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PERSPECTIVE

Crystal Ball Series

Confessions of a thin-fat Indian

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As an aspiring molecular biologist I learnt about the initiator codon AUG, the f-Met-tRNA and Nomura's ribosome cycle in 1970 [1] but little did I know that methionine would shadow me for the rest of my life! I was super excited about Jacob and Monod's Operon model which taught me how nutrition and environment could guide the genome to respond appropriately [2]. Low methionine status, hyperhomocysteinemia, vitamin B12 deficiency and the associated epigenetic foetal programming have dominated my research in the quest to understand the high susceptibility of Indians to diabetes [3]. Circumstances drove me to become a doctor rather than a molecular biologist in 1971.

My tryst with diabetes research began when I was training in Medicine at the Sassoon General Hospital, Pune. I was required to take nutritional history and measure body mass index of diabetic patients. The scales used measured weight in pounds and height in feet and inches. Unable to afford a calculator, I used a log table to calculate the body mass index (BMI) (kg/m^2). The first ten patients revealed that they were young and thin, unlike the textbook description of a diabetic as old and obese. Discussions with the boss resulted in a decision that passing the MD examination was a priority rather than challenging the dogma! After obtaining my MD, I applied to five leading diabetes centres in the United Kingdom, and just when I was ready to give up, Derek Hockaday offered me a registrar's position in Oxford. Later I learned that Sheikh Rashid of Dubai had generously donated to diabetes research in Oxford, and I was one of the beneficiaries.

In 1981, I arrived in Oxford which to me was the 'mecca of diabetes' in the United Kingdom. My biggest lesson to learn was that unless you frame a proper question, there won't be an answer. Interested in investigating the 'malnutrition-related' diabetes (MRDM) in Indians I tried to impress on Derek that even the WHO considered MRDM as a major class of diabetes [4]. He quipped, 'who's WHO to convince you about MRDM?' I learnt a whole lot of things in Oxford: patient care, clinical record keeping, and the newly described association between 'central' obesity, insulin resistance and diabetes. In addition, Edwin Gale introduced me to the world of dose response between insulin, glucose, fatty acids and ketones.

Things were gradually becoming clearer. I decided to spend a month in Pune to collect data on clinical characteristics and blood samples of Indian diabetic patients to compare with those in Oxford. This simple comparison clarified many things to me, but I did not write it up until many years later. Indian patients were younger, shorter and thinner, but had larger subscapular skinfolds compared to the English patients, and they also had higher insulin concentrations [5] (Fig. 1). It was a bit counterintuitive.

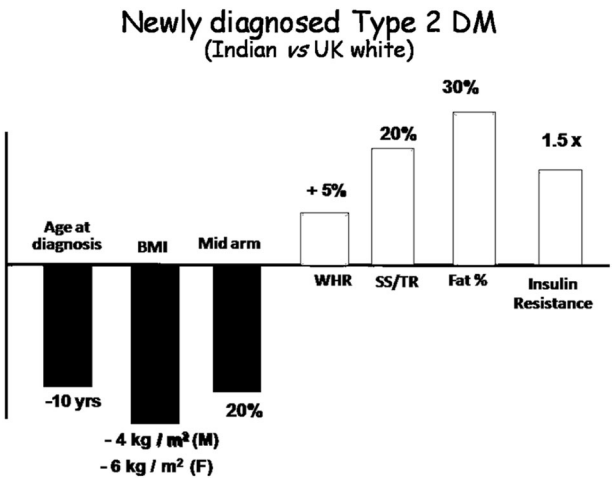

Fig. 1 Comparison of patients with type 2 diabetes from India and United Kingdom. Indian patients are diagnosed at younger age, have less generalized obesity and thinner limbs, but have a higher adiposity, higher central adiposity and are more insulin resistant (measured by the HOMA model) than patients from the United Kingdom. WHR, waist: hip ratio; SS/TR, subscapular:triceps skinfold thickness (Adapted from Yajnik et al. [5])

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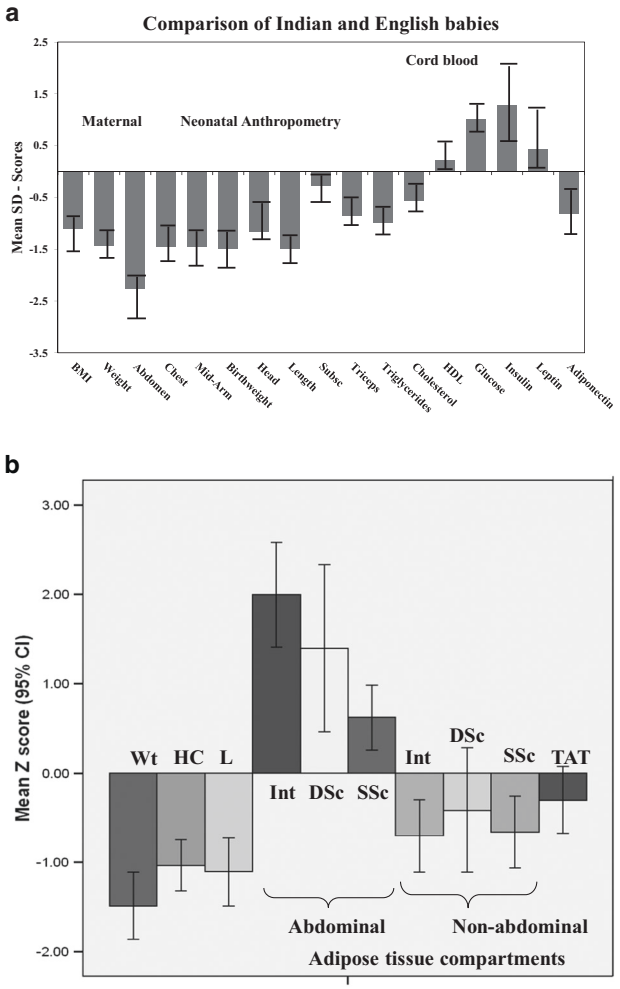

Z scores (mean ± 95% CI) for Indian Babies with white British babies as baseline

Fig. 2 Thin-fat Indian baby. **a** It shows the SD scores of different anthropometric measurements. Indian babies were 800 g lighter and smaller in all measurements but had almost similar subscapular skinfold (Adapted from Yajnik et al. [14]). **b** It shows whole-body MRI measurements of newborn Indian babies compared to English babies. All three compartments of abdominal fat are higher in Indian babies (Adapted from Modi et al. [17])

Explanation came soon. I was a 'volunteer' for some of the research studies in Oxford. The laboratory came back surprised because they found my insulin concentrations twice as high as that of Edwin Gale, who was 15 cm taller and 25 kg heavier, which contradicted the standard curve to be sure! After surviving a few radioactive infusions at the hands of David Mathew and John Hosker (CIGMA), I found myself in the unenviable position of being the most insulin-resistant diabetes doctor at the Radcliffe Infirmary. I was only 20 kg/m^2! Incidentally, the ever cycling Andrew Hattersley was the most insulin-sensitive. I put it down to karma and started pedalling around Oxford on a borrowed bike. When results of the Southall survey were reported at a British Diabetic Association meeting, it was no surprise to me that Indians had a much higher risk of diabetes compared to the local English folk [6]. As a result I declined an offer to do a PhD in Oxford; my destiny and destination was India.

I got a job as a pool officer of the Council for Scientific and Industrial Research (CSIR) at the BJ Medical College and the Sassoon Hospital. Soon, I started some studies in MRDM with support from Oxford, and made some useful observations. It was very gratifying to work in my alma mater, but it was not a place to set up long-term cohorts and studies. The CSIR would not transfer me to the KEM Hospital, it had to be facilitated by the then Prime Minister of India—Mr Rajiv Gandhi. I felt so fortunate. I was ready to set up my own research. Dr Bridget Ogilvie, the Director of the Wellcome Trust was intrigued that I was asking for help to settle in India rather than migrate. She persuaded Derek to visit Pune to confirm that I had the necessary infrastructure. He did, and in 1987 we launched the Wellcome Diabetes Study to 'characterize diabetes in Indians'. Soon after, we published the importance of central obesity (waist–hip ratio) over generalized obesity (BMI) as a risk factor for diabetes in Indians [7]. We described the associations of insulin resistance with cardiometabolic risk factors [8], and described the spectrum of exocrine–endocrine pancreatic involvement in different types of diabetes in Indians [9]. George Alberti and Paresh Dandona helped in every way.

Joe Hoet visited India as the President of the IDF and discussed his protein-deficient rat model with me [10]. He was very supportive of the idea that undernutrition in utero increased the risk of diabetes, and encouraged me to pursue the idea. On the other hand, Norbert Frienkel suggested that I study pregnancy metabolism and fuel-mediated teratogenesis of diabetes [11]. As a clinician I didn't know how, and thought it was for animal experts to sort this out.

Weaned on the 'thrifty genotype' and the 'fuel-mediated teratogenesis' ideas, I was shocked on a February morning in 1991 to hear from David Barker and Caroline Fall that low birthweight was a precursor to type 2 diabetes, hypertension and cardiovascular disease [12]. Instantly it dispelled my long-standing confusion. The thin and insulin-resistant self was born less than 5 pounds. David connected the work of the ground floor of my alma mater (which housed a busy diabetes clinic) with the fourth floor (which delivered dozens of growth restricted babies every day). I suggested to David that he call his idea a 'thrifty phenotype'. Soon we roped in Dr Anand Pandit and prepared a concept note for low birthweight research in Pune. The Pune Children's Study confirmed the association between low birthweight and insulin resistance [13]. David Barker convinced me to continue birthweight research rather than go back to clinical diabetology, and I launched on a trajectory which took me to an entirely different world.

I promised David that I would help by doing something which he would find difficult to do in the United Kingdom. The Pune Maternal Nutrition Study (PMNS) was born

(www.kemdiabetes.org). It is now in its 25th year of existence and has provided rich and pioneering ideas in the field of foetal programming. We reported that Indians are born 'thin-fat' [14] (Fig. 2) and that micronutrient deficiencies and deranged 1-C metabolism influence foetal growth and programming of diabetes [3].

The Vitamin B_{12} story owes to a serendipitous dinner meeting between a visiting Rotary fellow, Helga Refsum, and my cardiologist friend, who referred her to me when she started discussing 'homocysteine', which he had never heard of. It took us 6 years to publish the 'B_{12} deficiency paper' [15] because no one believed in us. Six years was also the incubation period for the 'thin-fat Indian baby' paper which most of the Editors did not believe, coming from an obscure Indian in an obscure place. They said, 'this will be of no interest to our readers'. The popularity of the thin-fat phenotype awaited publication of the Lancet picture in 2004, which showed I had more than twice the body fat percentage than my friend John Yudkin despite an identical BMI [16]. Unfortunately, we did not patent this picture (Fig. 3). Final acceptance of the thin-fat baby depended on the comparison of magnetic resonance imagings of the newborn Indian and English babies, which was done in collaboration with Nina Modi [17] (Fig. 2). It is remarkable how 'blackbox' pictures from high-tech machines convince the critics but not the simple and obvious measurements.

The success of the PMNS owes to a simple but careful design and the diligence of the staff in field activities, laboratory measurements and data management. The field staff are all local folk who have a very close rapport with the community. We constructed a mobile van with a basic laboratory and an ultrasound machine, which allowed us to carry out door-to-door investigations. A weekly meeting of investigators and staff ensured a forum for discussion and improvement. Dr Banoo Coyaji, Dr VN Rao and Dr Kurus Coyaji supported all the efforts. We executed over 500 oral glucose tolerance tests at home and were able to measure more than 90% of babies within 72 h of birth in home deliveries. The news of a delivery would reach us either on foot, via a phone call from a local telephone booth, a telegram, or a brother or the husband trotting or cycling to the field office. Pagers and mobile phones came much later. It was customary for families to bury the placenta in an earthen pot, which we ceremoniously exhumed, weighed and reburied. Siddhi Hirve supervised all the field operations, Shobha Rao supervised nutrition data and Arun Kinare supervised sonography. I travelled to Southampton for a sabbatical in the summer of 1997, and using a Casio FX-82 calculator found that the tiny Indian baby was fatter than the English baby (Fig. 2). I had become more tech-savvy since the days of log table BMI calculations!

The children born in the PMNS are now in their early twenties. We have more than 90% follow-up rates

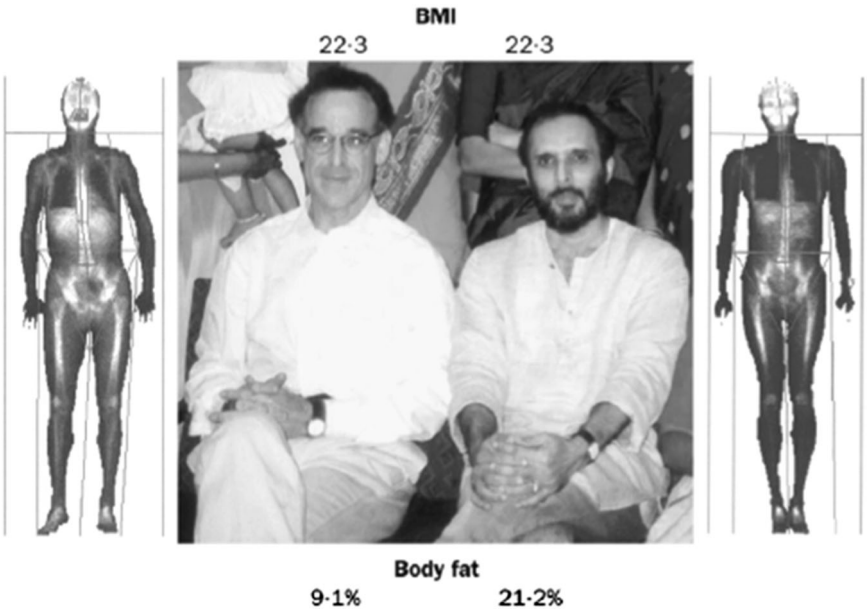

Fig. 3 The two authors share a near identical body mass index (BMI), but as dual X-ray absorptiometry imagery shows that is where the similarity ends. The first author (figure, right) has substantially more body fat than the second figure (author, left). Lifestyle may be relevant: the second author runs marathons, whereas the first author's main exercise is running to beat the closing doors of the elevator in the hospital every morning. The contribution of genes to such adiposity is yet to be determined, although the possible relevance of intrauterine undernutrition is supported by the first author's low birthweight. The image is a useful reminder of the limitations of BMI as a measure of adiposity across populations

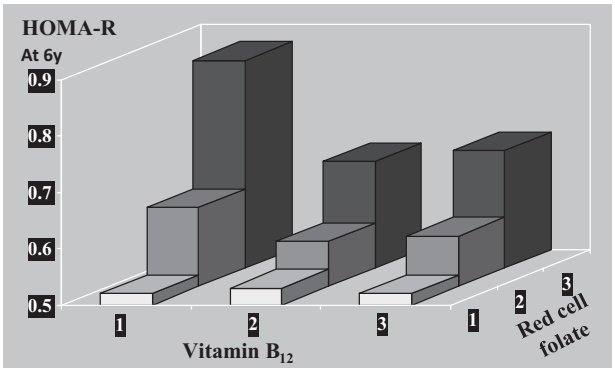

Fig. 4 Insulin resistance (HOMA-R) in the children at 6 years in relation to maternal vitamin B_{12} (18 weeks) and erythrocyte folate (28 weeks). Children born to mothers with lowest vitamin B_{12} and highest folate concentrations were the most insulin resistant (Adapted from Yajnik et al. [19])

and have documented the nutritional and socioeconomic transition in the society. Serial measurements have also allowed establishment of life-course evolution of cardiometabolic phenotypes and vitamin B_{12} deficiency [18]. We have set up perhaps the most unique biobank of samples: it includes samples from both urban and rural men and women, and children and adults. Samples of cord blood, placenta, blood, urine and stool are stored for measurements of DNA, RNA, metabolites, hormones, and so on. This will be a unique legacy for future investigators.

Equipped with observational data [19] (Fig. 4) and Mendelian randomization analysis [20] to support a causal role for 1-C metabolism and vitamin B_{12} deficiency in foetal programming of adiposity and insulin resistance, we started what may be the first trial of supplementation in adolescents intended to improve the non-communicable disease (NCD) risk in offspring [21]. It is a trial in an ongoing cohort with life-course information in F0 and F1 generations and outcomes in the F2 generation. Meticulous planning by Pallavi and sleepless nights of research assistants waiting for a delivery to happen to collect that crucial cord blood and placental tissue has ensured near 100% success in sample collection. Only time will tell if our hopes of influencing intergenerational epigenetic mechanisms of NCD risk are well founded. When all this was happening, my student and colleague Anandu (Anandvardhan Hardikar) worked to set up a 50 generation undernourished 'thrifty jerry' rat model which would provide crucial mechanistic clues to developmental origins [22].

The Crystal Ball

What do I see for the future? I am a bit miffed by the expectation that high-throughput science will solve nutritional problems of the world. A conversation about novel metabolic pathways by a software-driven postgrad is a bit frightening. Unless we use common sense and understand the nutritional issues in individuals and communities we are unlikely to make relevant progress.

Nutritional programming as a basis of Developmental Origins of Health and Disease (DOHaD) is here to stay, although there is a long way to go. Observational research and animal models have taught us a lot, but real success will depend on successful interventions to promote intergenerational health and reduce the burden of disease. The window of opportunity is gradually unfolding, but the success of an intervention depends on undoing the already imprinted epigenetic signatures which may take some time. History of a population determines its future. As Sorren Kirkegard asserted 'life is best understood backwards'. The long latent periods before the outcomes manifest do not go well with the short cycles of current research funding and with the politicians who would like to wish away all problems in the 4-year election cycle. There is a considerable need to impress the stakeholders with the great potential of nutritional DOHaD research.

Finally, I would like to stress that I am not a nutritionist nor am I an obstetrician or a neonatologist, but have been able to make some useful observations for foetal programming of diabetes in Indians. This was possible because of academic parenting, guidance from some fantastic teachers, tireless contribution from colleagues and my ability for somewhat lateral thinking. I owe a debt of gratitude to everyone who has contributed; my world conspired to make it all possible. As Atticus said, we are made up of those who made us and broke us.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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