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Coronary Heart Disease In Indians

Possible Role Of Nutritional Factors

W. Philip T. James

It is not long ago that any nutrition scientist proposing to discuss adult chronic disease in India would have naturally been seen as someone having a very limited view of the real nutritional problems of developing societies. Elsewhere, I have set out my concern about the recently recognised problem of adult malnutrition which afflicts the Indian population to an unusual degree[1].

However, there are now two reasons for focussing on those conditions usually referred to as diseases of affluence. First, the problem is becoming a major concern in Indian cities and could lead to a redirection of those scarce resources needed for combating the major priorities of vitamin A, iodine and iron deficiencies and childhood protein-energy malnutrition. Secondly, studies emerging from Europe suggest that South Asians are unusually susceptible to these conditions, reasons for which remain unclear. The present analysis is, therefore, meant to be a contribution to the gathering debate in this field which has already been highlighted by the Nutrition Foundation of India[2].

Diabetes, coronary heart disease (CHD) and cancers are the major causes for concern because they will soon constitute the principal causes of death, as societies are transformed by economic change and as they cope more effectively with communicable diseases[3]. In Thailand, heart diseases are already the principal cause of death, with cancers occupying third place (the second place going to deaths from accidents, poisoning and violence). In India, overall death rates are currently dominated by problems of health affecting the majority living in rural circumstances, but there seems little doubt that adult chronic diseases are on the rise now.

CHD IN INDIANS

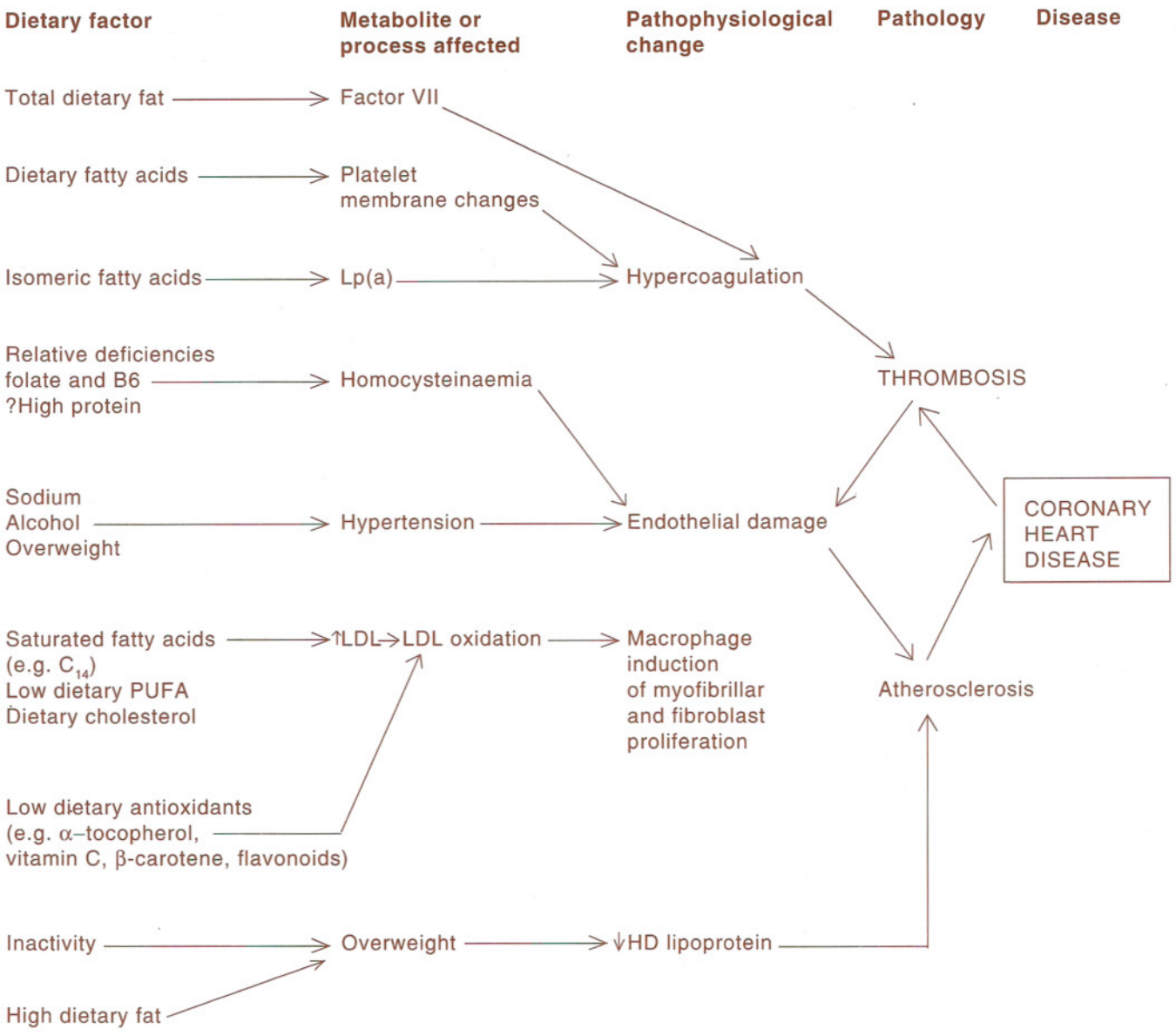
The first reports of the unusual susceptibility of Indians to CHD came from several regions of the developing world: first in Singapore, then in Uganda, South Africa, Fiji and later in Trinidad[4]. In Britain, Gujaratis, Punjabis, Southerners and Muslims living in poor communities, all have high mortality rates from coronary artery disease with a risk that is 40-60 per cent in excess of the average for England and Wales. This excess mortality occurred in recent immigrants, and thus led McKeigue *et al* to presume that in Gujarat, Punjab, Bangladesh and Pakistan, those communities from which the migrants were drawn, also have high rates of CHD[4]. Limited data from Chandigarh in the mid-1960s suggested a seven- to eight-fold difference in electrocardiographic abnormalities between urban and rural dwellers; the rates in Chandigarh were equivalent to those in the US before CHD rates began to fall so drastically.

It is surprising how often a clinical perspective of the basis of CHD concentrates on genetic predisposition whereas the biochemist or physiologist tends to emphasise the endless complexities of the problem. From a nutritional point of view, however, we can now describe a series of pathophysiological sequences and the way in which environmental factors (particularly diet) affect each of these processes (Figure 1)[5]. The development of a myocardial infarct is now clearly recognisable as involving a thrombotic component as well as the classic process of atherosclerosis, and diet modulates both processes. Sudden death also arises usually from a cardiac arrhythmia which is particularly likely if there is a poor intake of n-3 fatty acids[6] and this is a particular problem in Asian diets[7].

The three classic risk factors for CHD — smoking, hypertension and hypercholesterolaemia — still apply to Indians as well as to other groups. These relatively crude clinical indices interact metabolically and explain the observed synergy of risk seen in Western societies. Thus, not only can toxic components — including the carbon monoxide in cigarette smoke — affect the integrity of the endothelium, but

CONTENTS

Figure1
A Modern View Of The Development Of Coronary Heart Disease



there is now impressive evidence that smoking acts as a powerful pro-oxidant which affects membrane function and enhances the oxidation of lipoproteins. Oxidised lipoproteins are effective experimental inducers of the sub-endothelial microphage mediated proliferative process which is considered to underly atherosclerosis[8]. In smokers, vitamin E is destroyed in the lungs by the impact of an estimated 10^{14} free radicals inhaled with each puff of a cigarette; vitamin C catabolism is also markedly enhanced in smokers and the membrane changes can be reversed by giving smokers supplements of vitamin E[9]. Smoking is also a much greater risk factor for CHD in Northern Europe than in the Mediterranean countries[10]. A plausible explanation for this difference relates to the abundant intake of vegetables and fruit in Mediterranean populations which may well combat the pro-oxidant effects of smoking[11]. The antioxidant intake in France and Switzerland is derived from an unrecognised high intake of α-tocopherol (the biologically active form of vitamin E, obtained from sunflower oil consumption)[12].

These observations do not deny the fundamental causal role of cholesterol-rich, low density lipoproteins in the development of atherosclerosis as shown by Goldstein and Brown's work[13] who showed that a single amino acid change in the hepatic LDL receptor impairs its function and can lead to a complete absence of effective hepatic clearance of circulating LDL. In children with familial homozygous hypercholesterolaemia, CHD develops by five to 10 years of age, which is proof of the causal role of high LDL cholesterol with poor LDL clearance in CHD. Nevertheless, high cholesterol levels, hypertension and smoking only account for 50 per cent of the observed variance in CHD, so the problem is to determine those additional factors in non-smoking, non-hypertensive South-east Asians which make them so particularly susceptible to CHD.

Most epidemiological studies fail

to provide any firm evidence that certain ethnic groups are unduly susceptible to CHD. Migrant studies amplify the importance of environmental factors since the migrants tend to acquire the CHD rates of their new country as they adopt the new lifestyle.

GENETIC FACTOR

There are two possibilities for the genetic clustering of genes which might amplify the risk of CHD in Indians.

First, the incidence of maturity onset diabetes of the young (MODY) is appreciably greater in Indians studied, for example, in South Africa[14] and a genetic linkage with a mutation in mitochondrial DNA has recently been proposed[15]. Nevertheless, the problem of MODY is not sufficiently prevalent to account for the widespread susceptibility of Indians to CHD[16].

More important, perhaps, is the possibility that Indians have a high frequency of Lp(a) which is a genetically inherited mutant of plasminogen. In western societies there is great variability in the inheritance of Lp(a). The assay for Lp(a) is difficult because different individuals have a variable number of copies of the kringles found in their plasminogen.

When susceptible people induce additional Lp(a) synthesis by consuming the trans-fatty acids from margarines, the Lp(a) blocks the plasminogen receptor, thereby impairing the generation of plasmin. Plasmin is now also known to promote fibrinolysis and reduce the TG_{β} induction of atherosclerosis[17]. Thus, if Indians eat a margarine or perhaps a *ghee*-rich diet and have a high prevalence of Lp(a)-related genes, then this would be one relatively simple explanation for their additional susceptibility to CHD.

MATERNAL NUTRITION

Alternative explanations have been considered *in extenso* by McKeigue and his colleagues[4] who suggest that insulin resistance linked to abdominal obesity is a special feature of Asians who frequently display 'syndrome X', that is, abdominal obesity, hypertension, diabetes and heart disease with insulin resistance. Hales and Barker have recently suggested that this syndrome may be programmed by changes in maternal nutrition[18]. Limited pancreatic β-cell replication in the foetus, they suggest, may account for the more rapid emergence of diabetes as the offspring age. However, other evidence suggests that the first sign of susceptibility to abdominal obesity, hypertension and diabetes is peripheral insulin resistance[19]. So the issue perhaps should be one of whether insulin resistance, rather than poor insulin secretion, is the primary feature induced by foetal malnutrition. I believe it is now possible to link Edwards' hypothesis on the foetal basis of adult hypertension [20] with Bjorntorp's analysis[21] of the importance of psychological stress in determining central adiposity.

It may be proposed that the low protein content of the rice-based Indian diets eaten by Indian mothers leads to a fall in placental 11 β-glucocorticoid dehydrogenase activity and this leads to an excessive transfer of maternal cortisol into the foetal circulation. Experiments in rodents show that this sequence leads to the offspring developing hypertension[22]. Why hypertension develops remains unclear, but it is now important to study the impact of low protein diets on the genetic expression of renal endothelin-I since the renal excretion of endothelin-I has been recently linked to salt-responsive hypertension as well as pregnancy toxaemia in adult humans[23]. An excess of corticosteroids is well known to alter the developmental expression of enzymes in the gut, so a plausible mechanism may be revealed for cortisol mediated renal endothelin-I programming *in utero*.

If we assume a greater foetal exposure to cortisol in maternal malnutrition, then the early postnatal morbidity of severely underweight-for-dates babies may relate to relative cortisol deficiency. If the foetus is already programmed to maintain a higher circulating cortisol level than normal once postnatal adjustments have been made, then this could entrain other metabolic changes. Excessive cortisol production postnatally will, in the long term, engender insulin resistance as soon as environmental factors are conducive to this. Excessive corticosteroids are already recognised to induce abdominal obesity in man along with insulin resistance and a propensity to diabetes. Insulin resistance itself also amplifies the risk of cardiac arrhythmia as well as changing the thromboxane/prostacyclin balance by reducing the rate of desaturation of the essential fatty acids (EFAs) of both the n-6 and n-3 series. These EFAs are already in short supply in many Indian diets and hence atherosclerosis, thrombosis and cardiac arrhythmias could be promoted in these individuals prone to insulin resistance. McKeigue finds insulin resistance with abdominal obesity the single most important feature of the excess susceptibility of South-east Asians to diabetes and CHD[4]. Bjorntorp and his colleagues have now demonstrated that the physical and psychological stresses of pain and mental arithmetic lead to greater increases in plasma cortisol in subjects with abdominal obesity and these individuals also show a greater cortisol response to a standard test dose of an ACTH analogue [21]. Primates also show the development of adrenal hyperplasia and excess coronary atherosclerosis[24] under psychological stress. Evidence from the UK suggests that disproportionate growth *in utero* is also linked to the development of abdominal obesity in adulthood, so a coherent metabolic picture is beginning to emerge.

Thus, the issue to be established is whether corticosteroid responses are greater in South-east Asians who have inappropriate foetal development and to assess whether they display these features before the emergence of other evidence of insulin resistance, for example, glucose intolerance and CHD. Clearly the distinction between the induction of hypertension and of CHD has to be recognised because of the extraordinarily high levels of hypertension but low CHD rates in other rice-eating areas, such as Japan and China. However, these differences may reflect the important impact of differences in salt and fat consumption in populations equally susceptible to 'syndrome X', if the dietary conditions are conducive to weight gain.

OTHER DIETARY FACTORS

It has been observed that Indian women produce small babies, particularly when they have a body mass index (BMI) below 18.5; half the babies produced by women with a BMI less than 16.0 — that is, about 10 per cent of the Indian population — weigh less than 2.5 kg[25]. Godfrey has also found maternal anaemia to be powerfully associated with increased placental/foetal weight ratios[26] and Indian women have high rates of anaemia. Koletsko has observed high trans-

fatty acid levels in the blood of mothers producing small-for-date and premature children and has found high trans-fatty acid levels in foetal blood with evidence of EFA deficiency[27]. Dutta-Roy has discovered an EFA transport system with which trans-fatty acids compete markedly, so margarine or *ghee* eating by Indian mothers may exacerbate their problem of foetal growth[28]. More intriguing is the observation that Indian girls marry early and consummate their marriage at a time when they have not completed their pubertal growth. Experimental studies on sheep at the Rowett Research Institute, UK, (sheep being the recognised experimental model for human foetal development research) suggest a profound degree of competition for nutrition by the young pubertal female whose own tissues compete for nutrients with the placental-foetal axis. The relationship of IgF_1, to pubertal growth[29] and the induction of IgF_1 by feeding will normally tend to promote the maternal deposition of proteins. This could then take preference over foetal transfer (J. Wallace, personal communication). Thus, young Indian girls may well be particularly susceptible to producing small babies with a high placental/birth-weight ratio because in addition to their low protein intake they enter pregnancy with low body reserves as indicated by their low BMI and then compete with their own foetus for nutrients.

CONCLUDING COMMENT

None of these hypotheses can be seen as anything other than the bringing together of a wide variety of observations from many different disciplines. They do not deny the importance of many of the currently well-recognised factors involved in promoting diseases of affluence. But we do now have new ways of tackling the basis for Asian susceptibility to coronary heart disease. If some of these factors prove to be significant it will add urgency to our long-standing emphasis on improving the health of young women before as well as during pregnancy.

Foundation Day Lecture delivered at NFI on November 23, 1994.

The author is Director, Rowett Research Institute, UK.

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NUTRITION NEWS

● Dr C. Gopalan gave the Academy Oration titled 'Expanding Frontiers Of Nutrition Science' at the Annual Conference of the National Academy of Medical Sciences on March 18, 1995 at Madras.

● Dr Vinodini Reddy retired from her post as Director, National Institute of Nutrition (NIN), Hyderabad. Dr Reddy had served the NIN with commendable distinction and dedication for 34 years. She is shortly joining the Johns Hopkins University, USA, as Visiting Professor in International Health.