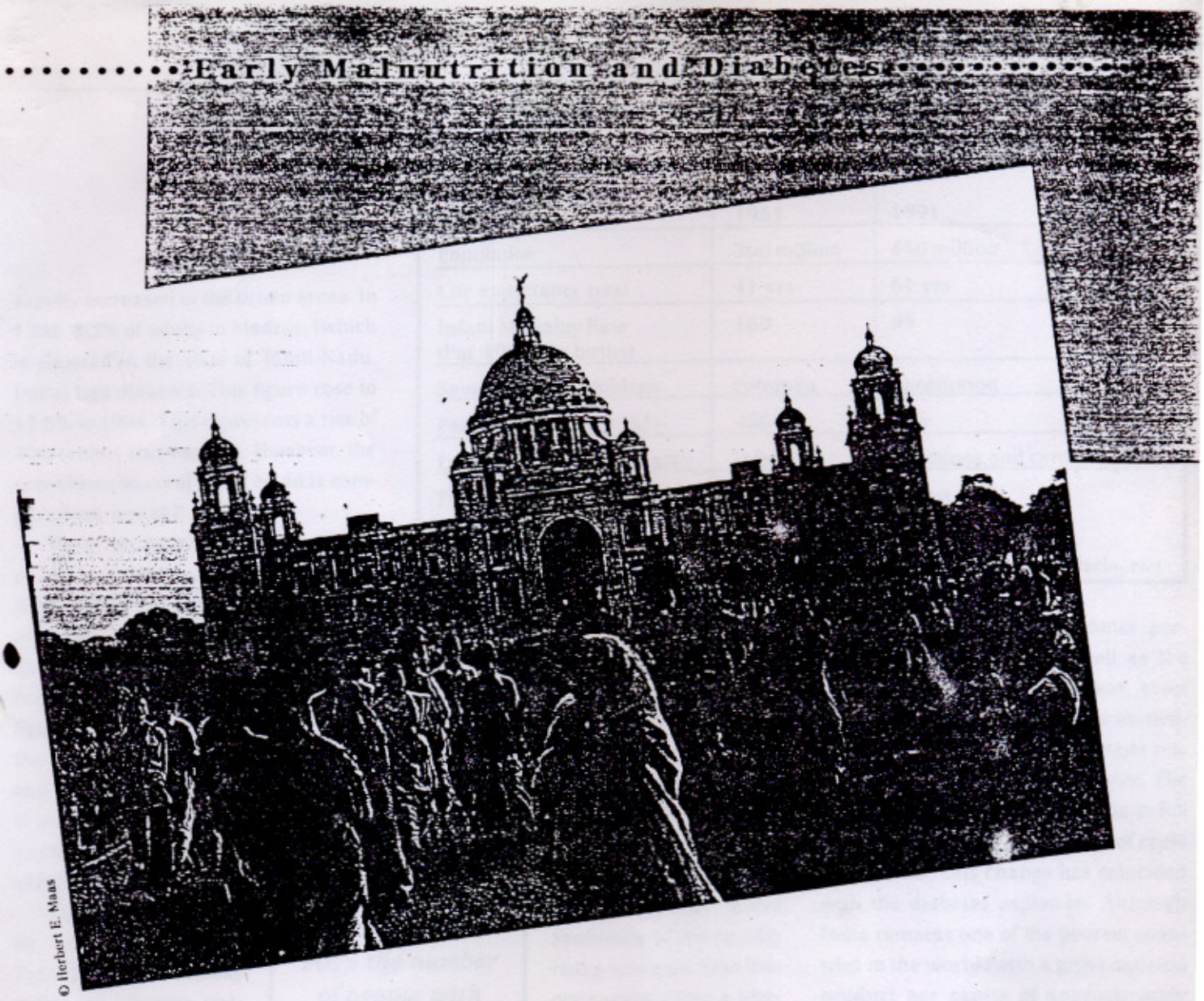


The Insulin Resistance Epidemic in India: Small at Birth, Big as Adult?

Dr CS Yajnik

The Spreading Epidemic of Diabetes in India and other Developing Countries

Not long ago Type 2 diabetes, as well as Coronary Heart Disease (CHD), were considered problems of the affluent obese in the Western world. However, the last 3 decades have seen a rapidly increasing epidemic in the developing countries as well. In 1975, a survey carried out by the Indian Council of Medical Research showed that in India, 2.3% of the urban adults and 1.5% of the rural adults had diabetes (1). Since then, the clinical burden of this condition has

Table 1.
Vital Statistics of India.

	1951	1991
Population	360 million	850 million
Life expectancy (yrs)	41 yrs	61 yrs
Infant Mortality Rate (Per 1000 live births)	160	95
Severe PEM in children	common	uncommon
Per capita income (US$)	<50	365
Leading causes of mortality	Infections	Infections and cardiovascular
Prevalence of diabetes in adults	Urban<1.5% Rural <1%	Urban 8.5% Rural 2.5%

PEM = Protein Energy Malnutrition (kwashiorkor, marasmus, keratomalacia, *etc*)

rapidly increased in the urban areas. In 1988, 8.2% of adults in Madras, (which is situated in the state of Tamil Nadu, India) had diabetes. This figure rose to 11.6% in 1994. This represents a rise of 40% within six years (2). However, the prevalence in rural Tamil Nadu is comparatively low at 2.4%.

Today an estimated 18-20 million people in India have diabetes. It is projected that by the year 2025 the number of people with diabetes in the world will double, rising from a figure of 120 million to 250 million. Of this figure, 75% will be from the developing countries and the largest number of people with diabetes in any single country will be in India (3).

The clinical profile of an average Indian with Type 2 diabetes usually defies the Western textbook descriptions (4). At diagnosis, they are a decade younger, shorter, considerably thinner (particularly in the limbs) but centrally more obese (see Figure 1). Surprisingly, despite their thinness, Indians are more insulin resistant and hyperinsulinaemic. Metabolic components of the 'insulin resistance syndrome', *ie*, high circulating triglycerides and a low level of high-density-lipoprotein cholesterol (HDL-cholesterol), are prominent in Indians, thus increasing their risk of CHD. Such a profile raises questions about the possible determinants of Type 2 diabetes in India and other developing countries.

Today an estimated 18-20 million people in India have diabetes. It is projected that by the year 2025 the number of people with diabetes in the world will double, rising from a figure of 120 million to 250 million. Of this figure, 75% will be from the developing countries and the largest number of people with diabetes in any single country will be in India.

Genes, Environment, Early Malnutrition, or a Combination?

The high susceptibility of Indians to Type 2 diabetes is largely unexplained and we remain mute spectators to the rapidly rising epidemic. One theory suggests that a phenomenon we call the 'thrifty genotype' may be responsible, *ie*, genes once evolved to help store energy in the 'hunter-gatherer' societies of long ago, that tend to cause obesity and insulin resistance in the present modern days of plentiful food and reduced physical activity. Although no such genes have yet been specifically identified, it remains a useful teleological concept. Perhaps the only way to counter the detrimental effects of these genes would be to revert to the ancient way of life. On the other hand, the extreme rapidity with which the rise in diabetes prevalence has occured, as well as the statistical urban-rural gradient, overwhelmingly suggests that environmental determinants are playing a major role in this diabetes and CHD epidemic. The environmental situation in India is full of paradoxes and is in the midst of rapid change, and this change has coincided with the diabetes explosion. Although India remains one of the poorest countries in the world (with a gross national product per capita of approximately $350) there have been substantial socioeconomic achievements since independence (Table 1). The 'green revolution' has made the country self sufficient in food production.

Nevertheless, undernutrition still prevails, but this is now largely due to inequitable distribution. Today 70% of Indians live in villages and are chronically energy deficient, with a mean Body Mass Index (BMI) of 19.5 kg/m^2. Also, the population has swollen to over 900 million, with an ever increasing rate of urbanization where large numbers of villagers are migrating to cities in search of jobs, and often end up living in crowded slums and squalid conditions.

The fact that the urban lifestyle is fast becoming 'westernized' also adds to the problem. The intake of fast food is increasing, causing people's fat-intakes to

increase beyond acceptable levels. Rapid mechanization and advancement in technology have both served to reduce the general level of physical activity. Environmental pollution is also playing havoc. As a result of all these changes, the country is faced with a double burden of diseases: communicable and non-communicable. Communicable diseases become rife where the living conditions are less hygienic, and non-communicable diseases come as a result of westernization. In cities, the brunt seems to be borne by the lower and middle class people.

Having said all this, one should add the number of cases of the extreme protein-energy malnutritional conditions known as kwashiorkor and marasmus has fallen considerably. Control of many deadly infections and improved health practices have reduced childhood mortality and increased life expectancy. This has increased the size of the population susceptible to non-communicable diseases.

Another suggestion for the epidemic lies in the recently proposed 'thrifty phenotype' hypothesis, which ascribes adult diabetes to nutritional disturbances in the few days of gestation (5). There exists considerable data from different parts of the world which supports a link between intra-uterine growth pattern and adult diabetes, as well as CHD. Maternal nutrition in India is amongst the poorest in the world and Indian babies are amongst the smallest.

The high susceptibility of Indians to Type 2 diabetes is largely unexplained and we remain mute spectators to the rapidly rising epidemic.

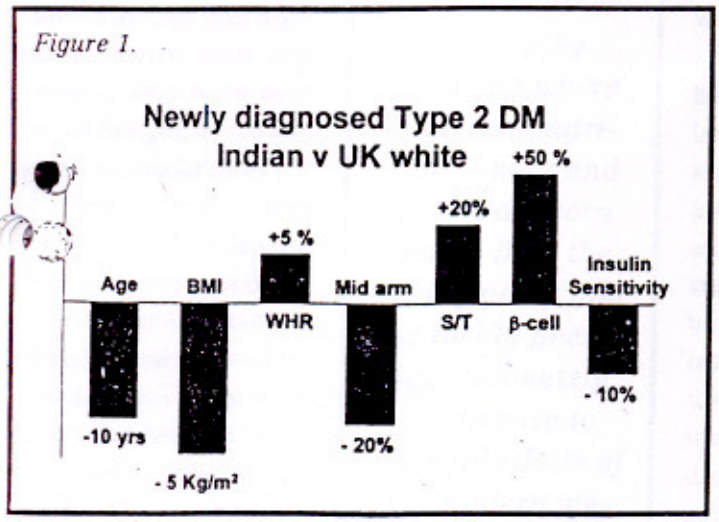
A third of Indian babies are born with low birth weight (<2500 g) mostly due to disproportionate intra-uterine growth retardation (IUGR). A priori, 'thrifty phenotype' could be responsible for the Indian epidemic of the insulin-resistance syndrome. If proven, it would have profound implications for the prevention of diabetes and CHD in the developing countries.

Indian Studies of the 'Thrifty Phenotype'.

In India, birth records are poorly kept, so tracing individuals is difficult. Health files are practically non-existent and death registers particularly inadequate. Therefore, cohort studies of the type which led to the 'thrifty phenotype' hypothesis are difficult. Up till now, only three formal studies in India have been done to investigate the 'thrifty phenotype'.

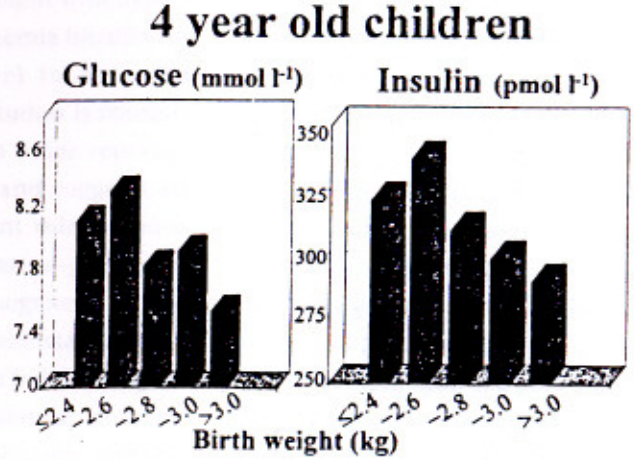
In collaboration with Professor Barker and his team, we studied children born at the K.E.M. Hospital, Pune. At four years of age, circulating glucose and insulin concentrations 30 minutes after an oral glucose load were related inversely

Figure 1.



Characteristics of newly diagnosed Type 2 people with diabetes from India compared to those from the UK (White). Based on many sources. Not drawn to scale. Bars above the line suggest higher values in Indians. BMI=Body Mass Index, WHR=Waist-Hip-Ratio, Mid arm=Mid arm circumference, S/T=Subscapular / Triceps skinfold ratio. b-cell & Insulin sensitivity calculated from HOMA model.

Figure 2.



Plasma glucose and insulin concentrations 30 minutes after oral glucose by birth weight categories. At four years of age, both glucose and insulin concentrations fall with increasing birth weight.

the life of scarcity in utero. This is the basis for the adaptation-dysadaptation hypothesis of insulin resistance and diabetes (10). This explains the high risk of diabetes in India (and other developing populations) at a relatively low BMI (not obese by 'international' criteria). Being small at birth predisposes to diabetes and the subsequent 'overgrowth' brings on diabetes later in life.

Premature deaths due to undiagnosed diabetes and CHD are a major concern in India. Previous studies on the 'thrifty phenotype' are inadequate due to the absence of reliable mortality data, which can seriously affect our conclusions and mislead us in our preventive strategies. Answers to many such vexing questions will come only from prospective studies. In collaboration with Professor Barker we have initiated a prospective study involving mothers of six villages near Pune, as to the relationship of maternal nutrition before and during pregnancy with the pattern of babies' growth in utero and the phenotype at birth. These babies will be followed-up to study cardiovascular risk factors and disease pattern in later life. Already, the preliminary analysis of the mater-foetal relationships in India in comparison to Professor Barker's findings have given surprising results.

The rural Indian mothers were small and thin and babies born to these mothers were small in all respects compared to the white Caucasian babies (see Table 2). There was a pattern in their smallness, suggestive of a differential body building in utero. An average Indian newborn weighed only 77% of an average Western baby but the brain (head) and skeletal (length) growth was substantially preserved, as was body fat, at approximately 95%. The major deficit

© Herbert E. Maas

Being insulin resistant from an early age predisposes to diabetes.

occured in non-fat soft tissues like the abdomen (at 86 % that of Caucasian babies) and the muscle content (84 % that of the Caucasian babies). This suggests that besides the obligatory preservation of brain and skeleton, a malnourished foetus favours adipose tissue deposition at the expense of muscle and abdominal viscera (including liver, pancreas and kidneys). In metabolic terms lipogenesis rather than structural protein synthesis was favoured in the small babies of small mothers. Such metabolic adaptations could have profound implications for the development of insulin resistance (muscle and adipose tissue are main players in this game). The adult Indian phenotype, thin but centrally obese, appears to be a continuation of the body composition at birth, and this is exaggerated in those that develop Type 2 diabetes (11). Poor development of the liver, pancreas and kidneys could be a highly relevant factor in the occurrence of a number of disorders in later life. Metabolic imprinting could also provide an explanation for the interesting phenomenon of 'ketosis resistance' in malnourished people with diabetes (the so-called malnutrition-related diabetes, MRDM) (12).

Premature deaths due to undiagnosed diabetes and CHD are a major concern in India.

To conclude, the ever increasing epidemic of diabetes (and CHD) in the developing world remains unexplained. If thrifty genes are responsible we know little about them. The 'thrifty phenotype' is the exciting new explanation which could be very relevant to India and other developing countries where maternal nutrition is poor and babies are born small. Both the thrifty genes and the thrifty phenotype ultimately predispose to harmful effects

of the modern lifestyle especially obesity. Infections, atmospheric pollution and psychosocial stress, three major accompaniments of urbanization, could also have important roles to play in this epidemic.

Which ever way, the health of young women and mothers may well become important targets for prevention of diabetes and CHD in near future. Perhaps Mahatma Gandhi's vision of a self-sufficient rural India supported by the 'spinning wheel' would appear more appropriate than the 'automobile' (not to mention 'atomic') model of development borrowed from the West.

GLOSSARY

Coronary Heart Disease
This is the name given to any disease of the coronary arteries. Coronary heart disease causes strain on the heart.

Insulin Resistance - is a condition which leads to Type 2 diabetes and obesity, in which the body fails to respond to insulin. As a result, food cannot be properly converted to energy. To compensate for this, the pancreas produces excess amounts of insulin. Therefore, insulin resistance is usually diagnosed by the detection of elevated insulin levels, as well as elevated blood-glucose levels.

After a time, the pancreas cannot continue to produce insulin at such a high rate, and ultimately fails. Blood sugar levels then rise. At a certain point, the condition is no longer considered to be insulin resistance, but fully-fledged Type 2 diabetes.

Both genetic and environmental factors are involved in the onset of insulin resistance. Of the environmental factors, smoking, a sedentary lifestyle, and obesity are the biggest players.

ß-cells - the insulin-producing cell found in the Islets of Langerhans in the pancreas.

References:

1. Ahuja MMS (1979) Epidemiological studies in diabetes mellitus in India. Interprint: New Delhi.

2. Ramchandran A, Snehlata C, Latha E, Vijay V, Viswanathan M (1997) Rising prevalence of NIDDM in an urban population in South India. Diabetologia: 40: 232-237.

3. King H (1997) Diabetes mellitus: a growing international health care problem. Int Diab Monitor: 9: 1-6.

4. Mohan V, Alberti KGMM (1997) Diabetes in the tropics. In: International Textbook of Diabetes Mellitus: 2nd ed. Alberti KGMM, Zimmet P, Defronzo RA, Keen H, Wiley (1997).

5. Hales CN, Barker DJP (1992) Type 2 (non-insulin dependent) diabetes: the thrifty phenotype hypothesis. Diabetologia: 35: 595-601.

6. Yajnik CS, Fall CHD, Vaidya U, Pandit AN, Bawdekar A, Bhat DS, Osmond C, Hales CN, Barker DJP (1995) Fetal growth and glucose and insulin metabolism in four-year old Indian children. Diab Med: 12: 330-336.

7. Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, Barker DJP (1996). Fetal growth and coronary heart disease in South India. Lancet: 348: 1269-1273.

8. Fall CHD, Stein CE, Kumaran K, Cox V, Osmond C, Barker DJP, Hales CN (1998) Size at birth, maternal weight and Type 2 diabetes in South India. Diabetic Medicine: (in press).

9. Reaven GM (1988). Role of insulin resistance in human disease. Diabetes: 37: 1595-1607.

10. Yajnik CS (1995). Diabetes and Insulin Resistance in Indians. Bulletin of the Nutrition Foundation of India: 16: 1-5.

11. Shelgikar KM, Hockaday TDR, Yajnik CS (1991). Central rather than generalised obesity is associated with hyperglycemia in Asian subjects. Diab Medicine: 8:712-717.

12. Yajnik CS, Sardesai BS, Bhat DS, Naik SS, Raut KN, Shelgikar KM, Orskov H, Alberti KGMM, Hockaday TDR (1997) The ketosis-resistance in fibro-calculous pacreatic diabetes 2. Hepatic ketogenesis after oral medium chain triglycerides. Metabolism: 46: 1-4.

What is Diabetes Mellitus?

There are two major types of diabetes mellitus: Type 1 [Insulin-Dependent Diabetes Mellitus (IDDM)], and Type 2 [Non-Insulin Dependent Diabetes Mellitus (NIDDM)]. Type 1 diabetes is caused by a destruction of the insulin-producing cells. Approximately 10% of all people with diabetes have this condition, which has to be treated with insulin. Type 2 diabetes is caused by a combination of decreased insulin-action (insulin resistance), and insufficient insulin production. The majority of people with diabetes belong to this group and are treated with diet, exercise and often with different blood-glucose-lowering drugs. Both types of diabetes have a genetic component.