NFI BULLETIN
Bulletin of the Nutrition Foundation of India
Volume 34 Number 3 July 2013

The first 1000 days and human development: implications for India

Reynaldo Martorell

It has always been recognised that the adequate nutrition and health care are essential prerequisites for the birth of well nourished healthy infant. Appropriate infant and young child feeding and optimal health care are needed for growth during infancy and early childhood. Growth during this period plays a vital role in setting the trajectory of growth in childhood and adolescence and stature in adult life. In recent years, the importance of critical 100 days is being recognised and many countries including India are focussing nutrition and health care to the mother-child dyad during this critical period. The objectives of this article are :

a) To describe patterns of growth in preschool children in India and in countries from around the world and to emphasize the importance of the first 1000 days for human growth and development.

b) To review the consequences of poor growth during early life for human capital and adult chronic disease risk factors. Two bodies of evidence are reviewed: long-term evaluations of nutrition interventions and famines and findings from prospective cohort studies.

c) To review the implications that the high level of undernutrition in women and children have for India's health and wealth.

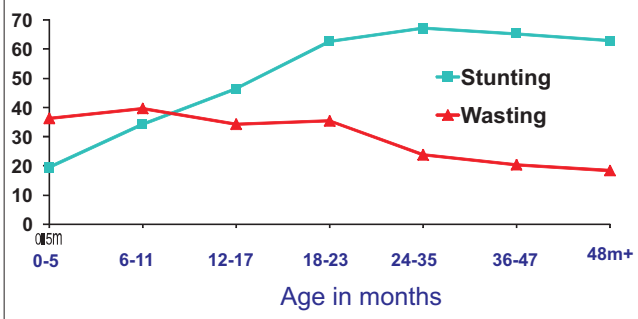
In an analysis of data from 54 national probability surveys from countries around the world, Victora et al (2010)[1] showed that linear growth failure in children less than 5 years of age is concentrated in the first 1000 days. This period includes pregnancy and the first 2 years of life (270 + 365+ 365 = 1000 days). The shape of the curve is strikingly similar across many diverse countries but the degree of growth failure varies. The prevalence of stunting in India is among the highest in the world, 48% in children less than 5 years according to NFHS-3 data from 2005-2006[2,3] and use of the WHO standards (Figure 1)[4]. In children 0-5 months, about 20% are stunted, suggesting that much of this retardation begins in the womb; the prevalence increases until about 23 months, when it approaches 60%. Values decline slightly thereafter, which means that the growth velocity in height is similar or slightly faster than in the WHO standard after 24 months. This pattern of growth failure in the first 1000 days identifies a "critical window of opportunity" during which nutrition and health interventions will have the greatest impact on nutritional status.

Wasting is also very common in India, particularly in early infancy when it affects 30% of children (Figure 1). However, this is a phenomenon that was uncovered by use of the WHO standards[4] rather than the older NCHS reference[5,6]. The WHO standards were developed with data from breastfed babies from five sites around the world, including New Delhi, India. The NCHS reference was entirely based on US children and used data from the Fels longitudinal study and from national surveys; most of the children included were bottle fed. With the NCHS reference, the peak prevalence of wasting appeared in the second year of life whereas with the WHO standards, this shifted to early and late infancy (Figure 2). This again underscores the role of nutrition in the prenatal environment and infancy.

The first 1000 days represent a window of vulnerability. A confluence of factors make this so. This is a period of rapid physical growth and development. The growth velocity in height over this period is faster than at any other time, including adolescence. The brain develops at a furious pace as do other organ systems. All of this is reflected in the high nutritional requirements of young children compared to adults, when expressed as nutrients per kilogram of body weight. Humans come into this world with naïve immune systems and infants are highly susceptible to infections. Humans are also born in a relatively immature state compared to other mammals, including primates. This makes infants fully dependent on others

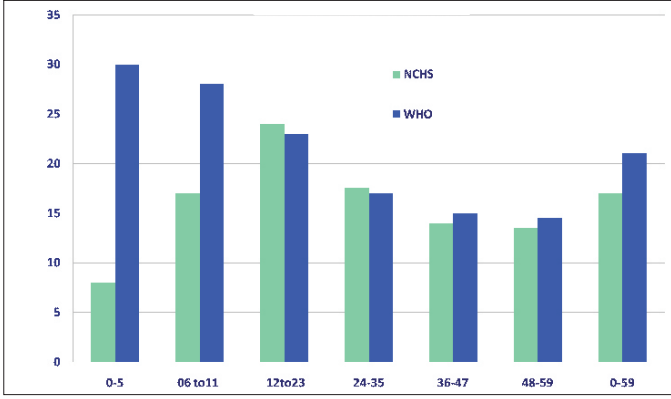
CONTENTS

Figure 1 % of children with stunting or wasting by age in Bihar (NFHS 3, 2005-2006)*



** WHO 2006 standards; total for India 48%, compared to 10% for China.*

Figure 2 Prevalence Wasting in relation to age (NCHS and WHO 2006)



for care and nurturing and when this is deficient, the consequences for growth and development are profound. Finally, any metabolic programming that may occur is more likely to develop during this critical early phase of development and thus be more consequential.

Marked growth failure of the type that leads to 48% of children being stunted as seen in India is a marker of widespread systemic dysfunction that also affects all organ systems. It is not surprising, therefore, that stunting is associated with adverse consequences in the short and long term[7]. In the short term, this leads to impaired resistance to infection, increased morbidity and higher mortality. The 2008 Lancet series on maternal and child undernutrition estimated that 2,800,000 die each year because of growth failure (notably stunting) and micronutrient deficiencies[8]. To this number one must add 1,400,000 deaths due to suboptimal breastfeeding[8]. In addition to loss of life, the consequences of poor nutrition in the first 1000 days include loss of human capital and increased risk of adult chronic diseases[7]. We can assess these consequences by studying the long term effect of nutrition interventions, the impact of famines and through prospective cohort studies.

Professor C. Gopalan has contributed much to the literature on stunting and its consequences. In response to a question about the main nutrition and health challenges facing India, he named the high levels of stunting among the poor and the rising incidence of obesity and Type II diabetes mellitus, particularly among the relatively affluent[9]. Earlier in a 1983 article in the Bulletin of the Nutrition Foundation of India, he dismissed the notion that stunting was a harmless adaptation that led to shorter people who, therefore, need less food. He wrote that to plead the virtues of "smallness" is "to acquiesce in the preservation of the status quo of poverty, undernutrition and socio-economic status"[10].

Breastfeeding and intelligence

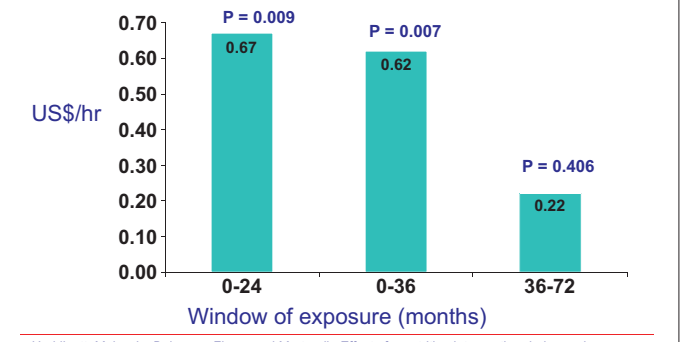
Many observational studies have shown a link between breastfeeding and intelligence but despite control for confounding, these findings are often dismissed. However, we now have results from a large cluster-randomized trial of breastfeeding promotion from Belarus on this important question[11]. The breastfeeding promotion intervention was modelled on the Baby-Friendly Hospital Initiative. Exclusive breastfeeding at 3 months was 43% for the experimental and 6% for the control group ($p<0.001$) and the duration of any breastfeeding was also increased. In an intent to treat analysis at age 6.5 years, verbal, performance, and full IQ (Wechsler) were 7.5, 2.9 and 5.9 IQ points higher, respectively, in the experimental group (all comparisons were significant). Breastfeeding not only lowers diarrhoeal morbidity and mortality but also builds human capital.

Long-term effects of a nutrition intervention in Guatemala

The follow-up studies of the Institute of Nutrition of Central America and Panama (INCAP) longitudinal study of 1969-1977 allow us to examine long-terms effects of improving nutrition during the first 1000 days. The original study was a community randomized supplementation trial; two communities (1 large, 1 small) received Atole, a nutritious supplement made from Incaparina (a vegetable protein mixture developed by INCAP), milk and sugar, and two (1 large, 1 small) received Fresco, a less nutritive drink[12]. The supplements were provided twice daily, midmorning and mid-afternoon, seven days a week for the duration of the study in a supplementation centre. All children 7 years or younger were included and were followed until they turned 7 years or the study end; also, all children born during the study were included and followed until 7 years or study end. Pregnant and lactating mothers attended and consumed the drinks. Consumption was ad-libitum but intake of Atole and Fresco was measured as were home dietary intakes. Total diets of children< 3 years from Atole villages were greater by 9 g/day of protein, 100 kcal/day, and in micronutrients when compared to diets of children from Fresco villages. Length was increased by 3 cm in Atole compared to Fresco villages but only in the first three years; most of the impact was observed by 2 years of age[13,14]. These findings have implications for programs. First, the dietary impact is within what has been observed in well run interventions, including nutrition education alone (i.e. without the provision of food). Second, food supplementation only impacts growth in young children; there was no impact of the Atole at ages 3 to 7 years.

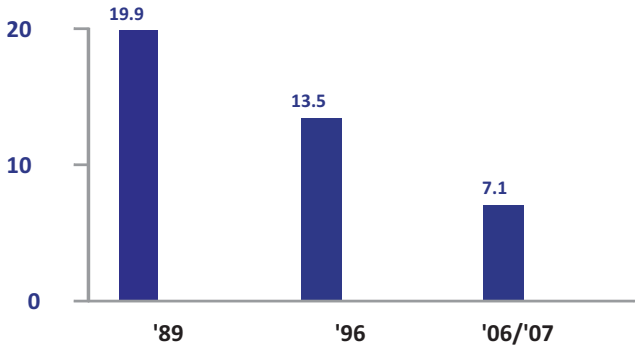
There have been several follow-up studies of the longitudinal study but the most relevant here is the Human Capital Study of 2002-04, carried out when the former participants were around 32 years of age[14]. Of 1856 former participants living in the country of Guatemala at the time, it was possible to measure 1560 men and women or 84% of the sample. This was done by focusing on adults who still resided in the villages as well as on migrants to

Figure 3 Impact of exposure to atole during early life on income in adult life



* Hoddinott, Maluccio, Behrman, Flores and Martorell. Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults (The Lancet, 2008).

Figure 4 Prevalence of Stunting in Brazilian children in three national surveys



Source :Recent Trends in Maternal, Newborn, and Child Health in Brazil: Progress Toward Millennium Development Goals 4 and 5 (Barros et al, 2010)

cities and villages throughout the country. The study was as a collaboration involving INCAP, the International Food Policy Research Institute (IFPRI), the University of Pennsylvania and Emory University.

The analytic approach of this study exploited the fact that children were exposed to Atole and Fresco at various ages depending on their birth dates. This permitted the testing of impact for any "window of exposure", using all subjects in a double difference model[14]. The 1988-89 follow-up study (ages 11-26 years) established that the Atole had long-term impact on height and on work capacity in males[14]. By the time of the 2002-2004 follow-up, all participants had finished schooling and were settled into an occupation allowing for assessment of impact on human capital. Among the most notable findings were that schooling was improved by 1.2 years but in women only and that reading and intelligence were improved in both men and women by about a quarter of a standard deviation[15]. Wages were improved in men only but only when exposure to Atole was prior to 3 years of age[16]. The largest effect was for exposure to two years of age, an increase of US $ 67 cents per hour; exposure to Atole from 3 to 6 years did not have a significant impact on wages (Figure 3). The increase in wages in those exposed to Atole in the first 3 years amounted to a 46 % increase over average wages and to an additional US $914 in annual income[16]. The lack of impact on wages in women probably reflects the low participation of women in the labour market. Effects of improved nutrition on cardiovascular disease outcomes were of small magnitude and inconsistent[17]. Finally, there were also intergenerational effects[18]. Offspring of women exposed to Atole (vs Fresco) were heavier at birth and were taller and had greater head circumferences in childhood than offspring of women exposed to Fresco. There were no effects on measures of adiposity. Interestingly, exposure to Atole in men had no effect on their offspring's growth.

Long-term effects of famines

Famines are perverse natural experiments that can provide information about the long term effects of nutrition in early life. The Dutch famine at the end of World War II is perhaps the best known and studied famine; unlike many famines in poor countries, it was brief, intense and affected a previously well-nourished population. Studies of the Dutch famine show that prenatal exposure to famine increased the risk of schizophrenia; however, famine did not result in adverse effects on human capital (height, cognitive function) and reported relationships with CVD risk factors can be described as weak and inconsistent[19].

The 1959-61 Chinese famine, precipitated by Mao's Great Leap Forward policies, like many famines have been throughout human history, lasted several years, was severe and affected an already malnourished population. Interest in the long-term effects of the Chinese famine has increased recently and these studies suggest that exposure during pregnancy and the first two years impacts adult height, wealth, income and mental health (schizophrenia; mental illness) and also has intergenerational effects on birthweight[20-24]. Surprisingly, some findings suggest "protective" effects of famine exposure, which might be explained by high mortality and intense selection of the hardiest[22-24]. There are few studies of exposure to the Chinese famine and CVD risk factors; associations have been reported for BMI, hypertension and hyperglycemia[19,21].

Cohort studies

Paediatricians and health workers in low and middle income countries (LMICs) often promote faster weight gain in infancy and childhood because it reduces morbidity and mortality[25]. However, there is substantial literature, mainly from high income countries, that suggests that rapid weight gain leads to increased risk of adult chronic diseases, particularly obesity and insulin resistance[25]. This so-called catch-up dilemma is a motivating factor for research about the long-term consequences of growth in early life and adult outcomes that is being undertaken by the Consortium for Health Orientated Research in Transitional Societies (COHORTS), involving 5 birth cohorts from India, the Philippines, South Africa, Brazil and Guatemala[26]. A key question has been: is there a trade-off resulting from faster growth in the first 1000 days of life between improved human capital and poorer adult health? In a meta-regression analysis of COHORTS data, lower birthweight and smaller size at two years were associated with shorter adult height, less schooling, and for women, lower offspring birthweight[7]. Lower birth weight and smaller size at two years were risk factors for high glucose concentrations , blood pressure and harmful lipid profiles once adult body mass index and adult height were controlled for, suggesting that rapid postnatal weight gain, especially after 2 years of age, is linked to these conditions. More recent analyses of pooled results have used conditional measures of growth that remove the association between size at any point in time and future growth and that also disentangle linear growth from weight gain[25]. Included in the models were birthweight and growth measures for three periods: 0-2 years, 2 to mid-childhood

and mid-childhood to adulthood. The findings were that larger birthweight and faster linear growth during the first two years of life were associated with substantial gains in height and schooling and gave some protection from adult chronic disease risk factors, with few adverse trade-offs. For example, while birthweight and linear growth from birth to 2 years were related to adult BMI, these two variables contributed to a greater extent to adult lean mass than fat mass. It was weight gain (independent of linear growth) after two years of age that was predictive of adverse chronic disease risk, and these effects became stronger with age. These findings point to the need to support interventions in LMICs to increase birthweight and linear growth during the first two years of life; they also point to the need to prevent overweight after 2 years of age.

Implications for India

Emory University recently completed studies about how maternal nutrition is perceived and the types and quality of programs implemented; this work included field work in Bihar, Uttar Pradesh and Tamil Nadu[27,28]. The general conclusion was that maternal nutrition is not given the priority it deserves. At the same time, there is increasing receptivity on the part of Government to address the needs of women and India boasts a wide range of programmatic experiences that can facilitate improvement of program design and implementation. In addition to elevating the priority given to maternal nutrition and implementing strategies to improve women's social and health status, programs can be strengthened by promoting integration of services, ensuring effective procurement mechanisms, establishing regional training facilities for improved program implementation and strengthening program monitoring and evaluation.

In addition, Emory University is collaborating with CARE India, other partners and the Government of Bihar in an ambitious project funded by the Bill and Melinda Gates Foundation. The Family Health Initiative in Bihar is developing, testing, and scaling-up innovative solutions to improve the capacity of frontline and first level facility family health services, to increase coverage and quality of life-saving interventions and improve survival, health and nutrition of women, new-borns and children (Table). The project operates in 8 districts of the state and plans to upscale innovations to the entire state in the future. Emory provides technical expertise in nutrition.

Bihar is one of the poorest states in India and its health statistics lag behind other states. The condition of women and children is poor (Table). Short stature and low BMI affect nearly half of the women. Women marry young and give birth at young ages. Some 60% of pregnant women are anaemic yet only 10% received the recommended 90 tablets of iron and folic acid in 2005-2006. Stunting, wasting and anaemia affect most children and infant feeding practices fall very short of international recommendations. The high prevalence of stunting and wasting in children 0-5 months (Figures 1 and 2) should not surprise anyone, given the condition of women in Bihar. For the first 500 days (pregnancy and the first 6 months) , women are the portal through which the nutrition of children should be improved; enhancing women's status, promoting better maternal nutrition during pregnancy and lactation and promoting appropriate infant feeding practices should be a high priority for Bihar and India.

In 1776, Adam Smith wrote "The Wealth of Nations"[29]. He believed that the wealth of nations depends not only on raw materials and other physical resources but also on the quality of the people, their health, skills and knowledge. He is the originator of the modern concept of human capital. Among his bold ideas was the theory that investing in health and education makes sense from an economic point of view because the returns in future productivity should exceed the initial investment made on the young.

India has great aspirations. Its future however, is compromised by its high levels of maternal and child undernutrition. The loss of young lives is appalling and the loss of human capital limits the future economic productivity of its people. The juxtaposition of child undernutrition and a changing environment where calories are more abundant and physical activity is less than in the past, presents a great challenge to India. Professor Gopalan is right: undernutrition and the emergence of obesity and chronic diseases are the two biggest health challenges facing India!

It is imperative that India addresses the problem of maternal and child undernutrition with urgency. It is not the case that the problem is unrecognized at the highest levels of Government. Prime Minister Manmohan Singh has called the high prevalence of undernutrition a "national shame". On February 2007, I was in India when the press picked up the news that the prevalence of underweight had remained basically unchanged in the previous seven years, despite impressive macro-economic growth[30]. As I was leaving Mumbai's airport, I saw the latest Forbes magazine. It had an article that reported that India had surpassed Japan as the Asian country with the greatest number of billionaires (in US $).

Clearly, economic growth is not enough. On the other hand, as the case of Brazil illustrates, good economic growth accompanied by equity-oriented policies that lead to marked improvements in living conditions is a proven formula for success[31,32]. Stunting declined precipitously in the poorest quintile of Brazilian households from a high of 60% prevalence in 1974-1975 to 11% in 2006-2007 (Figure 4) . The prevalence of stunting also declined in the richest quintile but the difference in prevalence between the two quintiles narrowed from 48 in 1974-1975 to 7% in 2006-2009 and is expected to continue narrowing. Regional inequalities have also narrowed considerably. Potential explanations for the declines in stunting are the continuity of policies and programs through different administrations, substantial efforts to improve the social determinants of health

Table 1 Nutritional status of women and children in Bihar (NFHS3 -2005-06)

Women	
Height below 150cm	51%
BMI below 18.5	45%
Anaemia in pregnancy	60%
Average age at marriage	16year
Gave birth before 18 years	44%
Consumed 90 IFA tablets	10%
Children	
Breast fed within 1 hour	4%
Exclusively breast fed (0-5 months)	28%
Stunting	56%
Wasting	27%
Anaemia	87%

(poverty reduction, increased female education, reduced fertility, etc.), the creation of a unified health system with emphasis on primary health care for underserved areas and the implementation of many interventions outside the health system (conditional cash transfers, water and sanitation, etc.). Not all is perfect however, as the emergence of obesity and related chronic diseases threatens to negate the gains in health.

India should consider the example of Brazil. Political will is essential. Priority must be given to improving the condition of women and improving nutrition and health in the first 1000 days. There must be sustained, effective investment in the social sector, including education, water and sanitation, family planning, and primary health care. Significant improvements in the quality and coverage of all programs are required. Inequities in delivery of services need to be reduced. As in the case of Brazil, India will have to address the rising epidemic of chronic diseases. Professor Gopalan tells us that "the key to preventing much of the overweight seen in South and South-East Asia may be to prevent underweight at birth. This leads us back to the nutritional status of mothers"[33]. To this I would add the need to prevent further deterioration of nutritional status in the first two years of life. Professor Gopalan also goes on to say that "…nutrition scientists need to adopt a life-cycle approach to the whole question of good nutrition. Early deprivation throws a long shadow"[33]. I could not agree more.

The author is Professor of International Nutrition, Hubert Department of Global Health Rollins School of Public Health, Emory University, Atlanta, USA This paper is based on the Gopalan oration that he delivered in 2012.

References

1. Victora CG, de Onis M, Hallal PC, Blössner M, Shrimpton R. Worldwide timing of growth faltering: Revisiting implications for interventions. Pediatrics. 125(3):473-480, 2010.
2. International Institute for Population Sciences. National Family Health Survey (NFHS-3), 2005-06: India. Vol I. Mumbai, India: International Institute for Population Sciences; 2007.
3. Martorell R, Young MF. Patterns of stunting and wasting: potential explanatory factors. Adv in Nutr. 3:227-233. 2012. Doi:10.3945/an.111.0011107.
4. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development. Geneva, Switzerland: World Health Organization, 2006.
5. Hamil PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM. Physical growth: National Center for Health Statistics percentiles. Am J Clin Nutr. 32:607-29, 1979.
6. Dibley MJ, Goldsby JB, Staehling NW, Trowbridge FL. Development of normalized curves for the international growth reference: historical and technical considerations. Am J Clin Nutr. 46:736-48. 1987.
7. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, Sachdev HS, for the Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: consequences for adult health and human capital. Lancet. 371:340-357,2008.
8. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera, for the Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet. 371(9608):243-260,2008.
9. Gopalan C http://www.ceche.org/programs/IndiaHealthChallenges/gopalan_QA.html
10. Gopalan C. Small is healthy? For the poor, not for the rich! NFI Bulletin. 4(3): 1-3, 1983.
11. Kramer MS, Aboud F, Mironova E, Vanilovich I, Platt RW, Matush L, Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Breastfeeding and Child Cognitive Development. New Evidence From a Large Randomized Trial. Arch Gen Psychiatry. 65(5):578-584,2008.
12. Martorell R, Habicht J-P, Rivera JA. History and design of the INCAP longitudinal study (1969-77) and its follow-up (1988-89). J Nutr. 125(Suppl. 4S):1027S-41S, 1995.
13. Habicht J-P, Martorell R, Rivera JA. Nutritional impact of supplementation in the INCAP longitudinal study: Analytic strategies and inferences. J Nutr. 125(Suppl. 4S):1042S-50S, 1995.
14. Martorell R, Melgar P, Maluccio JA, Stein AD, Rivera JA. The development and legacy of the INCAP Oriente studies 1969-2009: The nutrition intervention improved adult human capital and economic productivity. J Nutr. 140(2):411-4, 2010.
15. Maluccio JA, Hoddinott J, Behrman JR, Martorell R, Quisumbing AR, Stein AD. The impact of improving nutrition during early childhood on education among Guatemala adults. Economic Journal. 119:734-63, 2009.
16. Hoddinott J, Maluccio JA, Behrman JR, Flores R, Martorell R. Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults. Lancet. 371(9610):411-6, 2008.
17. Stein AD, Wang M, Ramirez-Zea M, Flores R, Grajeda R, Melgar P, Ramakrishnan U, Martorell R. Exposure to a nutrition supplementation intervention in early childhood and risk factors for cardiovascular disease in adulthood: Evidence from Guatemala. Am J Epidemiol. 164(12):1160-70, 2006.
18. Behrman JR, Calderon MC, Preston SH, Hoddinott J, Martorell R, Stein AD. Nutritional supplementation in girls influences the growth of their children: prospective study in Guatemala. Am J Clin Nutr. 90(5):1372-9, 2009.
19. Lumey LH, Stein AD, Susser E. Prenatal famine and adult health. Annu Rev Public Health. 32: 237–62, 2011.
20. Chen Y, Zhou L-A. The long-term health and economic consequences of the 1959-1961 famine in China. J Health Econ. 26: 659–81, 2007.
21. Huang C, Li Z, Wang M, Martorell R. Early life exposure to the 1959-1961 Chinese Famine has long-term health consequences. J Nutr. 140: 1874–1878, 2010.
22. Song S, Wang W, Hu P. Famine, death, and madness: schizophrenia in early adulthood after prenatal exposure to the Chinese Great Leap Forward Famine. Soc Sci Med. 68:1315–21, 2009.
23. Huang C, Phillips M, Zhang Y, Zhan Y, Zhang J, Shi Q, Song Z, Ding Z, Pang S, Martorell R. Malnutrition in early life and adult mental health: Evidence from a natural experiment. Soc Sci Med. In press.
24. Huang C, Li Z, Venkat Narayan KM, Williamson DF, Martorell R. Bigger babies born to women survivors of the 1959-1961 Chinese famine: a puzzle due to survival selection? J DOHaD. 1(6):412-418, 2010.
25. Adair LS, Fall CH, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, Sachdev HS, Dahly DL, Bas I, Norris S, Micklesfield L, Hallal P, Victora C.. Disentangling how relative weight gain and linear growth during early life relate to adult health and human capital in low and middle income countries: findings from five birth cohort studies. Lancet, in press.
26. Richter LM, Victora CG, Hallal PC, Adair LS, Bhargava SK, Fall CH, Lee N, Martorell R, Norris SA, Sachdev HS, Stein AD; the COHORTS Group. Cohort profile: The consortium of health-oriented research in transitioning societies. Intl J Epidemiol. 41(3):621-6, 2012.
27. Ramakrishnan U, Lowe A, Vir S, Kumar S, Mohanraj R, Chaturvedi A, Nozensky EA, Martorell R, Mason JB. Public health interventions, barriers, and opportunities for improving maternal nutrition in India. Food Nutr Bull. 33(2):S71-S92, 2012.
28. Nozensky EA, Ramakrishnan U, Martorell R. A situation analysis of public health interventions, barriers, and opportunities for improving maternal nutrition in Bihar, India. Food Nutr Bull. 33(2):S92-S103, 2012.
29. Smith, A. An Inquiry into the Nature and Causes of the Wealth of Nations, 1st edn, 1776, Vol. II of The Glasgow Edition of the Works and Correspondence of Adam Smith, edited by R.H. Campbell, A.S. Skinner and W.B. Todd. Oxford: Oxford University Press, 1776.
30. Sengupta S. Even amid its wealth, India finds, half its small children are malnourished. New York Times, Mumbai: New York Times, 9 Feb, 2007.
31.Monteiro CA, D'Aquino Benicio MH, Conde WL, Konno S, Lovadino AL, Barros AJD Victora CG. Narrowing socioeconomic inequality in child stunting: the Brazilian experience, 1974-2007. Bull World Health Organ. 88:305-311, 2010.
32.Monteiro CA, D'Aquino Benicio MH, Feldenheimer da Silva AC, Lovadino de Lima AL, Conde WL. Causes for the decline in child under-nutrition in Brazil, 1996-2007. Rev Saúde Pública. 43:1-8, 2009.
33. Gopalan C. My life in nutrition [Commentary]. World Nutrition. 1(4):185-203, 2010. (Obtainable at www.wphna.org)

Safety and efficacy assessment of bioactive Molecules/ functional foods/ nutraceuticals

B Sesikeran

Introduction

In the last two decades there has been increasing focus on research to identify functional foods, bioactive molecules and nutraceuticals that may have long-term benefits, especially in relation to prevention and management of non-communicable diseases. Before any food or drug is used in humans, the fundamental requirement is to determine whether it is safe to use. The second prerequisite, if the substance is a drug or a component of food that is meant to produce health benefits over and above the satiety function of food, is to determine the level of efficacy or benefit in this regard. There can be no food or food formulation that is 100% safe. The usefulness of a substance is dependent on the risk/benefit ratio. A plethora of claims about the health benefits of a wide variety of foods and related substances, often based on poor or no evidence and sometimes associated with potential health problems, have led to the increasing recognition of the need for regulation in this field. The Food Safety and Standards Authority of India has been established under the Food Safety and Standards Act, 2006, as a statutory body for laying down science-based standards for articles of food and for regulating the manufacturing, processing, distribution, sale and import of food so as to ensure safe and wholesome food for human consumption.

Since the standards for food regulation are based on the definitions of the various terms used in assessing the safety and efficacy of functional foods, bioactive molecules and nutraceuticals, it is essential to have a clear understanding of these definitions.

Definitions

Food is any substance consumed to provide nutritional support for the body. It is usually of plant or animal origin, and contains essential nutrients such as carbohydrates, fats, proteins, vitamins, or minerals. Food substances are ingested by an organism and assimilated by the organism's cells in an effort to produce energy, maintain life, or stimulate growth[1].

A nutrient is a chemical that an organism needs to live and grow, or a substance used in an organism's metabolism which must be taken in from its environment[2].

A functional food- is a food or food ingredient which bestows a health benefit additional to that provided by food itself.

A nutraceutical is a food ingredient which is used like a pharmaceutical. It is a product isolated or purified from foods, and is generally sold in medicinal forms not usually associated with food. A nutraceutical is required to have demonstrable physiological benefit or provide protection against chronic diseases.

A dietary supplement is a product that contains nutrients derived from food products. These are concentrated in liquid or capsule form.

A bioactive molecule is a naturally occurring molecule derived from any living system-plant/animal/fungi/bacteria/ algae/terrestrial/marine, which has a beneficial biological activity, e.g. anti-proliferative, anti-oxidant, anti-infective, growth-promoting, cholesterol-lowering. etc.

The following example may provide a better understanding of these often confusing and overlapping terms.

A carrot is a food ; it is a vegetable.

Carrots can prevent blindness caused by Vitamin A deficiency; in this role, the carrot may be termed a 'functional food'.

The β-carotene in the carrot-pro vitamin A-is a bioactive molecule.

A β-carotene supplement prepared from carrots is a nutraceutical/food supplement.

Some more examples of bioactive molecules are:

- lutein from green vegetables, capable of reducing the risk of macular degeneration
- lycopene from tomato, capable of reducing the risk of developing prostate cancer
- Omega-3 from fish and fish oils, potentially capable of reducing the risk of cardiovascular disease
- catechins and flavanoids from tea
- plant sterols and stanols

All these would be marketable as nutraceuticals/ food supplements.

Food, and nutrients from food, should be taken in quantities which give the maximum benefit and minimum harm to the consumer. The definition of some of the terms used to indicate these aspects are:

Recommended Dietary Allowance (RDA): -This constitutes the recommended levels of food and nutrient intake that, if consumed daily, would keep 95% of individuals healthy, and meet the needs of practically all healthy persons.

Average Daily Intake (ADI) is the average of the dietary intake in any population; in normal population groups, it would be adequate to meet the requirements of 50% of individuals in a population.

Safe Upper Limits (SUL) is a defined quantity of nutrient which is the safest upper level which can be consumed daily for the entire life time of a human being.

Factors to be considered in safety assessments

The following factors are considered while undertaking the

safety assessment of bioactive molecules

Characterisation of the test substance :

- Source/sources of the bioactive compound; taxonomy of the plant, e.g. lycopene present in tomatoes, red carrots, red capsicum, watermelon
- History of safe human use-from traditional knowledge or published data
- Safe level of consumption/upper safe limit. For example, according to traditional use, the safe level for consumption of fenugreek was considered to be 6g/ day, but as a functional food 20g/day was the recommended level. This required the generation of data for safety assessment.

Physico-chemical characterization

- Structure of the compound, molecular formula-i.e., the chemical fingerprint
- Whether available singly or as part of a family of molecules
- Category and variants; e.g. carotenoids/ curcuminoids
- Molecular weight, solubility, stability, etc.
- Thermodynamic and spectral data
- Isolation of compound/sample separation , synthesis
- Purity of final substance and impurities
- Preservation, storage, interactions with other substances

Pharmacokinetics

- Bioavailability
- Absorption
- Half-life
- Accumulation in tissue
- Distribution
- Metabolism
- Excretion

Biological Activity

- Anti-oxidant/ anti-inflammatory / anti-cancer, etc.
- Methods of assessing and quantifying the activity and validating assay methods
- In vitro and in vivo methods
- Effective Dose 50 (ED 50)-the level at which 50% of the treated animals would demonstrate the efficacy of the molecule

Toxicokinetics (Levels associated with adverse effect)

- LOAEL: Low Observed Adverse Effect Level-The lowest level/ quantity of the molecule which, when given to animals, produced an adverse effect
- NOAEL: No Adverse Effect Level-is one dosage level below LOAEL, producing no adverse effects

Safe Upper Limit and Acceptable Daily Intakes are derived from NOAEL or LOAEL and could be 10- to 100-fold below these levels, thereby providing the consumer a wide safety margin

Extrapolating from LOAEL to derive SUL (based on human data)

If the adverse effect is a biochemical change with no clinical or organ correlation, the extrapolation factor is 3. For example, if serum transaminase levels were found to be elevated when a bioactive molecule was given at 60mg dose, i.e., LOAEL, then the SUL would be calculated as 60/3 = 20 mg

Extrapolating NOAEL to derive SUL (based on ANIMAL data)

- If the adverse effect is a serious toxic change, then NOAEL should be used for extrapolation, with a factor of 10. For example, If NOAEL is 10 mg, SUL = 10 / 10 x 10 = 0.1 mg.

- The factor of 10 is to be applied for inter-species variation and also for inter-individual variation

Effect in physiological states like pregnancy and lactation and in children should also be determined through appropriate experiments, failing which these molecules cannot be recommended for these groups and would require a label warning.

Bioinformatics

In recent times, there has been a significant increase in the use of bioinformatics to arrive at the probable harmful effects of molecules. The method is based on the structure-function relationships of similar molecules based on information already available in data bases such as toxicity databases, and drug interaction databases and allergen databases.

Identification of biomarkers

These are critically important in both safety and efficacy assessments. Biomarkers have to be identified and validated for their predictive value. These biomarkers could be related to the relationship between the amount consumed and the bioavailability, for example, concentration levels of the bioactive molecule in plasma. Alternatively, biomarkers may be correlated to outcomes, playing the role of indicator markers/effect markers, for example, the lowering of serum cholesterol levels in response to stanol. If the markers are related to risk of disease they are known as susceptibility markers. Such risks may include ratio of LDL cholesterol to total cholesterol and reduction in the risk of CHD.

Risk assessment

The process of carrying out a risk assessment involves the following steps:

- Hazard identification (adverse effects)
- Hazard characterisation (including dose-response assessment)
- Exposure assessment
- Risk characterisation
- Risk/benefit analysis

Principles for addition of dietary active compounds in foods

For the purposes of regulation, the following principles should apply in order to avoid indiscriminate use of bioactive compounds and to minimize false claims of efficacy: The active compound

- should be present at a level which will not result in either excess or insignificant intake
- should be sufficient to exercise its beneficial effect
- should not result in an adverse effect on the metabolism of any other nutrient
- should be stable in food under customary conditions of packaging, storage, distribution and use
- should be biologically available from the food and
- should be capable of being measured

Data from Clinical studies

Data from clinical studies carried out in other countries are acceptable. However, variations in response could exist between ethnic groups and studies on appropriate Indian target populations should be carried out, for example in Indian men / women / children / the elderly. It would be advisable to carry out comparative studies of placebo vs. nutraceuticals, low-dose vs. high-dose nutraceuticals, and traditional vs test substances.

There should be clear-cut end points/outcomes, and biomarkers should be used only after proper validation.

Label claims which are permitted by food regulatory bodies

- Nutrient content claim: e.g. low sodium, low fat, rich in n3, high soluble fiber, etc.
- Structure/function claim: e.g. calcium builds strong bones, lycopene reduces prostate cancer risk
- Risk reduction claim: e.g. fibre associated with lowering of risk of CHD, folic acid associated with lowering of risk of neural tube defects in newborns

Conclusion

The following are the suggested sequence of events before a nutraceutical/ food supplement or a bioactive molecule is approved for marketing

- translate new knowledge into product
- ensure safety and quality
- evaluate efficacy
- produce evidence of content claim
- evaluate product for specific health outcomes with appropriately powered clinical trials
- make a claim of benefit

The author is a former Director of the National Institute of Nutrition, Hyderabad.

References

1. Aguilera, Jose Miguel and David W. Stanley. 1999 Microstructural Principles of Food Processing and Engineering. Springer,
2. Whitney, Elanor and Sharon Rolfes. 2005. Understanding Nutrition, 10th edition, p 6. Thomson-Wadsworth
3. Institute of Medicine, National Academy of Sciences, Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids, p. 3. Washington, DC: National Academy Press, 2000.

NUTRITION NEWS

The 45th Annual National Conference of the Nutrition Society of India will be held on 21st & 22nd November 2013 at the National Institute of Nutrition, Hyderabad. This will be preceded by a pre-conference workshop on 20th November 2013 at the same venue.

FOUNDATION NEWS

- **Training for CAB component of AHS**

The Government of India has been carrying out an Annual Health Survey (AHS) from April 2010 as a collaborative effort among the Ministry of Health and Family Welfare, the Ministry of Women and Child Development, and the Office of the Registrar General of India. The survey is being conducted in 284 districts in 9 states (Assam, Bihar, Chattisgarh, Jharkhand, Madhya Pradesh, Orissa, Rajasthan, Uttar Pradesh and Uttarakhand). A Clinical, Anthropometric & Biochemical (CAB) component of the Annual Health Survey has been taken up from June 2013; the CAB component of the AHS is expected to provide data on the nutritional status (height/length, weight, and haemoglobin) of all age groups. The survey will provide information on infant and young child feeding practices in all children under three years of age and morbidity due to infection in the last fortnight in all children below five years of age. Based on the data, it will be possible to assess the effect of these two important factors on nutritional status of under-three children. The survey will, for the first time provide district-wise data on the prevalence of hypertension and high fasting glucose in all the nine states surveyed.

The Nutrition Foundation of India (NFI) along with the National Institute of Health and Family Welfare has completed the orientation training of Master Trainers from partner institutions (Regional Medical Research Centre Dibrugarh; Regional Medical Research Centre, Bhubaneshwar; Regional Medical Research Centre, Jabalpur; Desert Medical Research Centre, Jodhpur and the National Institute of Nutrition, Hyderabad). Five orientation training sessions for 75 medical consultants from survey agencies have also been completed. Currently the training of survey personnel for the CAB component of AHS is underway and is expected to be completed by the end of July.

- **Study circle lecture**

"Dietary guidelines for management of Type 2 Diabetes Mellitus in Asian Indians" by Dr Seema Gulati (Head, Nutrition Research Group, Center for Nutrition & Metabolic Research: C-NET & National Diabetes, Obesity and Cholesterol Foundation; Chief Project Officer, Diabetes Foundation - India, New Delhi) on 25th April 2013.

Edited by Dr. Anshu Sharma for the Nutrition Foundation of India, C-13, Qutab Institutional Area, New Delhi - 110016, website : www.nutritionfoundationofindia.res.in
Design & Printed by Natural Impression