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'Late' Effects Of Foetal Undernutrition

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The subject of maternal health/nutrition is likely to acquire a new urgency and importance in the light of recent evidences that maternal malnutrition and consequent intrauterine growth retardation (IUGR) may have serious long-term implications, hitherto unsuspected. Earlier, it was thought necessary to ensure optimal maternal health/nutrition mainly in order to combat possible problems related to the mother and infant in the perinatal and immediate postnatal periods, such as increased risk of maternal and neonatal mortality and substandard growth in childhood.

There are now disturbing indications, so far largely based on epidemiological data, that the origin of major degenerative diseases such as diabetes and coronary heart disease in adults, may in fact be traced to IUGR arising from poor maternal nutrition during pregnancy. Wider recognition of this at the policy-making levels must obviously result in major shifts in public health policies and strategies.

To be sure, evidence in this regard is, thus far, epidemiological and 'circumstantial'. There is, undoubtedly, a need for a great deal more critical research and more extended observations in this area by independent groups before the claims find universal acceptance.

Review of evidences: Before we go on to a consideration of the evidences suggestive of possible late effects of foetal undernutrition, it may be useful to start with a review of the elegant epidemiological studies of the last two decades, notably those carried out by McKeigue and colleagues, pointing to the strikingly greater vulnerability of Indian migrants to foreign countries to coronary heart disease and diabetes, as compared to Europeans and other ethnic groups[1]. These studies do not attribute such increased vulnerability to IUGR; they nevertheless could provide a strong link in the chain of overall evidence, and lend added meaning to the studies discussed later, significantly linking IUGR with major degenerative diseases in adult life.

Syndrome X (insulin resistance syndrome): Epidemiological studies in different parts of the world during the last two decades, notably those carried out by McKeigue and his colleagues on Asian migrants, had shown that mortality from coronary heart disease in men and women of South Asian origin was higher than in other ethnic groups; and that this cannot be attributed to higher smoking rates or higher intakes of saturated fats [2,3,4]. Non-insulin-dependent diabetes has also been found to be much more common in South Asians overseas, for example, 20 per cent in Asian men and women aged over 40 years in the United Kingdom as compared to 5 per cent in Europeans[2]. Since a high proportion of South Asian patients with coronary heart disease have been found to be non-diabetic, increased prevalence of glucose intolerance alone cannot explain the increased coronary risk.

It has been postulated that the increased risk of diabetes and of coronary heart disease are both part of a syndrome — syndrome X[5], the central feature of which is insulin resistance. The other features of the syndrome are hyperinsulinaemia, hypertriglyceridaemia, low concentration of high density lipoprotein (HDL) and hypertension. Resistance to insulin-stimulated glucose uptake, leading to glucose intolerance and hypertension, and failure of insulin to suppress release of non-esterified fatty acids from adipose tissue, leading to hypertriglyceridaemia and low HDL, are believed to be the central biochemical defects. Insulin resistance in this syndrome is also prominently associated with a pattern of obesity in which a high proportion of body fat is deposited intra-abdominally — central (abdominal) obesity. Elevated waist to hip ratio reflecting abdominal obesity is found strongly correlated with glucose intolerance[6].

Though these observations have largely been made on Indian migrants in foreign countries, they now have increased relevance to Indians in

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India. The observations of Ramachandran *et al*[7] from South India, and of Chadha *et al*[8] from North India, go to show that diabetes and coronary heart disease are now emerging as major public health problems in India's urban population. Clearly the recent escalation in the incidence of coronary heart disease and diabetes among India's urban middle class is one of the effects of the ongoing developmental transition.

The reported remarkable differences in the prevalence of coronary heart disease as between urban Delhi and its rural environs[8], would suggest that the proneness of Indians to syndrome X probably finds expression in conditions of relative affluence — associated with migration to urban areas or to foreign lands. Since urban migration is bound to gather further momentum in the years ahead (at least one-third of India's population is expected to live in urban areas by the turn of the century), and since there is bound to be (hopefully) a progressive ascent in our country, from poverty to affluence, the problem is bound to acquire greater dimensions in the future. It, therefore, becomes extremely important to identify the factor(s) responsible for the proneness of a large proportion of Indians to syndrome X and not to dismiss it as probably a genetic trait.

It is in this context that the results of studies linking IUGR with increased risk of coronary heart disease and diabetes with syndrome X need to be examined. These studies would suggest that syndrome X could very well be the late effect of maternal nutritional deprivation during critical phases of foetal growth. From the point of view of public health in India, this is an important lead. Should this turn out to be true, then the strategies for the prevention of coronary heart disease and diabetes, as far as India is concerned, would be different from those being promoted and pursued in Europe and America — not emphasis on reduction of intake of saturated fats (the intake of which in any case is not unduly high in Indian diets) but on improved maternal nutrition in order to combat IUGR and low birth weights in the offspring.

Barker *et al*'s studies: There have been numerous observations on experimental animals over the last several decades clearly indicating that deprivation of different nutrients at different critical points of time during foetal growth could bring about permanent anatomical and physiological damage to a range of organs and tissues in the offspring [9,10,11,12]. The timing and nature of nutritional deprivation during gestation were important in determining the type of damage. These earlier observations on experimental animals had not excited much interest among those interested in human health and disease, largely because their relevance to humans was not clear. With the recent studies, notably those by Barker and his colleagues, these earlier observations on experimental animals have acquired a new meaning and relevance.

Barker *et al*'s initial studies were carried out in the United Kingdom on 1,586 men born in a maternity hospital in Sheffield during 1907-1925[13], and on 5,654 men born in Hertfordshire during 1911-1930[14]. These studies became possible, apparently because of the meticulous care with which records in these hospitals were entered and preserved. Barker is now extending his studies with data being gathered from two Indian hospitals — one in Pune and the other in Mysore.

Barker *et al*'s major observations are briefly listed below. No attempt will be made here to discuss their several other conclusions and the hypotheses that they offer in explanation of their interesting findings. As was pointed out earlier, further independent studies would be necessary to establish the validity of these far-reaching conclusions.

- Standardised mortality rates from coronary heart disease were three times higher (111) in men who had weighed 18 lb (8.2 kg) or less at one year of age than in those who had weighed 27 lb (12.3 kg) or more (42) at one year of age[14]. The association of increased mortality from heart disease with low birth weight was less strong than with low body weight at one year of age in the case of men, suggesting that increased risk of coronary heart disease associated with low birth weight may, to a certain extent, be minimised through improved weight gain during infancy, in the case of men. Curiously enough, in the case of women, risk of high cardiovascular mortality was more strongly associated with low birth weight rather than with weight at one year of age. The reason for this sex difference is not known.

- The prevalence of diabetes and impaired glucose tolerance fell from 27 per cent in subjects who had weighed 5.5 lb or less at birth to 6 per cent in those who had weighed 7.5 lb or more. It is postulated that in IUGR, development of endocrine pancreas is impaired and β cell mass is reduced as evidenced by high concentration of 32-33 split proinsulin in adult life[15]. If this is followed by attrition of β cell mass through ageing and insulin resistance, then insulin-dependent diabetes could develop.

- The prevalence of syndrome X fell from 30 per cent in men who weighed 5.5 lb or less at birth to 6 per cent in men who weighed 9.5 lb or more[16]. Low birth weights were associated with thinness, reduced mid-arm circumference and low ponderal index. It is postulated that low birth weight and thinness at birth are associated with abnormalities in muscle structure and function, and that this is the major cause of insulin resistance. Muscle biopsies have shown that insulin resistance is associated with a low density of capillaries in muscle, a lower proportion of type 1 muscle fibres and a greater proportion of type 2B muscle fibres[17].

These observations read along with those of McKeigue *et al*, will indicate that syndrome X, commonly prevalent in migrant and relatively affluent urban Indians, may not be a genetic trait but the possible results of IUGR. Barker *et al*'s subjects, who showed association of syndrome X with low birth weight, were Englishmen — not Indians. With one-third of all births in India falling in the low birth weight category (a majority of them SGA), it is to be expected that the late effects of IUGR will be more frequently seen in the relatively affluent Indian urban middle class.

- While IUGR of the *symmetric type* characterised by thinness, reduced head circumference, reduced mid-arm circumference and low ponderal index, attributable to maternal nutritional deprivation in mid-pregnancy, is associated with vulnerability to syndrome X, IUGR of the *asymmetric type*, attributable to nutritional deprivation in late pregnancy and characterised by normal head circumference, shortness and low abdominal circumference at birth, is associated with increased risk

of coronary heart disease in adult life — raised plasma concentrations of fibrinogen and low-density lipoprotein cholesterol[18].

A NOTE OF CAUTION

The observations and claims briefly set out above are undoubtedly important and challenging. But acceptance of these claims in toto in the present state of our knowledge, could be premature and unwise. The evidence thus far, while being quite persuasive, is by no means conclusive.

Precisely for the reason that the above observations of Barker *et al* and the connected hypotheses have far-reaching implications with respect to public health practice, they will need confirmation and critical validation through other *independent* studies carried out by *different* teams of workers with epidemiological expertise, before they find general acceptance. Recent epidemiological observations from Sweden[19,20] and Finland[21] run contrary to Barker *et al*'s conclusions.

What Barker *et al* have observed so far is no more than an *association* between IUGR and vulnerability to some degenerative diseases *in those locations where their studies had been carried out*. The question that first needs to be answered is whether a similar association is demonstrable in other locations and in other environments as well. Secondly, *association* of two factors need not necessarily signify *a cause and effect relationship*; more evidence will be needed to establish such a claim.

Barker *et al* postulate that the susceptibility of babies who start off with a low birth weight (small-for-date) to such diseases as diabetes, and coronary heart disease is the result of their being 'programmed' *in utero* 'in response to an adverse environment'. It is not clear as to how a 'programming process' which confers increased vulnerability to degenerative diseases is a 'response to an adverse environment'. A simpler (if less profound) explanation could be that the deprivation of essential nutrients to the foetus in critical phases of intrauterine growth could result in different types of organ and tissue damage, the deleterious results of which could manifest in later life. This is perhaps what Barker *et al* actually mean. Reduced child mortality, increased longevity and rising affluence, brought on by the ongoing developmental transition, could have made such late manifestations increasingly possible, especially among the urban middle class.

It is also agreed that the results of foetal damage may become manifest in adult life only where 'amplifying' factors are present in the environment. It will, therefore, be as important to identify and combat these 'amplifying' factors as it will be to prevent IUGR in the first instance through ensuring optimal maternal nutrition.

The postulate of "being programmed *in utero*", could carry the connotation of preordained inevitability — almost like the Hindu doctrine of *Karma*! From available data, it would appear that among millions of poor subjects born with low birth weights in developing countries, who grow and develop into adulthood and who continue to live under hard conditions of relative deprivation, the incidence of degenerative diseases, including coronary heart disease, is actually much less than in the affluent populations of developed countries and in the affluent sections of populations of their own (developing) countries. This would suggest that the 'amplifying factors' in the environment are far more important determinants of the vulnerability to degenerative diseases than IUGR.

It is tempting to draw the inference from these observations that those born in poverty and subject to IUGR, but who acquire affluence in adult life and adopt lifestyles characterised by the excesses and errors of the 'rich', are more vulnerable than those who are born 'poor' and remain 'poor'; or those who are born 'rich' but are careful to avoid unbridled consumption and stressful lifestyles in their adult life. If this inference is justified, then our goal must obviously be to ensure that our future citizens fall in this last category, that is, they start their life's journey without the initial disadvantages of IUGR, and that in later adult life, they avoid the pitfalls of unbridled affluence. Victims of IUGR may be less well-equipped than those starting with good birth weight, to withstand the deleterious effects of environmental 'amplifying factors' in adult life.

However, the Finnish study[21] mentioned above does not seem to support the above inferences. According to the Finnish study, upward socio-economic mobility was not associated with increased risk of coronary heart disease; indeed, the risks appeared greatest in those who started low and remained low in their socio-economic level. But then, 'upward socio-economic mobility' and 'low socio-economic status', as understood in Finland and India, could be widely different in their order and attributes. The starting point of 'upward mobility' in Finland may well be above the poverty line, unlike in India. Upward mobility in Finland could thus mean an ascent from affluence to superaffluence, not one from poverty and deprivation to affluence as in India. Even among communities of 'low socio-economic status' in Finland, it is doubtful if the incidence of low birth weight deliveries is ever as high as in India. These conflicting signals underscore the need for caution at this stage and for collection of more data before major conclusions with respect to public health policy become justified.

Finally, it must be pointed out that the importance of IUGR (and LBW) as a major public health problem does not rest on the relatively new claims with respect to the late effects of IUGR discussed above. The effects of IUGR on child growth and development, which are proven and well established, are serious enough to merit deep concern. Even if IUGR had no 'late' effects, it would still be a major public health problem. The observations on possible late effects discussed here have only served to reveal yet another, possibly even more sinister and ominous, dimension of the problem.

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