesh. The literature simply refers to all these different cultural groups as South Asians. Religion, culture, language, climate and geography all confer particular ethnic characteristics to people in the Indian subcontinent. In most countries, in the rest of the world, these factors influence dietary habits to a great extent, and will do so in India also.

It can also be argued that people who migrate are in some way different to those who do not, and thereby constitute a naturally-selected population. Most migrants from the Indian subcontinent move abroad for economic reasons. They tend to originate from small geographical clusters of a few villages, and when abroad, often live in self-segregated communities[8]. Looking at the greater picture, it often comes as a surprise that the Chinese, Jews, Africans or even white Europeans, have migrated in larger numbers than people of Indo-origin. There is, therefore, need for some caution in extrapolating from studies on a highly selected and skewed population of Indo-origin people living abroad. In Britain, for example, communities from the Indian subcontinent are well scattered, and in most areas, hospitals will see numerically fewer patients with CHD or diabetes mellitus, compared to the local white population. These points illustrate the difficulties in seeking a unifying hypothesis that embraces and explains the increased prevalence of CHD originating from the Indian subcontinent. However, to those who clinically work among people of Indo-origin, the diagnosis of CHD or diabetes mellitus is all too frequent a reality to be ignored. There is already much debate on the causation of CHD in the Western world[9]. The difficult question is whether people from the Indian subcontinent are more prone to CHD due to the presence of particular risk factors.

The answers to many of these questions lie in the characteristics and epidemiology of CHD in Indians living in India. Sadly, until recently, there were very few studies that provided data from India. This was mainly due to the lack of standardization of laboratory assays and epidemiological methods. Much of this criticism has been rectified in the last five years with the appearance of epidemiological studies from India that will stand up

to scrutiny world wide, although there is still a dearth of studies on the incidence of CHD. This issue of data from India is particularly important for planning preventive strategies in India where people are now generally living longer and surviving into decades where much of the problem of CHD appears in the West. In the West, and in Indians living abroad, the tragedy of CHD lies in its premature appearance in subjects who are generally in their prime and most productive. If a similar trend establishes itself in a large country such as India; where poverty co-exists with affluence and ignorance, with great strides in science and technology, then the burden of CHD would add greatly to the diseases relating to poor socio-economic conditions. It is, therefore, worth investing in setting up studies in India which will yield data that are sound. It is only from these studies that clues to the cause of the increased prevalence and mortality in Indians living abroad will become clear. The story becomes more intriguing in the United Kingdom with a comprehensive report on ethnicity and variations in mortality from CHD. In general CHD mortality is declining amongst people from the Indian subcontinent in the UK, although it remains higher compared to those not of Indo-origin[10]. The decline was greatest in Sri Lankans, Indians and East-African Indians, and smallest in Bangladeshis and Pakistanis. These rates of decline are very much linked to socio-economic status, where a higher status was associated with the decreased CHD risk. They further add to the conundrum of increased CHD risk in Indo-origin people.

Possible aetiology of increased coronary risk in people from the Indian subcontinent

It is a common refrain in journals and textbooks that the aetiology of CHD is multifactorial, and certainly there is no shortage of risk factors that are associated with CHD[11]. They range from mystifying ear lobe creases and residence in hard water areas to established risk factors such as smoking and hypercholesterolaemia. The large numbers of studies carried out in the area of causation of CHD have improved the ability to stratify risk in a clinical setting. For example, in a lipid clinic it is usual to ascertain coronary risk by determining whether a patient has a genetic hyperlipidaemia such as heterozygous familial hypercholesterolaemia or familial combined hyperlipidaemia or simple hyperlipidaemia due to dietary indiscretion or a mixed hyperlipidaemia associated with hypertension or glucose intolerance. Each of these carry a different degree of risk. The question is whether ethnicity itself is a particular risk factor or does coronary risk in people of Indo-origin operate through conventional risk factors.

In medicine, it is not always easy to separate the wheat from the chaff and the quality and paucity of risk factors in Indians makes it more difficult to sieve the facts. However, the literature does hold clues. The body of accumulating evidence would suggest that being of Indo-origin is associated with the metabolic syndrome that includes low HDL-cholesterol, high serum insulin, glucose intolerance and serum triglycerides that are nearer the upper limit of normal[12,13]. It is not clear whether these biochemical characteristics are prevalent in subjects without CHD also, or there is a further trigger or factor that leads to CHD.

Nature or nurture?

The metabolic syndrome does not occur uniquely in people of Indo-origin. In the West, it is all too frequently seen in preventive cardiology clinics[14]. However, it seems that the syndrome is more common in populations other than those of white European extraction. Many of these people have lived traditional subsistence lifestyles for many generations, but are now emerging in the post-colonial era, with more Western habits and, of course, affluence. So is the metabolic syndrome a result of Neel's thrifty genotype?[15] Whatever the 'genes' for diseases of civilization, they are bound to have been part of a normal genotype once upon a time. The thrifty genotype is said to offer survival benefits, but it seems too much of a coincidence that it operates in virtually all populations on all continents except in white Europeans. The thrifty genotype comes into play in all animals during times of physiological stress such as pregnancy, and also during starvation or trauma, in the form of insulin resistance. However, when it comes to obesity, it is difficult to know how a low metabolic rate and energy balance are influenced by genetic factors. At a population level there are no particular ethnic differences in energy metabolism and no major genes have been found to be widespread enough to account for differences in either insulin resistance or type 2 diabetes mellitus. There is even less information on other aspects of the metabolic syndrome.

If at present, we have no firm indication of a genetic cause for the metabolic syndrome in people of Indo-origin, then is it possible that environmental factors are to blame? There is no argument that the effects of the metabolic syndrome, and progression to either type 2 diabetes mellitus, or causation of CHD are influenced by increasing age, weight gain and physical inactivity[16], but the thrifty phenotype hypothesis put forward by Barker and his colleagues[17] proposes that low birth weight due to intrauterine malnutrition leads to several of the components of the metabolic syndrome. This effect has been shown in several countries in the world, including India[18,19].

What specific type of malnutrition is responsible is not entirely clear, but animal studies suggest that poor

maternal protein intake or the ratio of protein to energy intake may be to blame[20]. The data for the thrifty phenotype hypothesis are certainly convincing, but in many of the studies the numbers of subjects are small. Moreover, there is always the question of selection bias, especially relating to the perinatal mortality that is often prevalent in malnourished populations. Not all studies of those born during famine or a siege as a result of war, confirm these findings. Moreover, the very demonstration that secondary prevention of CHD is effective, indicates that the effect of intrauterine malnutrition may be influenced by factors in later life. Data from the Speedwell and Caerphilly Study would support this[19], although Hales disputes this by saying that this argument is true of most diseases[21]. He makes a case for investigating causation rather than susceptibility to disease. The thrifty phenotype may well be relevant in the causation of CHD in people of Indo-origin, if the hypothesis holds. This would account for the increase in diabetes mellitus and CHD seen in post-independence India. The real test of this would lie in the future, and in the West, in second generation people of Indian origin. The birth weights of infants born to second generation Indo-origin women are already higher than in those of first generation women[22].

Glucose tolerance and CHD

CHD is more frequent in diabetic subjects[23], and many patients with CHD also have glucose intolerance[24]. People of Indo-origin are more prone to diabetes[25,26] and must go through a pre-diabetic phase where blood glucose values are higher than in subjects who do not develop diabetes. One would have thought, therefore, that hyperglycaemia has a strong role in the causation of CHD, but the evidence linking glycaemia to CHD is not strong, even in subjects with diabetes mellitus. In non-diabetic people, the relationship between hyperglycaemia and CHD is linear in some studies[27–29], but in others only a threshold effect is apparent[30–32]. The lack of uniformity of epidemiological methods may be a cause of variability, but the results of the recent Chicago Heart Association prospective study would suggest that the effects of hyperglycaemia on CHD are mediated by cardiovascular risk factors, other than blood glucose[33]. Another factor amongst epidemiological studies is the variability in the assessment of glycaemia. Impaired glucose tolerance is defined following differing glucose loads, and in some studies fasting glucose levels have been used. Nonetheless, an integrated measure of glycaemia such as glycated haemoglobin also has a weak association with CHD[34]. In diabetic patients the story is different with increasing glycaemia being associated with CHD[35]. Improvement in glycaemia in these subjects, however, does not prevent CHD[16]. These findings suggest that hyperglycaemia *per se* is unlikely to be a risk factor for CHD in people of Indo-origin. CHD is more common in urban Indians[36]. A recent study from Southern India found that although type 2 diabetes mellitus was more frequent in urban areas compared to rural areas, the prevalence of impaired glucose tolerance was similar in both populations[37]. This further reinforces the fact that factors other than glycaemia play an important role in the causation of CHD.

Insulin resistance and CHD

Blood glucose may be a poor marker of CHD, but its co-conspirator, insulin resistance has, perhaps a more, convincing relationship to CHD. There are numerous reports documenting hyperinsulinaemia, and insulin resistance in people of Indo-origin who have had CHD or type 2 diabetes mellitus[38–40]. Moreover, the prevalence in insulin resistance is greater than that seen in other ethnic groups, and is prevalent in Indo-origin people in several countries and has also been documented in Indians living in rural areas in India[41]. Does all this add up to a genetic trait for insulin resistance in people of Indo-origin, which becomes worse with over-nutrition and obesity? It is interesting to note that when Reaven first described insulin resistance, it was mainly in hypertensive subjects who were lean[42]. Yet, the vast number of people who have insulin resistance are obese[43]. Studies to establish the genetics of insulin resistance are inconclusive, but the other features of the metabolic syndrome such as dyslipidaemia, seem to have a stronger genetic basis.

Is it, therefore, possible that decreased insulin sensitivity in Indo-origin people is a result of *in-utero* nutritional deprivation? The answers to these questions will come from studies on children of Indo-origin people living abroad who have had better nutrition, and also from studies on people in India where economic prosperity has increased lately. There are few major epidemiological studies of CHD in Indo-origin people and insulin resistance. The data from studies in white Europeans relating to insulin resistance and CHD, seem conflicting[23]. Interpretation is made difficult by variability in epidemiological methods and also in the definition of insulin resistance. It is likely that studies of the other features of the metabolic syndrome such as low HDL cholesterol, higher than average serum triglycerides, and other disturbances of lipoprotein metabolism will be more rewarding.

Lipoprotein abnormalities and CHD

One of the incontroversial hallmarks of CHD in Indo-origin people, is the presence of low HDL-cholesterol and high serum triglycerides. It may well be the case

that the effects of insulin resistance are working through this pathway, rather than a direct effect on either atherosclerosis or thrombosis. Although serum cholesterol and LDL-cholesterol have proved to be strongly linked to CHD[44], it is the dynamics of cholesterol movement in the body that strongly determines coronary risk. It is with cholesterol flux that low HDL-cholesterol and high triglycerides are intimately linked, and insulin resistance has a major effect on the process. It is, therefore, important to understand the processes that determine their concentrations. The links between CHD and cholesterol are well known, but an understanding of the mechanisms of hypertriglyceridaemia and low HDL-cholesterol is particularly relevant in elucidating the increased CHD prevalence in people of Indo-origin.

The role of serum triglycerides in CHD

The volume of literature relating serum cholesterol levels and CHD, and benefit from lowering cholesterol is large, but, in contrast, there continues to be much debate about the role of serum triglycerides in CHD. Part of the reason for this debate lies in the complexity of the metabolism of triglycerides, which plays an important role in energy metabolism, and thus their serum concentrations do not necessarily reflect their fate in the tissues. Cholesterol remains associated with the lipoproteins until it is delivered to the LDL receptor or 'shuttled' in the HDL pool, but triglycerides are constantly being hydrolysed by the action of lipoprotein lipase. The flux of triglycerides changes dramatically postprandially. It is therefore not surprising that epidemiological studies have shed little light on the association between serum triglycerides and CHD. Several case-control studies have linked elevated levels of serum triglycerides[45,46] and postprandial triglycerides to CHD[47,48].

Few epidemiological studies have been specifically directed towards examining the relationship between serum triglycerides and CHD[49], but data from Framingham[50–52], and more recently, from the PROCAM study[53] show a relationship. Serum triglycerides in these studies were independent risk factors, particularly in the presence of low HDL-cholesterol values. Serum triglycerides come out to be strong predictors of coronary risk, particularly in studies from Scandinavia[54] in women[55] and in patients with diabetes mellitus[56].

Austin's meta-analysis of 17 population-based prospective studies[57] indicates that plasma triglycerides are a risk factor independent of HDL-cholesterol levels. A one mmol/l increase in serum triglycerides was associated with a 32% increase in risk in men and 76% in women, but these figures fell to 14% and 37% respectively after adjustment for HDL-cholesterol. Most laboratories report 2 mmol/l as the upper limit of normal fasting serum triglycerides, but data from healthy subjects, case-control studies and epidemiological studies, now suggest that there may be benefit in keeping fasting serum triglycerides to below 1.5 mmol/l, a point where the small dense LDL subfraction starts to appear[58]. The presence of this type of LDL has been shown to be associated with CHD in several case-control studies[59]. Another feature of the high serum triglyceride and small dense LDL phenotype is the presence of low HDL-cholesterol concentrations: the atherogenic lipoprotein phenotype[60]. However, all three components of the phenotype are metobolically related and it is uncertain if the small dense LDL is an independent risk factor.

HDL-cholesterol as a risk factor for coronary heart disease

The evidence for the association between low HDL-cholesterol concentrations and CHD is quite strong[61], much of which derives from epidemiological studies, many of which were prospective[62–64]. There is also evidence for this association in studies linking HDL-cholesterol levels to rate of progression of CHD and extent of CHD on angiography[65]. This association is seen in virtually all countries and in both males and females.

Low HDL cholesterol confers greater risk compared to high serum triglycerides. HDL metabolism has not been fully elucidated, but it is becoming increasingly clear that low HDL-cholesterol concentrations are virtually always associated with abnormalities of lipoprotein metabolism that are atherogenic. The disturbances in lipoprotein metabolism that lead to the formation of small, dense LDL are also responsible for low HDL-cholesterol concentrations[66]. In addition, the low HDL-cholesterol levels are also associated with insulin resistance, hypertension, and diabetes mellitus, all of which increase the risk of CHD[67].

Cholesteryl ester transfer

An important function of lipoproteins is to transport lipids through a predominantly aqueous mileu interior and the LDL-mediated pathway is responsible for the delivery of cholesterol to the tissues. There is also a mechanism for removal of excess cholesterol from the tissues which is termed the reverse cholesterol pathway. HDL plays a pivotal role in this physiological process, which starts with the flow of free cholesterol from the cell membrane to HDL where it is esterified by the action of the enzyme lecithin:cholesterol acyltransferase (LCAT). Some of the cholesteryl esters generated are thought to be taken up by the liver directly. However, a substantial proportion are transported from HDL to VLDL, IDL or LDL by a lipid transfer protein called

cholesteryl ester transfer protein (CETP). This movement of cholesteryl ester from HDL to other lipoproteins is termed cholesteryl ester transfer (CET). CET is accelerated in patients with primary hypertriglyceridaemia[68], diabetes mellitus[69], and subjects with angiographic evidence of coronary artery disease[70]. An increased rate of CET leads to the enrichment of plasma lipoproteins with cholesteryl esters, the uptake of which by the liver and other tissues may not be detrimental, but their uptake by the arterial wall may well trigger atherogenic processes. In all the above conditions, the free cholesterol content of either LDL or VLDL is increased, indicating that the abnormal composition of these lipoproteins, rather than an increase in the mass of CETP, is likely to be instrumental in causing accelerated CET. A factor common to all the above disorders where CET is increased is that they are all associated with an increased VLDL secretion rate. An additional effect of increased CET is that LDL is altered to become small and dense which also makes it more prone to oxidation[71].

Apolipoprotein B

Several studies have demonstrated that patients of Indo-origin have elevated serum apolipoprotein B concentrations[72], often in the face of serum cholesterol values that are lower or not dissimilar to that seen in the West. This pattern of lipoprotein abnormalities is very reminiscent of hyperapobetalipoproteinaemia, a genetic trait that is characterized by overproduction of VLDL from the liver[73]. Such patients also have hypertriglyceridaemia, low HDL-cholesterol and an LDL particle that is small and dense. The latter kind of LDL is known to be more atherogenic, but in the one study of normolipidaemic Indo-origin people, this LDL phenotype was not present[74]. Nevertheless, stable isotope turnover studies in patients with type 2 diabetes mellitus, and in non-diabetic relatives of patients with diabetes mellitus, both suggest that insulin resistance and hyperinsulinaemia, can both influence VLDL apo B secretion and hepatic cholesterol synthesis[75,76]. Thus it is possible to tie in hypertriglyceridaemia, low HDL-cholesterol, elevated apolipoprotein B levels and increased hepatic VLDL production, along with insulin resistance.

There has been much debate as to whether insulin has a direct effect on VLDL secretion or whether the action of insulin is mediated by an increase in substrate for VLDL synthesis[56]. The argument essentially stems from differences in data from cell culture and animal model systems, but it is increasingly being recognized that non-esterified fatty acids (NEFA) have an important role to play. NEFA are produced mainly by hydrolysis of fat stored as adipose tissue, and a small contribution is made by hydrolysis of lipoprotein triglycerides. The plasma concentration of NEFA is also affected by peripheral utilization by liver or muscle[77]. Insulin affects NEFA production by suppressing the release of NEFA from adipose tissue. In the presence of insulin resistance NEFA levels are increased due to defective insulin action despite high serum insulin levels. This subnormal biological response is seen in several tissues other than adipose tissue.

NEFA are a substrate for VLDL synthesis[77] which is increased when NEFA levels increase. Although this effect of high NEFA levels may seem detrimental in these times of plenty (relative to past hunter–gatherer lifestyles), it is an appropriate response to starvation as not only do NEFA form a substrate for VLDL, but they are also channelled into formation of ketone bodies which can then enter the Krebs cycle, thereby bypassing the need for glucose for energy. It is not easy to disentangle the issue of whether insulin resistance or elevated NEFA levels are the primary problem. The evidence that insulin-mediated glucose uptake is inhibited by elevated NEFA is strong and it seems that both feed into each other, forming a vicious cycle. Reaven and colleagues have recently reported a relationship between resistance of insulin-mediated glucose uptake, and hypertriglyceridaemia and low HDL-cholesterol levels in people of Indo-origin[78]. Lipoprotein lipase plays an important role in the hydrolysis of triglycerides. In recent years there has been a suggestion that partial lipoprotein lipase deficiency can lead to premature CHD[79]. Such patients are characterized by mild to moderate hypertriglyceridaemia, but it is uncertain if people of Indo-origin have a genetic defect that is associated with defective lipoprotein lipase activity.

Elevated lipoprotein (a) in people of Indo-origin

There are several studies that indicate that Lp(a) is elevated in people of Indo-origin[41,80,81]. There is great debate on the origins and synthesis of Lp(a)[82] and this raises many questions on the mechanisms by which Lp(a) is associated with CHD. It is unclear whether Lp(a) contributes to atherogenesis or to thrombogenesis or to both. Even more intriguing is the recent suggestion that Lp(a) may be a marker for vascular or tissue injury[83]. If this is the case, then it is all the more important that ethnicity is taken into account before Lp(a) is considered a coronary risk factor. People of African origin also have elevated Lp(a)[81], but only develop CHD when other coronary risk factors are present. It is pure speculation, but is it possible that people of African and Indo-origin have high Lp(a) levels due to a remote molecular memory of frequent infections in their areas of origin? It is, of course, very likely that coronary risk related to Lp(a) in Indo-origin people comes into play in the presence of the metabolic syndrome or hypercholesterolae-

mia. The issues relating to CHD are further clouded by the lack of consensus on laboratory measurements of Lp(a)[84]. Any further research is perhaps best done in adequately calculated sample sizes which prevents selection bias by including isoform distribution, and by standardizing isoform measurement and antibody selection[85]. It is particularly important to exclude the effects of acute inflammation, and that data are obtained for linking CHD and Lp(a) to specific ethnic populations.

Homocysteine and coronary risk

Homocysteine is recognized as a risk factor for CHD and levels are of prognostic value in patients with established CHD[86]. The relationship has mainly been seen in patients with symptomatic atherosclerotic disease and has raised the issue, as with Lp(a), whether it is a marker of endothelial damage, rather than being causative. The importance of plasma homocysteine in people of Indo-origin lies in the fact that if nutritional factors are implicated to a certain extent in the causation of CHD, then folic acid supplementation can be used to lower plasma homocysteine levels, and decrease coronary risk. At present, there are no data on homocysteine levels in people of Indo-origin.

Chronic infections, inflammation and CHD

There is indirect evidence to suggest that chronic infections such as *Helicobacter pylori*, cytomegalovirus, herpes viruses, chronic dental or gingival sepsis and *Chlamydia pneumoniae*, may predispose to CHD[87]. The epidemiological evidence for *Chlamydia pneumoniae* and vascular disease is strong, and the organism is able to infect human smooth muscle cells, endothelial cells, and macrophages[88], although it is unclear if *C. pneumoniae* causes CHD or is just present in cells.

There is, of course, the possibility that chronic infections set in motion a process of inflammation and the 'response to injury' hypothesis argues that many of the changes that characterize the later stages of atherosclerosis, and plaque formation are inflammatory[89]. There are few data on these aspects of atherosclerosis in people of Indo-origin. Is it possible that exposure to chronic inflammation in the remote past may confer a certain genotype that makes this population more prone to respond actively to inflammatory stimuli that provokes inflammation?

The inflammatory process is closely linked to coagulation which plays a major role in the thrombotic event that is so frequent in people of Indo-origin. Abnormalities of coagulation are also linked to hypertriglyceridaemia and there are several reports of elevated fibrinogen and factor VII C in people of Indo-origin[90–92].

Diet and lifestyle factors

Most of the metabolic disturbances discussed in the foregoing sections need the presence of other coronary risk factors to lead to CHD. Even if people of Indo-origin have a genetic propensity for the metabolic syndrome or acquire coronary risk factors as a result of foetal malnutrition, one wonders about the risk factors that have led to the recently documented increase in CHD prevalence, both in India and abroad. It is also difficult to conceive nearly a billion people having the same unique genotype or phenotype compared to other populations. Before all people of Indo-origin are labelled 'prone to CHD', there is a need to collect more information than the woefully inadequate data from India, and a relatively-biased view of studies on Indo-origin people abroad. The answers come from studies examining the urban–rural differences in CHD prevalence in India and in other developing countries, and from comparisons of populations that have migrated from their countries of birth with those that have remained behind. A further source of information, particularly for people of Indo-origin, would be from metabolic studies on children of migrants born in their adopted countries.

There is an inherent difficulty in defining the changes that happen with migration, be it from the countryside to town, or from one country to another. From the data already available, urbanization and cross-country migration seem to produce similar changes in lifestyle[41,93], the latter perhaps having a greater impact than the former. Both cause an increase in body mass index, increases in serum cholesterol, a lower HDL-cholesterol, a higher blood glucose, and increases in blood pressure. These are the very risk factors that are thought to be responsible for increased CHD risk in white Europeans or Americans. The urban–rural comparison of people around New Delhi by Reddy and Shah[94] indicates that conventional risk factors are as important in people of Indo-origin as in any other population. A recent smaller pair-wise matched case-control study from India also lends further weight[95]. That the serum cholesterol in people of Indo-origin is not as high as that seen in white populations, may be due to a reflection of their dietary habits and body mass index. Nevertheless, the lack of threshold effect for serum and LDL-cholesterol and CHD seen in major studies[96] probably means that the prevalent serum cholesterol in a patient with CHD is much too high for that individual and that even small rises in serum cholesterol may become significant in people of Indo-origin.

The vast number of people who migrate, do so for economic reasons. Once these economic migrants move to either a city or another country, there are inevitable changes in diet. An initial period of struggle in most cases leads to easy access or ability to afford foods that

are high in energy, and which would have been occasional treats in times past, or in a rural setting. It is well known that dietary fat can influence insulin secretion[97]. Migration and urbanization are also inevitably associated with the stress of adaptation to the new environment and culture. Moreover, there is an additional source of stress with most migrants starting at a lower rung of jobs or businesses. Even in the West, low job control is closely associated with CHD[98], a finding that is bound to be amplified in migrant populations. Migrants consuming a high fat or high energy diet, are likely to replace fresh fruit and vegetables, which are more expensive in an urban setting, and until recently, were in relative short supply in the West. Thus a lack of antioxidants may also contribute to CHD in the long run. Many of these aspects of diet are obvious in Indo-origin people living in the West, but caution is needed with such studies in India. Ethnic variations in use of cooking oils, soluble fibre and other traditional foods also need to be taken into account, although the recent economic boom and disparity in standards of living are likely to make such studies even more difficult. Physical inactivity may also be an important factor that contributes to insulin resistance. City life in India and adoption of Western lifestyles abroad inevitably lead to reduced physical activity which is compounded by a lack of culture of sport and physical activity in Indo-origin people. This is particularly evident in the difficulties in health promotion strategies in the United Kingdom in this group.

The survey by the Anthropological Society of India and newspaper accounts indicate a surprising and substantial alteration in the lifestyle of the majority of Indians[99]. Prosperity in a large country like India is likely to be associated with many of the changes that lead to increased coronary risk. There will always be a movement of people from rural to urban areas, and it is very likely that at some stage risk factors for CHD will also increase in the semi-rural areas. This is certainly the experience in the West where there is a very small differential in lifestyles between the town and the country. As Indians live longer with improved conditions and greater economic prosperity, the pattern of disease will change to that of diseases of civilization. Improvement in socio-economic conditions will reduce the burden of diseases of poverty, but unless strategies are in place to educate parents and the new generation on coronary risk factors, CHD will claim people at their most productive, as it does in the West. CHD rates are falling in the West possibly as a consequence of increased awareness of coronary risk factors. A study from Mauritius, where people are predominantly of Indo-origin, has shown that lifestyle interventions can have positive effects[100]. Such initiatives need to be planned in India, but it is important to simultaneously characterize the rural–urban lifestyle differences in the major cultural and geographical regions of India. If these are done alongside cross-country studies, among people of Indo-origin living abroad, and second generation Indians abroad, it will markedly improve the quality of the data, and make a firm case for the types of interventions specifically needed for the people of Indo-origin.

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