



SIGHT AND LIFE

Magazine Issue N° 3/2007

[End of “Iron age”](#)

[WHO consultation: Control of iron deficiency in malaria](#)

[Golden Rice](#)

[School-based nutrition in Guatemala](#)

[Seasoning powders](#)

[Vitamin A research update](#)

[Behavior change research](#)

[Asian Congress of Nutrition](#)

[Inside SIGHT AND LIFE](#)

[Recent literature](#)

[Alumni in Community Eye Health](#)

[News](#)

[Letters to the editor](#)

[Publications](#)



Mosquito bite

Did the “iron age” end in Pemba?

The dilemma of iron supplementation in malaria-endemic regions

Until 2006, micronutrient supplements in the order of recommended dietary allowance (RDA) dosages, including that for iron, were considered inherently safe. The RDA values for iron for children in this age bracket are based on estimates to cover the requirements for growth and metabolism and to replace iron losses. Please read further on page 6.




Did the “iron age” end in Pemba? 6



Hierarchization of school-based nutrition for Guatemalan schoolchildren 23

Contents

Welcome	4	Golden Rice and biofortification	16
Did the “iron age” end in Pemba?	6	Hierarchization of school-based nutrition for Guatemalan schoolchildren	23
		Multiple micronutrient-fortified seasoning powders in preschool children in Chongqing suburb	28
Summary of the conclusions of the WHO consultation	14	Recent advances in vitamin A absorption and transport	32

Correspondents

Bruno de Benoist
William S. Blaner
Martin Bloem
George Britton
Ian Darnton-Hill
Omar Dary
Frances R. Davidson
John W. Erdman Jr

Philip Harvey
Richard F. Hurrell
Rolf D.W. Klemm
Donald S. McLaren
Regina Moench-Pfanner
Christine Northrop-Clewes
Noel W. Solomons
Florentino S. Solon

Alfred Sommer
David I. Thurnham
Andrew Tomkins
Emorn Wasantwisut
Keith P. West Jr
Yu Xiaodong
Chittaranjan S. Yajnik
Michael B. Zimmermann



Multiple micronutrient-fortified seasoning powders in preschool children in Chongqing suburb 28



Experiences of SIGHT AND LIFE Alumni in Community Eye Health at the International Centre for Eye Health 63



Applying behavior change research to promote micronutrients 38

10th Asian Congress of Nutrition 43

Inside SIGHT AND LIFE 47

Recent literature 50



Experiences of SIGHT AND LIFE Alumni in Community Eye Health at the International Centre for Eye Health 63

News 68

Letters to the editor 73

Publications 75

Welcome

Biofuels or *biofools*?

The tragic consequences of global warming, such as floods, droughts and shortage of clean water, hit the poorest populations of the developing world the hardest. The prognosis for the most vulnerable populations is poor as the increased frequency and severity of these climate-related disasters stretches their resilience and adaptive capacity to the limits. But climate-related humanitarian emergencies are not new, particularly in parts of the world that are familiar as sites of major floods and food insecurity, such as sub-Saharan Africa, Bangladesh, etc.

To put this into perspective, however, it must be stated that there is a clear link between increasing economic growth and social development (as represented by per capita GDP, accompanied by improvements in health, such as increased life expectancy and child survival) and increasing carbon dioxide and other greenhouse gas emissions resulting from increased energy consumption. Improved health and increased wealth in large parts of the world, most markedly in Asia and Latin America, have literally been fueled by carbon-intensive operations. In short, development needs energy.

Given the centrality of energy needs to human development and well-being, one of the major global responses to mitigate climate change has been to seek alternative, low carbon-emitting sources of energy. Of all the options currently available (solar, wind, hydro, nuclear, etc.), the candidate that appears most promising as the fastest way to reduce dependency on fossil fuel-based energy sources is the class of crop-based renewable energy sources known collectively as biofuels. Yet, this potential solution has been fraught with controversy as current major sources of biofuels are also major staple food crops (the most controversial being corn, palm and soybean oil) and their use for energy production could compete with food supply, particularly in poor countries that depend on imports – or aid donations – of these commodities.

How “biofoolish” is the use of food crops for biofuel production instead of meeting the ever-increasing demand from global food needs?

Clearly, the possibility of choking the climate through continuing reliance on fossil fuel-based energy sources, or of poverty-stricken masses starving as food crops fill gas tanks instead of stomachs, are both undesirable outcomes. We all want a world which Nature defines as tolerable for all life on Earth; we also want to ensure that there is enough nutritious food to eradicate global hunger and malnutrition. We have already declared our commitment to achieving these outcomes in the first and the seventh Millennium Development Goals. Do we now really stand at a crossroads where we must choose one or the other?

A closer analysis of the issues reveals more complex relationships between a whole host of factors relating to food production and use. Critics of biofuels warn that large-scale fuel production could divert agricultural production away from food crops, and result in increased food prices as the increased demand for these commodities outstrip the available capacity to supply them. However, energy, agricultural and export policy, adverse weather, and greater numbers of people moving out of poverty are also important factors. Recent disruptions caused by bad harvests have affected food supply far more than the current demand resulting from biofuel production. Another significant factor is rising wealth, particularly in the developing world: the rise of per capita income in emerging markets is responsible for as much as one-third of the current food-price inflation. With increasing incomes, households can more regularly consume higher-value, micronutrient-rich foods, such as meat and dairy products. In China, beef consumption has risen by 26% since 2000, and pork – an already popular meat – has risen by 19%. Even in India, where much of the population is vegetarian, chicken consumption has almost doubled since 2000. Between these two most-populated countries, such percentage increases represent millions of people.



Rising demand for biofuels and high fuel prices are having a dramatic impact on millions of people relying on food aid. The overall cost of the World Food Programme reaching a hungry person has gone up by 50% over the last five years. Biofuel critics also point to the reduction in the quantity of food aid from the United States, the largest donor of food aid, to beneficiary countries, even as the needs continue to rise. However, reports have suggested that the proportion of the food aid budget spent on overhead (i.e. shipping) has also increased significantly as a result of rising fuel prices, meaning less funds for actual food procurement in addition to increased commodity prices.

Nonetheless, the biofuel rush cannot escape all the criticism leveled against it. In the near term, while farmers in countries that account for a majority of the world's biofuel crop production (i.e. USA, Brazil, Malaysia and Indonesia) will enjoy the promise of markedly higher commodity prices and incomes, the urban and rural poor in food-importing countries will pay much higher prices for basic food staples and there will be less grain available for humanitarian aid.

With undernutrition affecting over 800 million people (and hidden hunger affecting about 2 billion people) worldwide and the demand for crop commodities expected to exceed supply in the near future, food security will depend as much on technological advances in increasing crop yields and production of micronutrient-rich food as it does on poverty alleviation and more equitable food distribution.

Connected to the topic of biofuels and climate change are tropical diseases, such as malaria, which inspired me to use the recent observation in Pemba, Zanzibar on iron supplementation in malaria-endemic areas as the cover story for this issue of the Magazine (see page 6 for a commentary and page 14 for a summary of the WHO recommendations). The dilemma of mitigating iron deficiency anemia in these areas was also intensely discussed at the first meeting of the Micronutrient Forum, which took place last April in Istanbul, Turkey. The theme was "Consequences and Control of Micronutrient Deficiencies," and we are pleased to include a supplement on this meeting in this issue of the Magazine. The reporters, particularly Christine Northrop-Clewes and David Thurnham, did a wonderful job of compiling the results of this high-profile meeting.

Further topics in this issue of the Magazine include an update on recent developments in Golden Rice (page 16), a study on multiple micronutrient-fortified school meals in China (page 28), and a report from a recent conference organized by ILSI Asia Pacific on consumer behavior and nutrition (page 38).

With best regards,



Did the “iron age” end in Pemba?

Klaus Schümann

Central Institute for Nutrition and Food Science, Technical University Munich, Freising-Weihenstephan

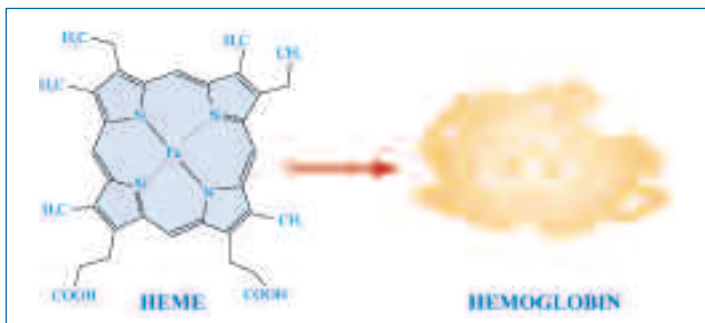
Frank Christ

Department of Anaesthesiology, University Hospital Grosshadern, Ludwig Maximilians University, Munich

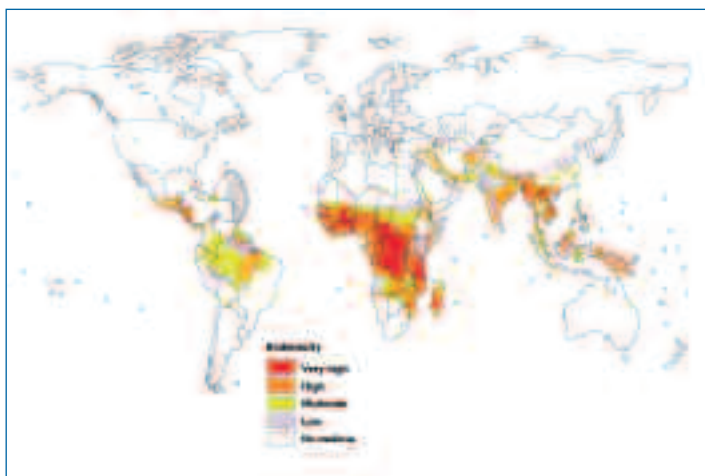
Correspondence: Klaus Schümann, Central Institute for Nutrition and Food Science, Technical University Munich, Am Forum 5, 85350 Freising-Weihenstephan, Germany
Email: kschuemann@schuemann-muc.de

The dilemma of iron supplementation in malaria-endemic regions

Until 2006, micronutrient supplements in the order of recommended dietary allowance (RDA) dosages, including that for iron, were considered inherently safe (1). The RDA values for iron for children in this age bracket are based on estimates to cover the requirements for growth and metabolism and to replace iron losses. The corresponding upper level (UL) for safe dietary intake in children is 40 mg Fe/d (2), based on side effects after oral intake in the form of supplements; this suggests a relatively broad margin of safety for iron in children. In this context, the WHO recommendation to supplement 12.5 mg Fe + 50 µg folic acid when the prevalence of anaemia exceeded 40% in children 6–36 months of age (3) seemed safe and prudent. This continuum of assumptions was severely disturbed when an excess number of hospital admissions and deaths occurred in malaria-exposed children during iron supplementation (4).



Hemoglobin structure



Malaria transmission risk areas.
From WHO-UNICEF World Malaria Report 2005

oral intake in the form of supplements; this suggests a relatively broad margin of safety for iron in children. In this context, the WHO recommendation to supplement 12.5 mg Fe + 50 µg folic acid when the prevalence of anaemia exceeded 40% in children 6–36 months of age (3) seemed safe and prudent. This continuum of assumptions was severely disturbed when an excess number of hospital admissions and deaths occurred in malaria-exposed children during iron supplementation (4).

Iron is essential for the malaria pathogen, *Plasmodium falciparum*, and for its human hosts alike. During their intra-erythrocyte stages plasmodia cannot access the erythrocytes' ample heme iron content; for rapid reduplication they depend on adequate non-heme iron supply. As most malaria-endemic areas are located within the tropical iron-deficiency belt, iron supplementation programs performed in these regions are likely to relieve iron-deficiency in the human population, but also in plasmodium parasites. As reviewed by Oppenheimer (5), two questions emerged regarding iron status and malaria outcomes: Data from a considerable number of studies were conflicting as to whether supplemental iron is more beneficial for the pathogen or the host, or whether low iron status is

Moreover, some of the endemic anemia in early life will be attributable to causes other than iron deficiency. The Pemba findings (4) put into relief the potentially problematic nature of *one-size-fits-all* solutions in public health. Many valuable and positive lessons can be derived from the Pemba saga and its aftermath. First, the Data Safety Management Board of the study was vigilant, and implemented measures to mitigate subjects' risk in a timely and transparent manner. The overseeing entities appropriately terminated the iron supplementation arms of the study.

Considerations on the folic acid component

It is worth bearing in mind that iron was not the only common factor in the “iron treatment” groups; each daily supplement contained also 50 µg of folic acid. It has been suggested that simultaneous administration of folic acid may be deleterious, since anti-folate metabolites are the basis of anti-malarial medications used to treat malaria attacks (9). Though this comment deals with the safety of iron administration, it should be understood that a comprehensive approach to malaria prevention requires other measures in parallel, such as insecticide-treated bed nets and malaria medication.

How can the dilemma be tackled?

As observed in several commentaries (10, 11), iron is a particular “problem nutrient” for complementary foods fed in the weaning period. Some guidance is available, though, to cut this “Gordian knot” of the supplement or no-supplement dilemma for young children. Firstly, alternative approaches to ease iron-deficiency, other than routine, daily iron supplementation, should be considered. These include measures such as delayed cord clamping during birth, increasing food choice and food security, providing iron-fortified complimentary foods and implementing hookworm treatment programs in endemic areas. Specifically within the domain of food choice is the recent notion to rely more heavily on the heme iron of muscle and organ meat (11). It is suggested, from contemporary hunter-gathers, that the evolutionary weaning food was pre-masticated meat. This is rich in highly bioavailable heme-iron.

When the usual cereal gruels or paps are part of the weaning culture, liberation of the iron from the iron-phytate complexes comes in as a potentially feasible strategy to provide greater uptake of iron from traditional grain-based complementary foods (12). The most basic approaches to phytate reduction involve soaking or germination of the seeds (13). Specific low-phytate varieties of grains, such as maize, have been developed. A substantial increase in iron absorption efficiency was seen from corn tortillas prepared from low-phytate maize (14). Fungal phytase preparations, capable of digesting phytate in the dough or even within the digestive tract have been developed (15). However, when considering children as young as 6 months of age, any exposure to undenatured fungal allergens should be limited.

A final approach to improving iron delivery and to prevent or reverse IDA in infants in malarial areas would be the application of oral iron supplements, but with specific precautions to mitigate the adverse consequences seen in the Pemba experience (4). These mitigating strategies are detailed in the following section.

Can the safety of supplemental iron administration in malaria-regions be improved?

In addition to the alternative approaches mentioned above it may be necessary to entertain the notion of administering supplemental forms of iron to young children in malarial areas. Are there approaches that can improve the safety? Two caveats to the current practices can be identified. The first comes from an analysis of a subgroup with hematological evaluation in the Pemba trial. It showed that when a child in the iron-intervention arms of the study was actually iron deficient, he or she benefited from iron supplementation; it improved iron and hemoglobin status, while decreasing the number of hospital admissions, concomitant infections, and fatalities related to malaria. Iron-replete children, in contrast, had an increased risk for such events. Thus, the dilemma might be resolved, if the iron status in all participants of a public health supplementation program and their response to iron intervention could be monitored. All currently available options, however, have three drawbacks: 1) They add considerable costs to IDA mitigation programs; 2) They have yet to be tested for their applicability in the field; and 3) They generally involve the sampling of



Iron and vitamin B drops

blood, with all that implies for discomfort to the child, acceptability to the families, and blood-borne infection hazard to the handlers and the environment.

Assessment of anemia and iron status in a public health context

It is becoming more imperative to have methods, acceptable to the public and cost-efficient in nature, to screen populations to detect those individuals in whom iron treatment is indicated, in order to target therapy to the eligible and exclude exposure for those who do not need additional iron. The current options are to some extent both limited and problematic.

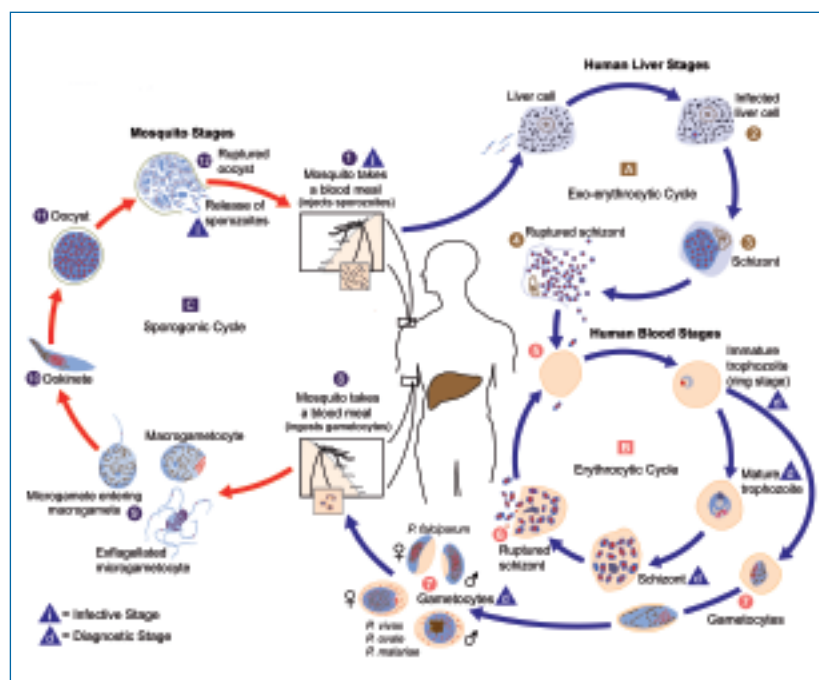
Screening with capillary blood samples

There are obvious trade-offs between costs and accuracy among the available options. The most accurate assessment of IDA includes data on hemoglobin (16) in combination with serum ferritin, transferrin receptor (TfR) plus C-reactive protein (CRP) (17), or AGP to control for inflammatory influences on serum ferritin. This “classic” set of variables can be determined in approx. 30 μ L serum from capillary blood samples with satisfactory validity and precision (18–20). Although other biomarkers, such as transferrin saturation, erythrocyte protoporphyrin, reticulocyte hemoglobin content, or percentage of hypochromic red blood cells (21) could be theoretically added, the basic package offers a very reliable assessment of iron and anemia status. Financing widespread screening could

be prohibitive. However, the costs of test chemicals for analysis of serum ferritin, transferrin receptor and AGP can be reduced to approx. \$1 US due to miniaturization (22). In addition, cost for blood-sampling devices, transport, laboratory equipment and staff come into prominence. The risk of blood-borne diseases, like HIV and hepatitis, should not be underestimated, as single-use lancets and cannula may be used repeatedly in developing country settings. Finally, since these tests require the extraction of blood, there are associated pain (albeit minimal), even with capillary blood, and cultural taboos about blood handling; both of these consequences may induce widespread rejection by the population, especially for application to such young children.

Inspection and questionnaire approaches

IDA-assessments by clinical inspection of sclera and pale skin, assisted by a questionnaire on risk factors of iron deficiency, may be put at the other end of the scale of cost, invasiveness, reliability, and precision. The questionnaire should contain questions to assess dietary intake, socio-economic and educational status of the family in analogy to earlier guidelines of the Center of Disease Control and Prevention (23) for the US, plus some more recent risk factors (e.g., overweight) (24). Similar approaches are used in veterinary health and require well-trained health workers (25). Their advantage is that they are inexpensive and non-invasive; but their sensitivity and specificity are very limited.



Malaria cycle. From US CDC

Non-invasive assessment of hematological status

A first attempt to quantify hemoglobin concentration by non-invasive methods was based on back-scattered light from human tissues *in vivo* as determined by the Erlangen microlight-guide photometer (26). More recent technology has gained much precision. It uses orthogonal polarization spectrometry to produce an image of the sublingual microcirculation at 548 nm, which permits hemoglobin measurement in the vessels *in vivo*. A probe the size of a pencil is connected to a portable processing unit and produces an image that is divided into vessel and background regions. The optical density in a number of vessel seg-

ments is used to determine hemoglobin concentration (27). Estimation of the subjects' systemic hemoglobin concentration was shown to be highly reproducible and closely correlated to conventionally determined hemoglobin concentrations in venous blood samples over a wide range of hemoglobin concentrations (28). Applicability in the field to assess the variability in a large number of subjects of different origin, however, has yet to be tested. As only about 50% of anemias in developing countries can be attributed to iron deficiency (29–31), the presence of iron deficiency needs to be established. This could be done *ex post facto* by measuring the response of anemia to 8 weeks of iron administration. This approach is non-invasive and promises to combine high accuracy with easy handling and low running costs beyond the expenses for the staff. Its applicability in the field, however, has yet to be tested.

Slowing the rate of uptake of oral iron from supplemental forms

Considerations to improve the safety of iron intake in malaria-endemic areas build on the observation that non-transferrin-bound iron (NTBI) activates the intracellular adhesion molecules ICAM-1, VCAM-1 and E-selectin in the vascular endothelium (32). These changes, in turn, seem to ease the adhesion of *P. falciparum* to the vascular endothelium and, thus, the prevalence for example of cerebral malaria manifesta-

tions (33). NTBI was observed to increase after pulse doses of readily available oral iron preparations (34) which are known to increase serum iron concentrations rapidly but only for comparably short periods (35). Thus, high concentration peaks of serum iron and, thus, of NTBI should be avoidable, if iron absorption were retarded.

A potential problem of oral slow release preparations for iron is that they may pass beyond the duodenum (i.e., the location of the highest iron absorption rate) before the iron is released from such galenic forms; this would impair its bioavailability and reduce its biological impact. Slow gastric delivery systems are an exception to this rule.

These preparations float on the gastric juice and release their iron over an extended period of time upstream of the duodenum. This type of preparation increases iron absorption rates (36) and also avoids high peak concentrations of free iron in the intestinal lumen, which significantly reduces intestinal side effects (37). At the same time the protracted release attenuates peaks in circulating iron (BS Skikne, JD Cook, unpublished observations, 1991, quoted by Simmons et al. (37)), which is likely to reduce NTBI concentrations. This, in turn, could reduce the prevalence of cerebral malaria manifestations. Although this concept offers promise, its scientific base is not yet very solid, as field experience is lacking. According to this concept, offering iron (e.g., via a gastric delivery system or with fortified food items over the whole day) should not increase the risk of severe malaria complications.

Non-invasive screening methods may offer promise

In this context, Sprinkles, Foodlets and iron-fortified spreads should be considered to be supplements, as they deliver the iron dosage for an entire day in a single dose. Several factors seem to influence the serum iron peak with these compounds. Among them would be the dose of iron, the iron status of the child, the matrix of the supplement, and the consistency of the meal. Presumably, the peak serum concentration reached after consumption of such ready-to-eat fortificants will determine whether they are harmful in a malarial setting or not.



Anemia assessment by pallor staging

Another alternative to avoid hazardous peak serum concentrations of iron would be to identify and use oral iron complexes that are absorbed as such. If such complexes release their iron slowly after having been absorbed, high peak concentrations of free iron are avoided. Such approaches, however, need more developmental work before they can be used in large-scale interventions in young children.

Commentary on the wisdom and limitations of the World Health Organization

Consultancy Statement

The United Nations did not remain idly on the sidelines in the face of public health and safety consequences of the Pemba experience. In April 2006, the World Health Organization and UNICEF issued an interim statement (38), announcing the convening of an Expert Consultancy Panel, among others, to provide guidance regarding routine prophylactic supplementation of iron in the preschool age group. The group met in Lyon, France; a summary of this Consultancy has been released and is reprinted in this issue of the SIGHT AND LIFE Magazine (page 14-15). The considerations in this commentary provide theoretical and practical linkage to an analysis of the lessons from the Pemba trial (4). The WHO-sponsored consultancies have offered sage and sound conclusions regarding the proscription of routine iron supplementation in malaria-endemic settings.

The WHO interim statement released early in 2006 (38) is to be praised for raising notes of caution with regard to universal, saturation iron supplementation in settings with a background of HIV and/or

tuberculosis (38). Moreover, the interim statement announced the drafting of a detailed research agenda as one of the main charges of the Expert Consultancy Panel. Despite the need to develop evidence to inform policy-makers on oral iron supplementation, the degree to which research protocols may be ethically challenged by the experience in Pemba cannot be overlooked. Finding a manner for inquiry that is safe for the study populations may not be easy. Independent from this issue, we touch on some gaps of knowledge below that relate to the WHO Consultancy Statement and seem to urge additional research.



Mother with anemic child

Comprehensive and effective healthcare

Healthcare measures mean to insure the public's health, and take on special relevance where holo-endemic malaria is established. Clearly, mosquito control and avoidance of the insect vector are fundamental. Beyond such measures, exclusive breastfeeding for the first 6 months of life is explicitly recommended. Technically, the administration of micronutrient syrups, for example, is considered a violation of exclusivity of breastfeeding (39). Recently, a suggestion that there is a need for early iron supplementation in all infants has been made (40) based on the consideration that *"only about 50% of their iron requirements*

during the first 6 months can be obtained from breast milk." How such a recommendation would be operative in malarial areas falls into the large incognitos of malaria pathology and supplemental iron exposures. This theme is best viewed as a subject for research prior to implementation.

Iron status screening

Insistence on some sorting and selection of individuals for oral supplementation in malaria endemic areas heralds a new and safer – but more complex – era of iron deficiency control. The putative clinical diagnosis of severe anemia by pallor staging mentioned here offers a low-cost, non-invasive approach with reasonable specificity but poor sensitivity. We see promise in improving the acceptability and accessibility of screening methods by use of miniaturized approaches using capillary blood (22), by non-invasive methods (27), or by well-tested approaches for IDA-assessments by clinical inspection, assisted by questionnaires on risk factors of iron deficiency. A view on cost issues, on the risk of blood-borne diseases, and on cultural acceptability seems paramount in all efforts to improve IDA assessment.

Screening to avoid iron exposure to the iron-replete has additional merits in populations that may not suffer malaria endemicity. The evidence is now convergent and virtually conclusive that iron-replete children grow more poorly when exposed to oral iron supplementation (41–43). This adds a strong rationale to consider screening before implementation of universal supplementation for pre-school-children. Finally, we underscore the need to move the proposed research agenda on routine universal iron supplementation where

“other infections” are prevalent. The pathogen biology of plasmodia is not that distinct from other infections with intracellular organisms, such as leprosy, tuberculosis or HIV, so that extension of the principles of the WHO Statement (38) and Summary (44) in terms of selective coverage with iron supplementation should now be seriously considered.

Home-fortification versus fortified foods as sources of prophylactic iron

The Consultancy rightly claims lack of certainty regarding the safety of oral iron when given with food. They apply the theoretical consideration around potential adverse consequences of rapid uptake of iron into the circulation reviewed above. Supplemental iron in proven deficiency is to be given with food, rather than on an empty stomach. Extending this logic within the safety considerations for home fortification with iron (which is discouraged), and commercial food-fortification (which is encouraged), the admitted uncertainty takes center stage. Definitive research, rather than tentative policy guidance, is the true priority in relation to additional oral iron in the context of meals.

Proscription of folic acid supplementation and fortification

The WHO Expert Consultancy Statement contains a recommendation for the total omission of folic acid from multi-micronutrient preparations in malarial areas, including in its traditional association with iron. There is a prudent basis to omit folic acid exposure, when anti-folate metabolism is the mainstay of anti-malaria therapy. However, the observation that the “*widespread folate deficiency not known to be a problem in infants and young children*” should not be given as a rationale to omit folic acid from preschool supplements. Folic acid should be seen as a *companion hematinic* nutrient to iron. Presumably, in the anticipation of a major reticulocytic response and rapid restoration of the red cell mass enabled by adequate iron supplementation, an additional presence of folates will be needed for the proliferative response in the bone marrow.

Conclusion

Meanwhile, policy decisions and program operations that dismiss the warnings of the WHO Consultancy Statement on blanket, routine oral iron supplementation imperil the health and lives of children living within a background of chronic and recurrent malaria, in spite of good intentions. To maintain the *first do no harm* mandate for infant and toddler iron supplementation we need to insure a better and safer way to deliver iron in this age group. Meanwhile, we should seek creative ways to ensure that children absorb the iron that is afforded by their diet and retain the iron they absorb. For those who still show obvious clinical signs of iron deficiency, a targeted approach with supplements should be employed, preferably with galenic compositions that release as little free iron into the systemic circulation as possible. In the long run, screening for iron deficiency by innovative

methods should be developed to reduce the exposure to iron for those who have no need for additional amounts of the nutrients and to satisfy the requirement of those who could benefit from repletion of their iron reserves.

Mosquito control and avoidance of the insect vector are fundamental

References

1. Gross R. Micronutrient supplementation throughout the life cycle. New York: UNICEF, 2001.
2. Food and Nutrition Board, Institute of Medicine, Dietary Reference Intakes: Vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington DC: National Academy Press, 2001.
3. Stoltzfus RJ, Dreyfuss ML. Guidelines for the use of iron supplements to prevent and treat iron deficiency anemia. Washington DC: ILSI Press, 1998.
4. Sazawal S, Black RE, Ramsan M, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006;367:133–43.
5. Oppenheimer SJ. Iron and its relation to immunity and infectious disease. *J Nutr* 2001;131:616S–5S.
6. McKay HM. Anemia in infancy: its prevalence and prevention. *Arch Dis Child* 1928;3:117–47.
7. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics* 2000;105:E51.
8. Tielsch JM, Khartry SK, Stoltzfus RJ, et al. Effects of routine prophylactic supplementation with iron and folic acid on preschool children mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. *Lancet* 2006;367:144–52.

9. English M, Snow RW. Iron and folic acid supplementation and malaria risk. *Lancet* 2006;367:90–1.
10. Brown KH, Dewey KG, Allen LH. Complementary feeding of young children in developing countries: A review of current scientific knowledge. Geneva, WHO/UNICEF, 1998.
11. Krebs NF, Westcott JE, Butler N, Robinson C, Bell M, Hambidge KM. Meat as a first complementary food for breast-fed infants: feasibility and impact on zinc intake and status. *J Pediatr Gastroenterol Nutr* 2006;42:207–14.
12. Hurrell RF. Phytic acid degradation as a means of improving iron absorption. *Int J Vitam Nutr Res* 2004;74:445–52.
13. Gibson RS, Yeudall F, Drost N, Mtitimuni B, Cullinan T. Dietary interventions to prevent zinc deficiency. *Am J Clin Nutr* 1998;68(2 Suppl):484S–7S.
14. Mendoza C, Viteri FE, Lönnerdal B, Young KA, Raboy V, Brown KH. Effect of genetically modified, low-phytic acid maize on absorption of iron from tortillas. *Am J Clin Nutr* 1998;68:1123–7.
15. Zhang H, Onning G, Oste R, Gramtkovski E, Hulthén L. Improved iron bioavailability in an oat-based beverage: the combined effect of citric acid addition, dephytinization, and iron supplementation. *Eur J Nutr* 2007 (Epub ahead of print).
16. Muñoz M, Romero A, Gomez JF, Manteca A, Naveira E, Ramirez G. Utility of point-of-care measurement in the HemoCue-B haemoglobin for initial diagnosis of anaemia. *Clin Lab Haematol* 2005;27:99–104.
17. Fleming DJ, Jaques PF, Massaro JM, D'Agostino RB, Wilson PWF, Wood RJ. Aspirin intake and the use of ferritin as a measure of iron status. *Am J Clin Nutr* 2001;74:219–26.
18. Erhardt JG, Estes JE, Pfeiffer CM, Biesalski HK, Craft NE. Combined measurement of ferritin, soluble transferrin receptor, retinal binding protein, and C-reactive protein by an inexpensive, sensitive and simple sandwich enzyme-linked immunosorbent assay technique. *J Nutr* 2004;134:3127–32.
19. Baynes RD. Refining the assessment of body iron status. *Am J Clin Nutr* 1996;64:793–4.
20. Olivares M, Walter T, Cook JD, Hertrampf E, Pizarro F. Usefulness of serum transferrin receptor and serum ferritin in diagnosis of iron-deficiency in infancy. *Am J Clin Nutr* 2000;72:1191–5.
21. Coyne D. Iron indices: what do they really mean? *Kidney Internat* 2006;69:54–8.
22. Biesalski HK, Erhardt J. Diagnosis of nutritional anemia – laboratory assessment of iron status. In: Kraemer K, Zimmermann MB, eds. *Nutritional Anemia*. Basel: SIGHT AND LIFE Press, 2007:37–44.
23. Center of Disease Control. Recommendations to prevent and control iron deficiency in the United States. *Morbidity and Mortality Weekly Report* 1998;47:1–29.
24. Nead KG, Halterman JS, Kaczorowski JM, Auinger P, Weitzman M. Overweight children and adolescents: a risk group for iron deficiency. *Pediatrics* 2004;114:104–8.
25. van Wyk JA, Bath GF, Groeneveld HT, Stenson MO, Malan FS. Extensive testing of the FAMACHA© system for accuracy of clinical evaluation of anaemia caused by oxidative haemolysis. Proc. 5th Int. Sheep Veterinary Congress. Cape Town, South Africa, 2001.
26. Gross R, Gliwitski M, Gross P, Frank K. Anaemia and haemoglobin status: A new concept and a new method of assessment. *Food Nutr Bull* 1996;17:27–36.
27. Nadeau RG, Groner W. Orthogonal polarization spectral imaging: state of the art. In: Mesmer K, ed. *Orthogonal Polarization Spectral Imaging*. Basel: Karger, 2000:920.
28. Nadeau RG, Groner W. The role of a new non-invasive imaging technology in the diagnosis of anemia. *J Nutr* 2001; 131: 1610S–4S.
29. Allen LH, Rosado JL, Casterline JE, et al. Lack of hemoglobin response to iron supplementation in anemic Mexican preschoolers with multiple micronutrient deficiencies. *Am J Clin Nutr* 2000;71:1485–94.
30. Straubli Asobayire F, Adou P, Davidsson L, Cook JD, Hurrell RF. Prevalence of iron deficiency with and without concurrent anemia in population groups with high prevalences of malaria and other infections: a study in Côte d'Ivoire. *Am J Clin Nutr* 2001;74:776–82.
31. Schumann K, Romero-Abal ME, Mäurer A, et al. Hematological response to heme iron or ferrous sulphate mixed with refried black beans in moderately anemic Guatemalan preschool children. *Pub Health Nutr* 2005;8:572–81.
32. Kartikasari AER, Georgiou NA, Visseren FLJ, van Kats-Renaud H, Sweder van Asbeck B, Marx JJM. Endothelial activation and induction of monocyte adhesion by nontransferrin-bound iron present in human sera. *FASEB J* 2005;20:353–5.
33. Gray C, McCormick C, Turner G, Craig A. ICAM-1 can play a major role in mediating *P. falciparum* adhesion to endothelia under flow. *Mol Biochem Parasitol* 2003;28:187–93.
34. Hutchinson C, Al-Ashgar W, Liu DY, Hider RC, Powell JJ, Geissler CA. Oral ferrous sulphate leads to a marked increase in pro-oxidant nontransferrin-bound iron. *Eur J Clin Invest* 2004;34:782–4.
35. Hoppe M, Hultén L, Hallberg L. The validation of using serum iron increase to measure iron absorption in human subjects. *Br J Nutr* 2004;92:485–8.
36. Cook JD, Cavuigiaga M, Kahn SG, Schalch W, Skikne BS. Gastric delivery system for iron supplementation. *Lancet* 1990;335:1136–9.
37. Simmons WK, Cook JD, Bingham KC, et al. Evaluation of a gastric delivery system for iron supplementation in pregnancy. *Am J Clin Nutr* 1993;58:622–6.
38. World Health Organization/UNICEF. Iron supplementation of young children in regions where malaria is intense and infectious disease is highly prevalent. Joint statement. Geneva: WHO, 2006.
39. World Health Organization. Indicators for assessing breastfeeding practices. Report of an informal meeting in June 1991. Geneva: WHO, 1991.
40. Kraemer K, Stoecklin E, Badham J. Conclusions and research agenda. In: Badham J, Zimmermann MB, Kramer K, eds. *The Guidebook: Nutritional Anemia*. Basel: SIGHT AND LIFE Press, 2007:48–50.
41. Idjradinata P, Watkins WE, Pollitt E. Adverse effect of iron supplementation on weight gain of iron-replete young children. *Lancet* 1994;343:1252–4.
42. Majumdar I, Paul P, Talib VH, Ranga S. The effect of iron therapy on the growth of iron-replete and iron-deplete children. *J Trop Pediatr* 2003;49:84–8.
43. Lonnerdal B, Lind T, Persson LA. Iron supplementation for iron replete Indonesian infants impairs growth (abst). ESPHAGAN Meeting, 2007.
44. de Benoist B, Fontaine O. Summary of the Conclusions of the WHO Consultation on prevention and control of iron deficiency in infants and young children in malaria endemic areas. Lyon France, 12–14 June 2006. *SIGHT AND LIFE Magazine Issue 3/2007*, 14–15.

Summary of the conclusions of the WHO consultation

Prevention and control of iron deficiency in infants
and young children in malaria-endemic areas
Lyon, France, 12–14 June 2006

Bruno de Benoist

Department of Nutrition for Health and Development, WHO, Geneva

Olivier Fontaine

Department of Child and Adolescent Health, WHO, Geneva

Correspondence: Olivier Fontaine, Department of Child and
Adolescent Health, WHO, Geneva

Email: fontaineo@who.int

Iron deficiency anemia is common in young children

and there is substantial evidence that iron deficiency has adverse effects on child health and development. Therefore provision of additional iron to infants and young children who are iron deficient should be a public health priority.

Two large trials, coordinated and supported by WHO, were conducted in Zanzibar, Tanzania, and in Nepal to evaluate the impact of zinc and/or iron-folic acid supplementation on the mortality and severe morbidity of preschool children (1, 2). In Zanzibar, an area of stable, perennial and intense transmission of *Plasmodium falciparum* malaria, routine iron-folic acid supplements given with or without zinc resulted in an increased rate of severe adverse events in children (morbidity and mortality). A concurrent substudy suggested that the adverse events occurred in supplemented children who were not iron deficient. In Nepal the trial showed no difference in mortality or the incidence of the common infections between children receiving

iron-folic acid with or without zinc, and those who received zinc alone or a placebo. The results from the study in Zanzibar, Tanzania (1) raised the issue of the safety of administering additional iron to infants and young children in areas of malaria endemicity and its public health implications.

WHO convened an expert Consultation to examine this issue, in Lyon, France, 12–14 June 2006. The objectives of the Consultation, which focused on infants and young children in malaria-endemic areas, were: 1) To review the scientific evidence on the safety and efficacy of different ways of administering iron to control iron deficiency and iron deficiency anemia; and 2) To provide guidance on the safest, most feasible and effective ways of delivering additional iron to control iron deficiency and anemia in such areas.

The participants to the Consultation reached consensus on several important issues related to providing additional iron to infants and young children in malaria-endemic areas:

- Strategies to control iron deficiency should be carried out in the context of comprehensive and effective health care, including the provision of insecticide-

Control of iron deficiency in the context of comprehensive health care

treated nets and vector control for the prevention of malaria, and prompt recognition and treatment of malaria and its complications with effective anti-malarial and antibiotic drug therapy. They should also include control of other prevalent parasitic diseases and infections, and the promotion of exclusive breastfeeding for the first six months of life followed by consumption of nutrient dense and/or processed fortified complementary foods (3, 4).

- Universal iron supplementation (i.e., use of medicinal iron as pills or syrups) should not be implemented without the screening of individuals for iron deficiency, because this mode of iron administration may cause severe adverse events in iron-sufficient children.
- The safety of iron preparations administered through home fortification of complementary foods for infants and young children (i.e., powders, crushable tablets, and fat-based spreads) is uncertain in malaria-endemic areas. Although there is reason to believe that those preparations may be safer than iron supplements, they cannot be recommended until this has been demonstrated.
- An option would be to administer additional iron to infants and young children as processed complementary foods fortified with iron. Although the safety of their use in malaria-endemic areas has not been documented, this is likely to avoid the potential adverse effects of a large bolus of iron taken in a single dose, since the iron would be consumed in smaller amounts throughout the day and therefore absorbed more slowly.
- Infants and young children who have malaria and are diagnosed with iron deficiency (3) or severe anemia, should be treated with antimalarial and where appropriate antibiotic therapy as well as iron therapy, which should always be administered with food. The



Anemic child

reservations concerning the harmful effects of universal iron supplementation do not diminish the need for adequate iron therapy when iron deficiency is diagnosed.

- Because widespread folate deficiency is not known to be a problem in infants and young children, and supplemental folic acid may interfere with the efficacy of antifolate antimalarial drug therapy, supplemental folic acid or foods fortified with folic acid should not be given to infants and young children in areas where anti-folate anti-malarial drugs are used.
- The potential pathophysiological mechanisms governing the relationships between iron metabolism and infection, and the risk of severe adverse events after iron administration were also discussed, but it was felt that there are insufficient data to draw conclusions that would justify changing public health programs. Further research on this topic is required.

References

1. Sazawal S, Black RE, Ramsan M, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet* 2006;367:133–43.
2. Tielsch JM, Khattry S, Stoltzfus R, et al. Effects of routine prophylactic supplementation with iron and folic acid on preschool child mortality in Southern Nepal: community-based, cluster-randomised, placebo-controlled trial. *Lancet* 2006;367:144–52.
3. WHO, CDC. Assessing iron status of populations. Report of a joint World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level, Geneva, 6–8 April 2004. Geneva: WHO, 2005.
4. WHO, UNICEF. Iron supplementation of young children in regions where malaria transmission is intense and infectious disease highly prevalent. Joint Statement. Geneva: WHO, 2006

Golden Rice and biofortification

Jorge E. Mayer

Golden Rice Project, Campus Technologies Freiburg,
Germany

Email: jorge.mayer@goldenrice.org

Tackling micronutrient malnutrition

Breeders have only recently gone beyond increasing crop yields and started paying attention to quality traits, among which micronutrient content is of the utmost relevance for developing countries. Because of indirect cause-effect relationships and the great variability of nutritional status within populations, establishing the link between micronutrient malnutrition (MNM) and various afflictions has been a daunting statistical task (1).

More recent population-wide survey data on health and nutrition has made it possible to identify MNM, also known as ‘hidden hunger,’ as one of the main culprits of a number of syndromes. In Southeast Asia, the burden imposed by the combined deficiencies of iron, zinc and vitamin A – common among low-income populations – leads to a loss of disability-adjusted life years (DALYs) comparable to that caused by HIV/AIDS or tuberculosis, and is only second to respiratory infections, cardiovascular and diarrhoeal diseases (2). Globally, around 5 million children under the age of five die every year as a direct consequence of MNM. Supplementation with zinc and vitamin A alone could save the lives of a

quarter of those children; a more inclusive approach could save many more (3).

Starchy staples, like rice, cassava, maize, and sorghum, are the main calorie sources in developing countries, with good storability characteristics, but their micronutrient content is generally low. A vast proportion of the population in those countries cannot afford a balanced diet to cover their daily micronutrient requirements. Moreover, people need regular access to vegetables, fruits and animal sources to meet their daily micronutrient needs, but these are seasonal and perishable goods, and often unaffordable or culturally unacceptable.

Supplementation and industrial fortification programs are presently the best options to combat MNM. The latter is well suited for urban populations with access to fortified foodstuffs, like vitamin A-fortified oils and margarine or iodinated salt. Supplementation programs, on the other hand, suffer from the recurring costs. While the cost of vitamin A capsules is only around 10 cents per unit, operational costs add another 90 cents to every capsule (4). Five-hundred million capsules are donated and distributed every year around the world! Recurring costs for small

countries, like Nepal or Ghana, are around \$2 million per year (5); covering just 50% of India would require more than \$100 million annually (2). As a result, globally, only 55% of the target population has access to supplementation (6). Moreover, coverage fluctuates from year to year due to the vagaries of geopolitics and civil unrest (7).

Biofortified crops with the genetically inbuilt capacity to produce or accumulate vitamins and minerals at higher concentrations offer a novel approach that does not attract recurring costs and is capable of reaching remote rural populations (1, 8-10) (**Table 1**). Micronutrient-dense crop plants can be obtained through conventional breeding or, in the absence of genetic variability for the trait, by genetic engineering.

Nutritious mutants

Micronutrients are not always present in the desired plant tissues. Sometimes, in nature, mutations lead to the activation of carotenoid biosynthesis in usually non-carotenogenic tissues, as was the case with carrots (*Daucus carota*), a vegetable introduced from Afghanistan and which came initially in various colours, except for orange. Carrots with purple-red anthocyanins were first grown in the

Middle and Far East, along with white, red, yellow, green and black versions. An orange carrot mutant that accumulated up to 6 mg/g dry weight of β -carotene (provitamin A) in root tissues – the nature of the mutation is not yet understood – became popular in the Netherlands in the 16th century because of its association with the royal House of Orange.

But large amounts of β -carotene are not necessarily synonymous with high availability, as we know from green leafy vegetables, where only 1 μ g vitamin A turns up in our blood stream from 24 μ g of β -carotene. The bioavailability of β -carotene in raw carrots is limited because it is deposited as crystals in the roots. Bioavailability can be raised by cooking and serving with some oil. The retention of carotenoids after heat treatment is very high and cooking generally increases its bioavailability, as has been shown for orange-fleshed sweet potato (11).

Another more recent example is an already commercially-available orange-coloured cauliflower (*Brassica oleracea var botrytis*). This semi-dominant mutation is due to the insertion of a retrotransposon into the so-called Or allele (Or for orange) (12). The mutation possibly interferes with the sequestration of carotenoids into chromoplasts. The principle can be applied to other crops, as was shown by the generation of transgenic yellow-fleshed potatoes expressing the Or gene (12). The downside of this approach thus far is that, in homozygous plants, growth is stunted, probably due to poorly understood pleiotropic effects.

The advent of Golden Rice

Golden Rice is a prime example of the metabolic engineering of a nutrient-enhanced crop. The development of the first Golden Rice prototype took a concerted seven-year effort, culminating in 1999, by the collaborating groups of Ingo Potrykus and Peter Beyer, work-

ing at the Swiss Federal Institute of Technology and University of Freiburg, respectively. Their ambitious goal was to re-engineer the biosynthetic machinery of the rice grain to produce and accumulate β -carotene, a pigment found in the green tissues of rice but not in the grain. This ran into the scepticism of many experts, based on the knowledge that carotenogenic tissues not only possess active metabolic pathways, including the presence of precursor molecules, but also deposition mechanisms, such as carotenoid crystallization, formation of oil droplets, sequestration of carotenoids into membranes or protein-lipid complexes. The non-carotenogenic starchy endosperm of rice is very low in lipids and apparently lacks the means for carotenoid deposition. Nonetheless, the inventors relied on recent advances in the fields of genetic transformation and the understanding of carotenoid biosynthesis to achieve their goal.

Basically, Golden Rice technology succeeded because rice grains – though not carotenogenic – produce carotenoid precursor molecules and some of the enzymes responsible for further downstream processing. The addition of only two genes was sufficient to render the pathway fully functional and consequently capable of accumulating β -carotene in the seed endosperm (13). As it turns out, carotenoid production can also be spurred in other plant species by increasing the production of precursor molecules, filling in the enzymatic gaps, or by blocking the synthesis of catabolic enzymes downstream of the desired product.

The clockwork orange

Geranylgeranyl-diphosphate (GGDP) is a key biosynthetic intermediate of isoprenoids, a substance class that includes carotenoids. GGDP is the precursor of several key compounds, including tocopherols (vitamin E), tocotrienols, carotenoids, abscisic acid (a phytohormone involved in regulatory processes, like bud and seed dormancy, and various stress responses), gibberellic acid (another phytohormone promoting growth and cell elongation), chlorophyll, and other components of the photosynthetic machinery. The complexity of the metabolic turntable of GGDP was what fed the scepticism of many experts (**Figure 1**).

Golden Rice technology relies on two transgenes (**Figure 2**). The first codes for phytoene synthase

Table 1: Advantages of biofortification

- One-off research investment with no maintenance costs
- Seed-borne technology
- Concept applicable to many crops
- Amenable to introgression into many varieties
- Utilizes the usual seed distribution channels
- Capable of reaching remote populations
- Sustainable and cost-effective
- Compatible with ongoing fortification, supplementation and education programs

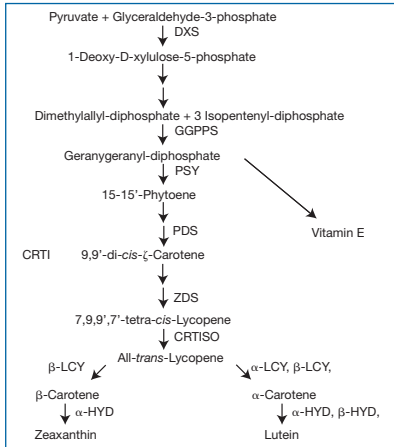


Figure 1: Carotenoid biosynthetic pathway and genetic intervention points in Golden Rice. DXS, 1-deoxy-D-xylulose-5-phosphate synthase; GGPPS, geranylgeranyl-diphosphate synthase; PSY, phytoene synthase; CRTI, bacterial carotene desaturase; PDS, phytoene desaturase; ZDS, ζ-carotene desaturase; CRTISO, carotene cis-trans-isomerase; LCY, lycopene cyclase; HYD, carotene hydroxylase. In Golden Rice two transgenes have been introduced to reconstitute the complete pathway, the other necessary enzymes are present and active in the rice grain. The two genes are *Psy*, from daffodil (*Narcissus pseudonarcissus*) in GR1 or maize (*Zea mays*) in GR2, and *CrtI*, from the soil bacterium *Erwinia uredovora*. CRTI replaces PDS, ZDS and CRTISO. Desaturation by CRTI proceeds via all-trans intermediates, as opposed to the plant enzymes

(*Psy*) from daffodil (*Narcissus pseudonarcissus*) or maize (*Zea mays*), which utilizes GGDP to form colourless phytoene. The product of the second transgene is carotene desaturase (*CrtI*), from the bacterium *Erwinia uredovora*, which converts phytoene into the fully conjugated β-carotene precursor molecule lycopene. The endogenous enzyme, β-lycopene cyclase (LCY), then leads to the formation of β-carotene. The bacterial *CrtI* is a multifunctional enzyme that replaces at least three plant enzymes, namely the

carotene desaturases: phytoene desaturase (PDS), ζ-carotene desaturase (ZDS), and carotene isomerase (CRTISO) (13,14). Due to its multifunctionality and minimal co-factor requirements, *CrtI* was chosen over the plant desaturases for the generation of Golden Rice.

The predominance of β-carotene over α-carotene in Golden Rice is aided by the fact that the lycopene isomer ratio leads preferentially to β-carotene formation. Further processing of β-carotene to hydroxylated derivatives in rice grains occurs at a reduced rate, leading to greater β-carotene accumulation.

Spreading of a concept

Most starchy crops lack adequate amounts of micronutrients. Potato, for example, is one of the major staple crops in the world, but in most cultivars, β-carotene is present only in trace amounts. While the yellow wild potato species *Solanum phureja* may contain high levels of carotenoids, only a small fraction consists of β-carotene.

The complexity of introducing a trait for β-carotene production by breeding and the fact that pota-

atoes are vegetatively propagated demand a Golden Rice-like approach. High-β-carotene potatoes have already been generated by either blocking the expression of ε-lycopene cyclase (ε-LCY), which diverts lycopene into the α-carotene and lutein branch of the pathway (15), or by the introduction of a “mini-pathway” consisting of three genes from *Erwinia*: phytoene synthase (*CrtB*), phytoene desaturase (*CrtI*), and lycopene β-cyclase (*CrtY*) (16). In the latter, total carotenoid content increased 20-fold while β-carotene increased 3600-fold, up to 47 μg/g dry weight.

Indian mustard (*Brassica juncea*), a popular source of cooking oil in India, was transformed with bacterial *Psy* and *CrtI* genes so as to deliver highly bioavailable β-carotene to target populations. This project is now awaiting an *ex-ante* socio-economic assessment before going ahead. Similarly, a Golden Maize (*Zea mays*) is being produced for Africa using the bacterial *CrtB* and *CrtI* genes. Lines capable of meeting 50% of the estimated average requirement (EAR) of vitamin A for children have already been generated.

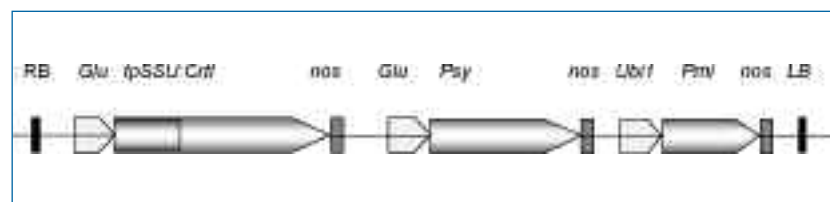


Figure 2: Gene construct used to generate Golden Rice. RB, T-DNA right border sequence; Glu, rice endosperm-specific glutelin promoter; tpSSU, pea ribulose bis-phosphate carboxylase small subunit transit peptide for chloroplast localization; nos, nopaline synthase terminator; Psy, phytoene synthase gene from *Narcissus pseudonarcissus* (GR1) or *Zea mays* (GR2); Ubi1, maize polyubiquitin promoter; Pmi, phosphomannose isomerase gene from *E. coli* for positive selection (GR2); LB, T-DNA left border sequence. Carotenoid biosynthetic pathway and genetic intervention points in Golden Rice. DXS, 1-deoxy-D-xylulose-5-phosphate synthase; GGPPS, geranylgeranyl-diphosphate synthase; PSY, phytoene synthase; CRTI, bacterial carotene desaturase; PDS, phytoene desaturase; ZDS, ζ-carotene desaturase; CRTISO, carotene cis-trans-isomerase; LCY, lycopene cyclase; HYD, carotene hydroxylase

Within the Grand Challenges in Global Health Initiative, the Bill & Melinda Gates Foundation is funding four biofortification projects, led by the Queensland University of Technology for banana (*Musa spp.*), Ohio State University for cassava (*Manihot esculenta*), the Africa Biofortified Project for sorghum (*Sorghum bicolor*), and the University of Freiburg for rice (*Oryza sativa*). Within the frame of this project, genes are being added to Golden Rice to promote the accumulation or bioavailability of iron, zinc, vitamin E, and high-quality protein in rice grains. The other groups are pursuing similar goals, also incorporating genetic traits for biotic and abiotic stress resistance or tolerance.

Similarly, efforts to increase iron content and bioavailability in rice are well underway (17-20). More recently, re-engineering of the folate biosynthetic pathway in tomato was reported (21); this approach has meanwhile been duplicated in rice (22). This could be an important development, as

folate deficiency leads to hundreds of thousands of babies being born with neural tube defects, thus leading to *spina bifida* syndrome (23).

From proof of concept to a product

For Golden Rice to attain a positive impact on health, β -carotene must be present at a high enough concentration, taking into account its bioavailability. At 1.6 $\mu\text{g/g}$ carotenoid, the first Golden Rice prototype could have been regarded as a dietary supplement but it was recognized early on that, in the absence of a more varied diet, an improved version would be required to cater for the needs of the target populations.

The first improved version, GR1, contained the same two genes as the prototype, only that both genes were expressed exclusively in the grain endosperm, rather than constitutively, to avoid potential interference with photosynthesis in leaves (24). The amount of β -carotene obtained with GR1 was 6 $\mu\text{g/g}$ on average, an

almost four-fold increase over the prototype. Preliminary bioavailability trials suggest that GR1 could possibly provide the Recommended Nutrient Intake (RNI) for children – even more so if we factor in a modest intake of vegetables and fish or other animal sources, as is usually the case in the rural diets of Southeast Asian countries (Figure 3). The good results are not completely unexpected, since the rice grain represents a simple, highly digestible food matrix, comparable to that of maize (25).

Complex biosynthetic pathways are usually regulated by a rate-limiting step – in this case, phytoene production by *Psy*. The comparison of *Psy* genes from different plant sources revealed that the maize and rice genes were better than the daffodil (used in the prototype version) and other homologues. This finding led to the development of GR2, which uses a maize *Psy* gene (26) (Figure 4). One GR2 line, acceptable from the regulatory perspective, contained 37 $\mu\text{g/g}$ total carotenoids, 80% of which was β -carotene, representing a 23-fold increase over the prototype.

Considering that the RNI of vitamin A for 1–3 year-old children is 400 μg and based on a retinol equivalency ratio for β -carotene in Golden Rice of 6:1 (preliminary results indicate that bioconversion values could be even better), half the RNI could be provided in around 50 g of GR2. Children in target countries eat 100–200 g per day.

The *golden* trait could, in principle, be directly engineered into many different rice varieties. However, due to stringent regulatory requirements, the aim is to have only one regulatory clean event as the starter material for introgression in parallel breeding programs. The transfer

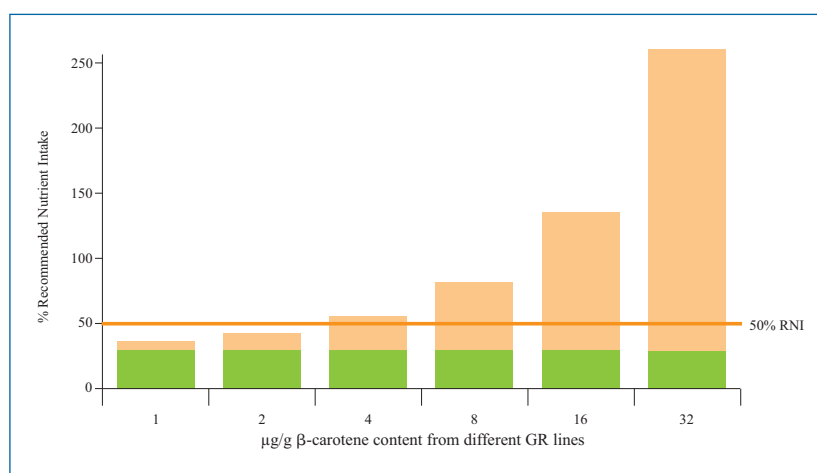


Figure 3: Capacity of Golden Rice lines with varying carotene content to supply the recommended nutrient intake of vitamin A. The values on the graph were calculated based on the following assumptions: Recommended Nutrient Intake (WHO/FAO) for 1–3 year-olds (RNI) is 400 μg Retinol Equivalents (RE); a conservative bioconversion of β -carotene into vitamin A for Golden Rice of 1:6; a low baseline of 112 μg RE obtained from other foodstuffs, as observed for children living in rural Bangladesh; retention of β -carotene after cooking 80%; and ingestion of 200 g of rice on a daily basis

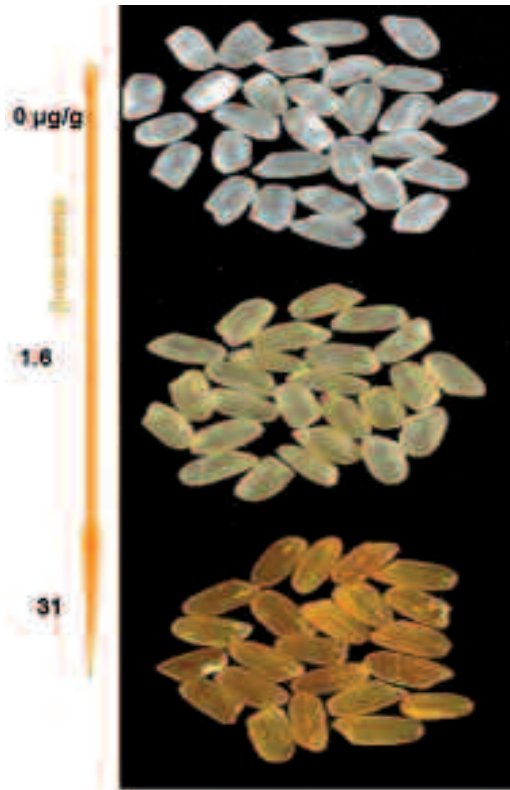


Figure 4: Improvement of Golden Rice over time. Top, control rice; middle, Golden Rice prototype; bottom, GR2

of the trait from selected transgenic lines into locally adapted varieties is coming along in priority target countries by conventional breeding techniques.

Getting road-ready

Moving Golden Rice from the laboratory to the field is a stony path, which is being mastered under the strategic guidance of the Humanitarian Board, a group of international experts from reputed institutions, and in collaboration with a network of national institutions participating in the development and distribution of locally adapted varieties. To date, the Golden Rice Network includes 16 national institutions in Bangladesh, China, India, Indonesia, Nepal, the Philippines, Viet Nam, and South Africa.

Investment in the public sector to develop Golden Rice has been rela-

tively modest thus far (\$2.4 million over nine years). Product development, however, is time-consuming and requires substantial additional funding, which is normally not available for public sector projects. The maturation of the Golden Rice technology was carried out within the framework of a public-private partnership, by the agribusiness Syngenta, which then donated the improved products to the humanitarian project.

Expenses increase even more dramatically when it comes to biosafety assessment, as required for regulatory approval. Even then, however, the costs are well below the additive recurrent costs of supplementation programs. Furthermore, once a novel, biofortified variety has been approved and handed over to farmers, the system can develop its full potential. From this point on, the technology is built into each and every seed and does not require additional investment.

Golden deal

From the onset, Golden Rice was conceived as a humanitarian project to alleviate malnutrition in developing countries. Contrary to what many would expect, patenting of the technology was key to accessing a number of ancillary key technologies used in the production of Golden Rice. The patent paved the way to the public-private partnership with Syngenta and provided access to free humanitarian-use licences to technologies from various sources. By providing freedom to operate to develop locally-adapted Golden Rice varieties, the arrangement opened the way to collaborations with public rice research institutions in developing countries.

Golden Rice does not preclude the use of traditional varieties nor does it need more agricultural inputs than

the parental varieties. The *golden* trait can be bred within two years into any local variety by performing three to four conventional backcrosses with the help of molecular marker-assisted breeding. The locally-adapted golden varieties will become the property of smallholders, who will also be able to use part of their harvest as seed for the next growing season. Local trade and distribution are desirable, and only export to high-income countries is not allowed under the terms of the licence agreement.

The regulatory hurdle

Worldwide, there is plenty of goodwill in the public and in the private sectors to exploit the potential of green biotechnology for the benefit of the poor. However, without a realistic, science-based risk assessment approach and funds for public research, the technology will not be able to develop its full potential. The often-times arbitrary use of the precautionary principle stands in the way of scientific progress and product development, and thus the population at large may not benefit from this promising technology.

Our plans for India and the Philippines are to hopefully release locally-adapted Golden Rice varieties within three to four years, pending regulatory approval. Considering that Golden Rice could substantially help reduce morbidity and mortality in many developing countries, it is difficult to understand why the project is not getting wider international support to fast-track it through the regulatory process. Approval of a new transgenic line might cost in the range of \$4 million to comply with all the requirements of toxicology and allergenicity testing, biochemical equivalency analyses, environmental effects, and other tests. Golden Rice has already undergone numer-

ous greenhouse tests and two field trials carried out in Louisiana because, at the time, target countries had no biosafety regulations in place. Also, the transgene products have been cleared by bioinformatic analysis as not being potential allergens.

Socio-economic outlook

Support for biofortification also comes from a number of *ex-ante* socioeconomic impact studies on Golden Rice and other biofortified crops in selected target countries. A recent World Bank report concluded that the potential welfare improvement for Southeast Asian countries derived from the adoption of Golden Rice would be in the range of billions of dollars annually (27). This gain in terms of health improvement of the population at large and the economic benefit to the country could dwarf the negative impact that the adoption of a transgenic technology could have on trade, due to import bans imposed on transgenic commodities. In most developing countries, the largest share of the rice production and most other crops is consumed locally anyway.

More than 50% of under-five child deaths in India and Bangladesh could be averted if Golden Rice were widely adopted (28-30). The recovery on investment for this intervention would be very fast and maintenance costs minimal compared to present interventions (Table 2). Golden Rice and other biofortified crops could substantially help mitigate MNM worldwide, thus contributing to the achievement of the Millennium Development Goals in respect of health improvement and poverty alleviation. Biofortification is compatible with tradition and has the potential to generate a huge economic windfall for countries presently affected by micronutrient malnutrition.

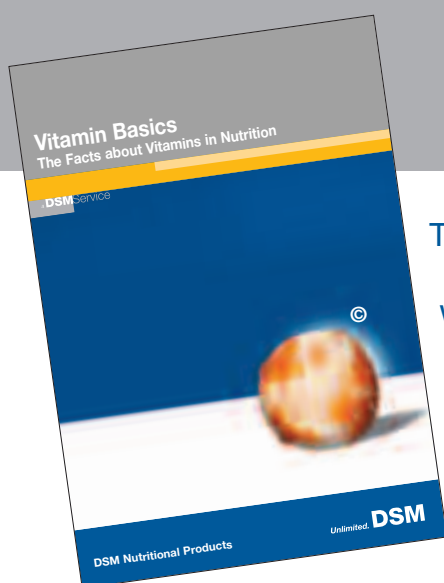
References

1. Welch RM, Graham RD. Breeding for micronutrients in staple food crops from a human nutrition perspective. *J Exp Bot.* 2004; 55:353-364.
2. Stein AJ, Sachdev H, Qaim M. Can genetic engineering for the poor pay off? An ex-ante evaluation of Golden Rice in India. In: University of Hohenheim, ed. *Research in Development Economics and Policy* 5. Vol 5; 2006.
3. Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS, and the Bellagio Child Survival Group. How many child deaths can we prevent this year? *Lancet.* 2003; 362:65-71.
4. Neidecker-Gonzales O, Nestel P, Bouis H. Estimating the global costs of vitamin A capsule supplementation: A review of the literature. *Food and Nutrition Bulletin.* 2007; 28:307-316.
5. MOST, USAID Micronutrient Program. Cost analysis of the national vitamin A supplementation programs in Ghana, Nepal, and Zambia: A synthesis of three studies. Arlington, Virginia, USA; 2004.
6. Allen LH. Ending hidden hunger: the history of micronutrient deficiency control. Background analysis for the World Bank-UNICEF Nutrition Assessment Project. World Bank, Washington, D.C; 2000.
7. Vijayaraghavan K. Control of micronutrient deficiencies in India: obstacles and strategies. *Nutr Rev.* 2002; 60:S73-76.
8. Graham RD, Welch RM, Bouis HE. Addressing micronutrient malnutrition through enhancing the nutritional quality of staple foods: principles, perspectives and knowledge gaps. In: Sparks D, ed. *Advances in Agronomy.* Vol 70; 2001:77-142.
9. Nestel P, Bouis HE, Meenakshi JV, Pfeiffer W. Biofortification of staple food crops. *J Nutr.* 2006; 136:1064-1067.
10. White PJ, Broadley MR. Biofortifying crops with essential mineral elements. *Trends Plant Sci.* 2005; 10:586-593.
11. van Jaarsveld PJ, Faber M, Tanumihardjo SA, Nestel P, Lombard CJ, Benade AJ. Beta-carotene-rich orange-fleshed sweet potato improves the vitamin A status of primary school children assessed with the modified-relative-dose-response test. *American Journal of Clinical Nutrition.* 2005; 81:1080-1087.
12. Lu S, Van Eck J, Zhou X, et al. The cauliflower Or gene encodes a DnaJ cysteine-rich domain-containing protein that mediates high levels of beta-carotene accumulation. *Plant Cell.* 2006; 18:3594-3605.
13. Ye X, Al-Babili S, Klöti A, Zhang J, Lucca P, Beyer P, Potrykus I. Engineering the provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science.* 2000; 287:303-305.

Table 2: Disease burden of vitamin A deficiency in India and impact and cost effectiveness of Golden Rice intervention (28). Even in a worst-case adoption scenario the cost per DALY saved with Golden Rice is well below that of conventional supplementation. DALYs, Disability-Adjusted Life Years

Annual vitamin A deficiency disease burden	
Annual DALY loss	2,328,000
Lives lost	71,600
Potential impact of Golden Rice	
Lives saved	5,500 to 39,700
DALYs saved annually (worst-case to best-case scenarios)	204,000 to 1,382,000 (8.8 – 59.4 %)
Cost effectiveness of intervention (cost per DALY saved)	
WHO benchmark	\$620 – \$1,860
World Bank benchmark	\$200
Conventional supplementation	\$134 to \$599
Golden Rice (biofortification)	\$3 to \$19

14. Schaub P, Al-Babili S, Drake R, Beyer P. Why is Golden Rice golden (yellow) instead of red? *Plant Physiology*. 2005; 138:441-450.
15. Diretto G, Tavazza R, Welsch R, et al. Metabolic engineering of potato tuber carotenoids through tuber-specific silencing of lycopene epsilon cyclase. *BMC Plant Biol*. 2006; 6:13.
16. Diretto G, Al-Babili S, Tavazza R, Papacchioli V, Beyer P, Giuliano G. Metabolic engineering of potato carotenoid content through tuber-specific overexpression of a bacterial mini-pathway. *PLoS ONE*. 2007; 2:e350.
17. Grusak MA, DellaPenna D. Improving the nutrient composition of plants to enhance human nutrition and health. *Annu Rev Plant Physiol Plant Mol Biol*. 1999; 50:133-161.
18. Lucca P, Hurrell RF, Potrykus I. Genetic engineering approaches to improve the bioavailability and the level of iron in rice grains. *Theor Appl Genet*. 2001; 102:392-397.
19. Gross J, Stein RJ, Fett-Neto AG, Palma J. Iron homeostasis related genes in rice. *Genetics Molec. Biol*. 2003; 26:477-497.
20. Goto F, Yoshihara T, Shigemoto N, Toki S, Takaiwa F. Iron fortification of rice seed by the soybean ferritin gene. *Nat Biotechnol*. 1999; 17:282-286.
21. Diaz de la Garza RI, Gregory JF, III, Hanson AD. Folate biofortification of tomato fruit. *Proc Natl Acad Sci U S A*. 2007; 104:4218-4222.
22. Storozhenko S, De Brouwer V, Volckaert M, et al. Folate fortification of rice by metabolic engineering. *Nat Biotechnol*. 2007.
23. Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong LY. Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. *Jama*. 2001; 285:2981-2986.
24. Al-Babili S, Beyer P. Golden Rice—five years on the road—five years to go? *Trends Plant Sci*. 2005; 10:565-573.
25. Howe JA, Tanumihardjo SA. Carotenoid-biofortified maize maintains adequate vitamin A status in Mongolian gerbils. *J Nutr*. 2006; 136:2562-2567.
26. Paine JA, Shipton CA, Chaggar S, et al. Improving the nutritional value of Golden Rice through increased provitamin A content. *Nature Biotechnology*. 2005; 23:482-487.
27. Anderson K, Jackson LA, Pohl Nielsen C. Genetically modified rice adoption: Implications for welfare and poverty alleviation: Centre for International Economic Studies; 2004: Discussion Paper No 0413.
28. Stein AJ, Sachdev HP, Qaim M. Potential impact and cost-effectiveness of Golden Rice. *Nat Biotechnol*. 2006; 24:1200-1201.
29. Stein AJ, Sachdev H, Qaim M. Genetic engineering for the poor: Golden Rice and public health in India. *World Development*. 2007; 36 (1) (in press).
30. Zimmermann R, Qaim M. Potential health benefits of Golden Rice: A Philippine case study. *Food Policy*. 2004; 29:147-168.



This publication can be downloaded from the internet:
www.vitamin-basics.com

DSM Nutritional Products Ltd.
 P.O. Box 3255, CH-4002 Basel
 Switzerland

Unlimited. **DSM**

Hierarchization of school-based nutrition for Guatemalan schoolchildren

J. De León Arana

Universidad de San Carlos, Guatemala City, Guatemala

F. Martínez Luzardo

Instituto de Ciencias Superiores, Cuba

Correspondence: J. De León Arana, Universidad de San Carlos, Facultad Ciencias Químicas y Farmacia, Guatemala City, Guatemala
Email: biousac@usac.edu.gt

Introduction

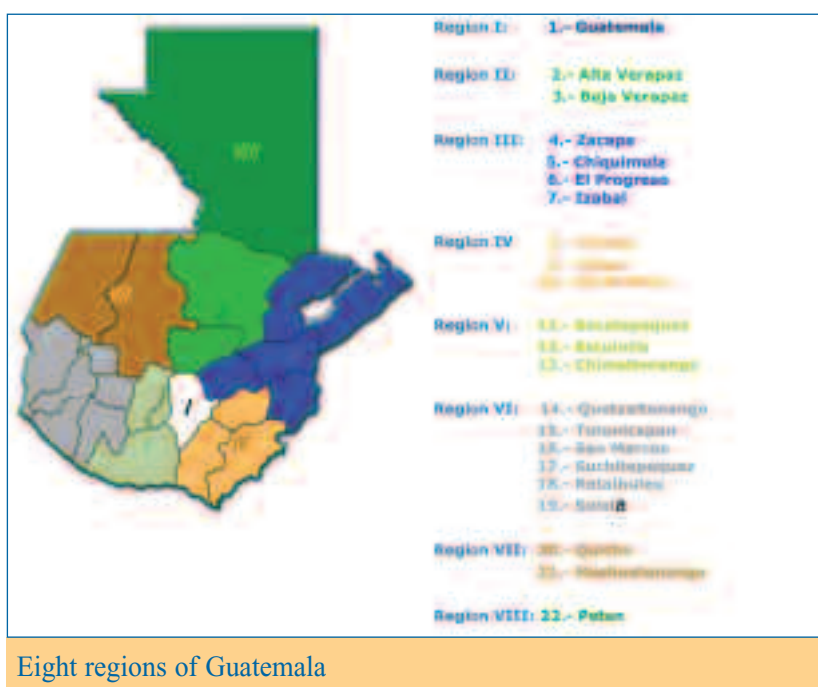
In Guatemala, the strategy for school-based nutrition interventions has not been modified since 1954, nor has the real impact of these programs been evaluated. Such interventions have never been based on comprehensive data that include nutrition and health indicators, and access to fortified foods and drinking water of a high quality in schools. Furthermore, lack of consideration of regional disparities and inequities means interventions were likely to have

been poorly targeted. Such programs have therefore failed to improve and/or safeguard the nutrition and health of schoolchildren in Guatemala.

The study reported here was aimed at developing two important indices – the Gini index, used in conjunction with the Lorenz curve, and a health inequity index (INIQUIS) – aimed at assisting in the hierarchization of future school-based nutrition interventions. These indices not only enable better planning of interven-

tions, but also facilitate the evaluation of interventions after they have been carried out to ensure the desired impact is achieved. To develop these indices, the study included all primary school grades in an integral evaluation that assessed rates of anemia, access to sugar fortified with vitamin A, access to salt fortified with iodine, microbiological quality of water, rates of infection with parasites, and the health-promoting environment of schools.

We propose that the distribution of resources for school lunches has been disparate and inequitable because the principal indicator governing this has always been chronic malnutrition (indicated by height-for-age z-score). However, this approach is incorrect because it does not take into account acute malnutrition (indicated by weight-for-height z-score), which is concentrated among a small percentage of schoolchildren (no more than 20%) that varies according to gender, age group and geographic region. This is the principal contribution made by interpreting anthropometric information and various aspects of health within the framework of the indices.



Eight regions of Guatemala

Even in situations where malnutrition is observed, there are disparities. These disparities become inequitable when allocations are made without the aid of a technical criterion to assess which region is worst affected. In the absence of such input, equal allocations are made, which favor regions that are less affected by malnutrition and disfavor regions where it is a serious problem.

In order to compile the data necessary to fulfill our aims, we implemented a conglomerated sampling procedure involving two stages: First schools were selected; then children were selected from each school. The data were subsequently classified according to the 8 regions into which Guatemala is divided (1).

The scientific novelty of this study lies in the use of the Gini index in conjunction with the Lorenz curve, and the inequity index. There are many examples of their use in the field of economics, however these indicators have rarely been applied in the health field. Here, their use has only been systematized since 2002, when, for example, the



Blood sampling

Revista Panamericana de Salud Pública (the Pan American Journal of Public Health) dedicated its May/June and December issues completely to the factors that determine health inequity and the measurement of disparity in health respectively (2, 3).

Past experience has shown that the allocation of funds in Guatemala has been made according to political interests. It was only since 2000, with the construction of poverty maps, and later the height census in 2001, that funds have been allocated using poverty as a guideline. But with time, it has also been observed that this approach does not match local realities either, because both the allocation of the funds and the limited evaluations of school-based nutritional programs are done at the central level, thus leaving out of the process those who are truly aware of the needs – the communities themselves.

By using these indicators, which are simple to create, the local authority – whether it be the municipality, the neighborhood committees or non-governmental organizations (NGOs) – will have very accessible information with which it can meet demands at the local level, allocate appropriate funds, monitor processes, and evaluate the results of the school lunch program. This would constitute the first undertaking of this kind in Guatemala.

Materials and methods

Population

The target population was established as 2,200,000 children attending classes during 2004 at one of the 15,226 primary schools in the Guatemalan public school system. Schoolchildren were of both sexes, aged between 5 and 14 years, in First to Sixth Grade, and attending morning or evening, urban or rural schools.

Sample

A sample size of 3,200 children was calculated by taking into account a non-response rate of approximately 10% among the selected children. The initial sample was thus 3,600 children. Methodological considerations are described in **Table 1**.



Weight measurement

Table 1: Variables measured in this study

Variable measured	Measurement scale (Dimension)	Indicators
Simple Variables		
Weight	Ratio (weight in kg)	Mean \pm SD
Height	Ratio (height in cm)	Mean \pm SD
Age	Ratio (age in months)	Mean \pm SD
Hematocrit	Ratio (percentage of packed cells)	Mean \pm SD
Intestinal parasites	Nominal (presence/absence and type of parasite)	Percent positive
Ectoparasites	Nominal (presence/absence)	Percent positive
Health promoting environment of schools	Nominal ('positive' if they comply with all items listed on the form, 'negative' if otherwise)	Percentage of schools that comply
Vitamin A in sugar	Ratio ($\mu\text{g/g}$ of retinyl palmitate)	Average standard deviation, then decreasing to a cut-off point of 10-20 $\mu\text{g/g}$ to demonstrate adequate fortification (reported as a percentage)
Iodine in salt	Ratio ($\mu\text{g/g}$ salt)	Average standard deviation, then decreasing to a cut-off point of 60-120 ng/g salt to demonstrate if fortified or not (reported as a percentage)
Microbiological quality of water for human consumption	Ratio (MPN of bacteria per mL)	Compared with COGUANOR Standard 29001 for both complying and non-complying schools (reported as a percentage)
Composite Variables		
Gini index, Lorenz curve	For boys older than 10 years of age, BMI was used; for boys younger than 10 year of age, WHZ, HAZ and WAZ were used	Reported in area, with a value of 0 indicating no disparity and a value of 1 indicating total disparity
Inequity indicator (INIQUIS)	Created from: 1. For children aged older than 10 years: BMI, % anemia, % fortification with vitamin A, % salt iodization 2. For children aged 5-10 years: WHZ, HAZ and WAZ, % anemia, % fortification with vitamin A, % salt iodization	Groups above the cut-off value of 0.5 are considered to be in a situation of above-average inequity

SD: standard deviation

MPN: most probable number (method) from serial dilutions

WHZ: weight-for-height z-score

HAZ: height-for-age z-score

WAZ: weight-for-age z-score

BMI: body mass index (kg/m^2)

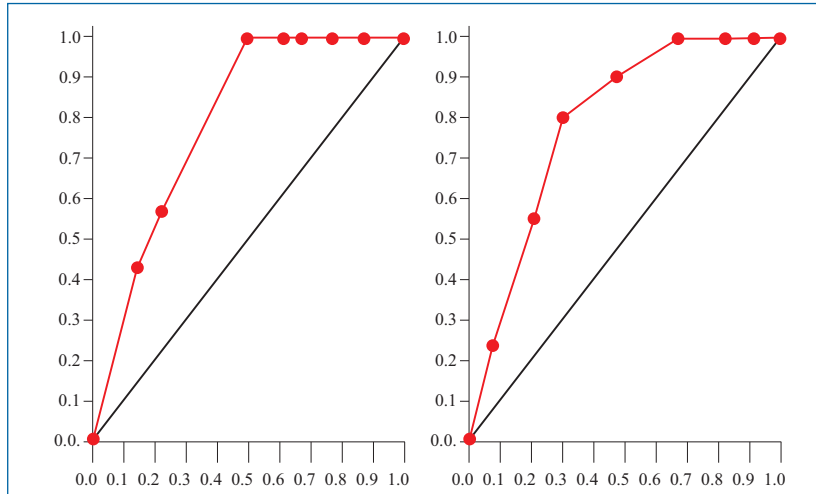


Figure 1: Lorenz curve for acute malnutrition (weight-for-height indicator) among boys (left) and girls (right) from 5 to 10 years of age

The vertical axis of the graph in **Figure 1** represents the accumulated number of cases in proportion to the accumulated population (horizontal axis), indicating that 50% of the cases were found among 20% of the population. This means that, across all the boys and girls in the sample, the cases of acute malnutrition were concentrated in less than 20% of the group.

The results from the inequity index, shown in **Table 2**, were varied.

Two data collection forms were used, as follows: a) A form to record anthropometric data, and b) A form to evaluate the health-promoting environment of the schools validated by the Institute of Nutrition for Central America and Panama (INCAP) (4).

The form for recording anthropometric data was validated using the group mean method, which typically bases the standardization process on 10 subjects. Each subject was measured twice but the interviewer was not allowed to see the results of the first measurement while taking the second one. The results of the initial measurement of the children were noted in the corresponding form and set aside until the second set of measurements had been made.

Results

Applying the Gini index, it was observed that the Lorenz curve only reported very obvious disparities along the weight-for-height indicator (acute malnutrition) for children aged between 5 and 10 years, with index values of 0.589 for girls and 0.583 for boys (shown in **Figure 1**).

For girls between 5 and 10 years of age, region 8, Petén, was shown to have the most unfavorable situation; for boys of the same age group, region 4, the southeast (which includes Santa Rosa, Jalapa and Jutiapa), was shown as being most unfavorable. Of these areas, Jalapa and especially Jutiapa have often been reported as being the poorest districts in the country (5). While other municipalities may also be poor, residents in several municipalities in Jalapa and Jutiapa survive on one Quetzal (approximately US\$0.13) or less per day, which easily meets globally-accepted definitions of extreme poverty.

Table 2: Inequity by age group and region

Age group	Indicators used	Initial indicator	Regions with values >0.5	Region identified as the most unfavorable
Girls 5 to 10 years	W/H, H/A, W/A, % anemia, sugar and salt fortification	H/A	1,2,4,5,6,8	8
Boys 5 to 10 years	W/H, H/A, W/A, % anemia, sugar and salt fortification	H/A	1,2,3,4,6,8	4
Girls older than 10 years	BMI, % anemia, sugar and salt fortification	BMI	1,4,5,6,7	1
Boys older than 10 years	BMI, % anemia, sugar and salt fortification	BMI	1,2,3,5,7	1

Clearly, the way in which resources are currently administered for school-based nutrition programs does not adequately resolve the nutritional problems of schoolchildren in every region.

Conclusions

We analyzed anthropometric and health data among schoolchildren aged 5 to 14 years in 100 schools in Guatemala to develop indicators for the prioritization of resources for school-based nutritional programs. When used simultaneously, we found that the Gini index and the inequity index are able to differentiate individual regions already known to be afflicted by malnutrition and lack of a healthy school environment, and that demand more urgent intervention.

Our results show that most of the schoolchildren did not suffer from acute malnutrition, although they did suffer from chronic malnutrition, which is indicated by a height that is lower than would be expected for children of their age.

The greatest disparity in relation to acute malnutrition, as indicated by weight-for-height, was found among boys and girls between the ages of 5 and 10. Furthermore, a large percentage of the boys and girls studied who presented severe

cases were concentrated in a few regions. For both genders, 50% of these cases were concentrated in 20% of the children studied.

The greatest inequities manifested in a very discrepant manner. Regions where the most inequities or unjustified disparities were observed differed according to sex and age group. For girls between 5 and 10 years of age, region 8, which corresponds to the district of Petén, displayed the greatest inequity; for boys of the same age group, it was the southeast region (the districts of Jalapa, Jutiapa, and Santa Rosa). For both boys and girls over 10 years of age, the greatest inequity was observed in region 1, the Guatemala City metropolitan area.

References

1. Scheaffer R, Mendenhall W, Ott L. Elementos de Muestreo. Grupo Editorial Iberoamérica, México, p 232-240, 1995.
2. Casanueva E. et. al. Nutriología Médica. 2da. Ed. México. Editorial Médica Panamericana, S.A. de C.V., 2001.
3. Ministerio de Salud Pública y Asistencia Social. Encuesta de Salud Materno Infantil 2002 – ENSMI, 2002.
4. Martorell R. Results and implications of the INCAP follow-up study. J Nutr 1995;S125:1127-38.
5. Programa Naciones Unidad Para el Desarrollo. Informe Desarrollo Humano, Guatemala, 2003.



Children receiving Albendazole medication



SIGHT AND LIFE



Manual on Vitamin A
Deficiency Disorders (VADD)
available soon



Multiple micronutrient-fortified seasoning powders in preschool children in Chongqing suburb

Chen Ke, Li Ting-Yu, Chen Li, Liu You-Xue, Qu Ping, Zhang Yi-Guan, Children's Hospital, Chongqing University of Medical Science, Chongqing, China

Correspondence: Li Ting-Yu, Children's Hospital, Chongqing University of Medical Science, Yuzhong District, Chongqing 400016, China
Email: tyli@vip.sina.com

Introduction

Vulnerable populations in developing countries generally suffer from multiple micronutrient deficiencies, among which deficiencies of iron, vitamin A, folic acid and iodine are the most commonly reported. Preschool children are particularly likely to suffer from multiple, concurrent deficiencies, as these deficiencies usually share the same causes. To address this problem, governments have implemented programs to fortify food, provide supplements and transfer knowledge aimed at increasing micronutrient intake – especially vitamin A and iron.

In developed countries, food fortification with multiple micronutrients has proven highly effective in reducing malnutrition (1). In China, several fortification methods have been developed but food products fortified with multiple micronutrients are currently not available on the market (2). Furthermore, the fortification of hand-made food products, which are widely consumed in China, is plagued with problems, such as the homogenization and stability of the nutrients, and hygiene conditions in the production facilities.

In 1995, a promising fortified product was developed in Thailand in the form of an instant noodle seasoning powder fortified with iodine, vitamin A, and iron,



Drawing blood during trial process

which met organoleptic acceptability, shelf life and product stability requirements (3). However, the product was not fortified with the full complement of multiple micronutrients – such as vitamin B1, vitamin B2, niacin, folic acid, zinc and calcium – and its efficacy had not been tested in China.

Consequently, the Children's Hospital of Chongqing University of Medical Science in China conducted a randomized controlled trial to investigate the efficacy of a multiple-micronutrient-fortified seasoning powder, containing iron, zinc, calcium, vitamin B1, vitamin B2, niacin, folic acid, and vitamin A, on biochemical micronutrient indices of preschool children aged 2–6 years in Chongqing suburb. The purpose of the study was to establish a safe and effective fortified food product for large-scale prevention of micronutrient deficiencies in an at-risk population.

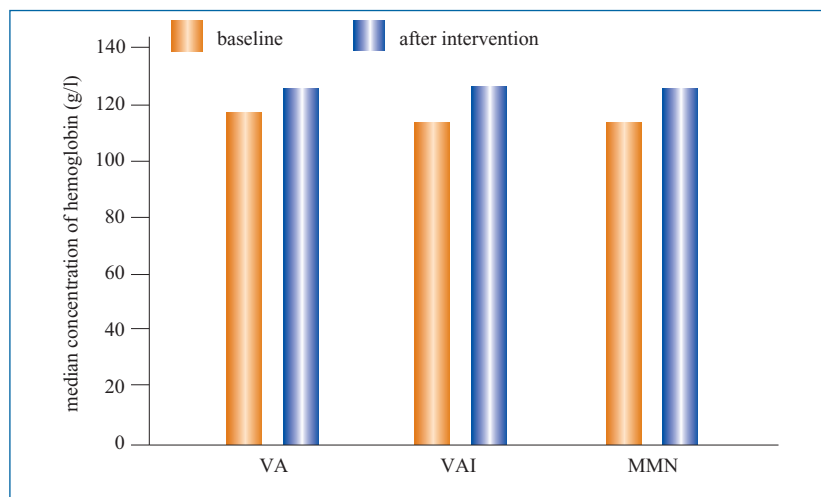


Figure 1: Change of hemoglobin by treatment groups



Children putting seasoning powder into boiled water by themselves (teacher was supervising)

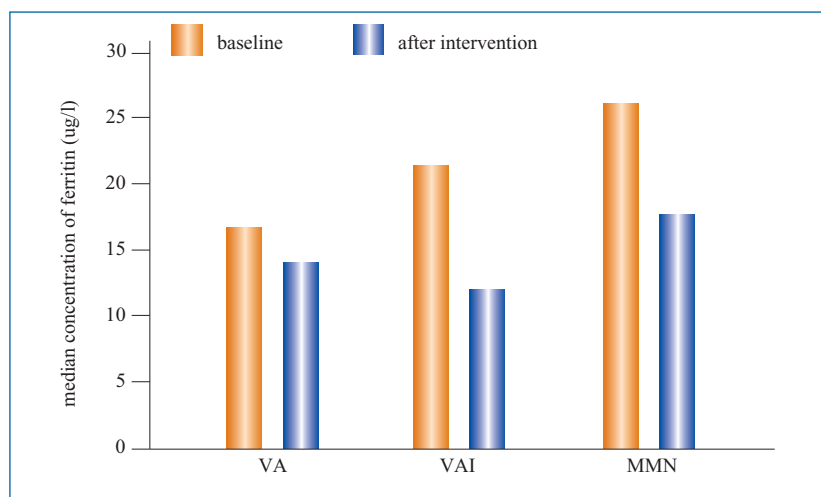


Figure 2: Change of ferritin by treatment groups

Material and methods

Subjects and ethical approval

The supplementation program was performed in the Banan District of Chongqing suburb from December 2005 to June 2006. Banan District is a middle-income suburb and had been the site of a previous child nutrition project supported by SIGHT AND LIFE. Over 300 preschool children aged 2–6 years were recruited from three nurseries randomly chosen from the region. Informed, written consent was obtained from parents and guardians who allowed their children to participate in the study. The research protocol was reviewed and approved by the institutional ethical committee of the Children’s Hospital.

Intervention

For the study, researchers applied the seasoning powder, fortified with various combinations of micronutrients, to cooked porridge, bean milk, soup or noodles. For the control, the same seasoning powder containing

maltodextrin as a filler was used; this was indistinguishable in color and packaging from the fortified powder, and had no unpalatable taste. Each serving of the fortified seasoning powder provided 100% of the recommended nutrient intake (RNI) of the different nutrients. Intervention subjects were assigned to three groups: Group VA received seasoning powder that contained 500 µg vitamin A; Group VAI received 500 µg vitamin A plus 12 mg iron; while Group MMN (multiple micronutrients) provided 500 µg vitamin A, 12 µg iron, 0.7 mg thiamine, 0.7 mg riboflavin, 200 µg folic acid, 7 mg niacin, 12 mg zinc and 800 mg calcium. The study was designed as a double-blinded randomized trial and the three groups consumed the fortified seasoning powder for six months.

Blood sampling and biochemical assessment

At the start and end of the six-month trial, approximately 3 mL of blood samples were collected by venepuncture from an antecubital vein from each subject before

breakfast. Using the hemiglobincyanide method, 1 mL was drawn into a container with heparin to measure hemoglobin (Hb). The concentrations of serum ferritin and serum retinol binding protein (RBP) were measured by the method of enzyme-linked immunosorbent and C-reactive protein (CRP) by particle-enhanced immunoturbidimetry. Serum retinol concentration was determined by using high-performance liquid chromatography (HPLC).

Results

At baseline, a total of 282 eligible preschool children were recruited for the study. The primary outcome – micronutrient status indicated by biochemical analysis and anthropometric indices – was obtained from the 226 preschool children (61, 71 and 94 from groups VA, VAI and MMN, respectively) who participated until the study was completed.

The age of the children (mean ± SD) was 4.0 ± 0.85 yr, and 50.1% were female. The total prevalence of anemia was 23.5%, with the majority of those affected (20.3%) having mild anemia. The proportions of children suffering from vitamin A deficiency (VAD, defined as serum retinol <0.7 µmol/L) and marginal VAD (defined as serum retinol 0.7–1.05 µmol/L) were 6.3% and 25.9%, respectively. Using a cut-off value of 12 µg/L for ferritin, 15.0% of these children were iron deficient. Differences in CRP among the groups were not apparent (data not shown).

After supplementation, the prevalence of anemia, VAD and marginal VAD decreased to 10.2%, 0.9% and 17.3%, respectively. The concentrations of Hb, ferritin, retinol and RBP at baseline and after six months are shown in **Figures 1–4**. The concentration of Hb increased significantly (P<0.0001) in all groups. However, there were no significant differences in Hb (P>0.05) among the groups. The concentration of ferritin decreased significantly in all groups with the smallest decrease in group VA (P<0.05). After supplementation, the concentrations of serum retinol in group VAI and MMN markedly increased (P<0.01). RBP decreased significantly in group VA (P<0.01) and increased in group MMN (P<0.0001) while no change occurred in group VAI (P>0.05).

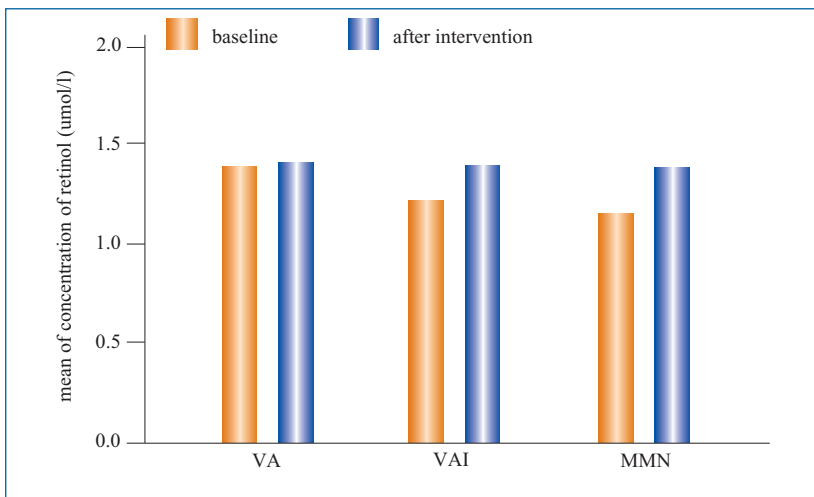


Figure 3: Change of hemoglobin by treatment groups

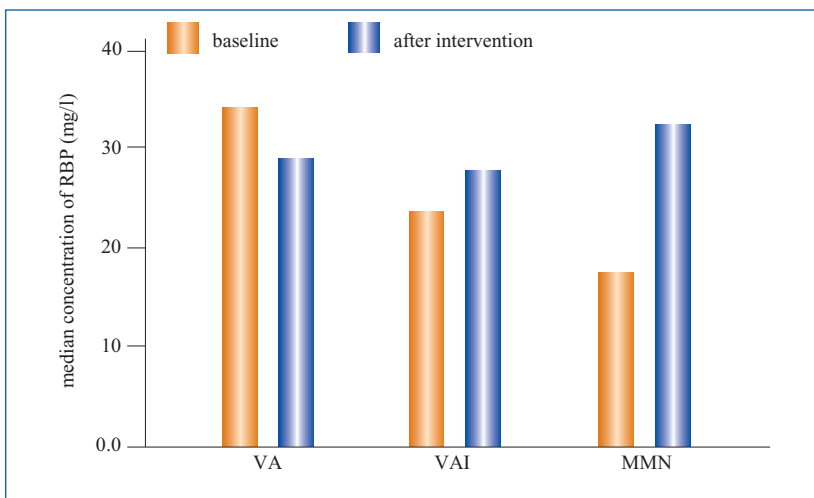


Figure 4: Change of RBP by treatment groups

The concentration of ferritin decreased significantly in all groups with the smallest decrease in group VA (P<0.05). After supplementation, the concentrations of serum retinol in group VAI and MMN markedly increased (P<0.01). RBP decreased significantly in group VA (P<0.01) and increased in group MMN (P<0.0001) while no change occurred in group VAI (P>0.05).

Discussion

Among all three groups, the concentration of Hb was markedly increased compared with the baseline level. However, the addition of iron to the fortified seasoning powder consumed by the the VAI and MMN groups had no additional effect on Hb compared with the effect of the product fortified with vitamin A alone. This may be associated with reasonably good iron status among the children at baseline, and the well-established positive effects of vitamin A on hematopoiesis (4).

Contradicting prior research (5, 6), the results of this study showed that the three different fortification regimes decreased ferritin levels



One of the trial sites: Dajiang Nursery

(an indicator of iron stores) after the six-month supplementation period. This decrease is likely due to the fortification with vitamin A of all the seasoning powder consumed by the groups, suggesting the mobilization of iron for hematopoiesis (7).

The results also indicate that adding other micronutrients to food fortified with vitamin A had an additional effect in improving serum retinol and RBP. As one of the studies had reported (8), fortified seasoning powder has several advantages as a supplementary vehicle. Firstly, it is packaged in a single-serving-sized sachet that can prevent an overdose and protects the contents from light, air and moisture. Secondly, seasoning powder can be used for many types of foods without the need for additional cooking before consuming it, thus avoiding losses due to thermal instability and/or leaching. Lastly, it is an ideal vehicle to incorporate into pre-existing nursery lunch programs, which would help program planners avoid the need for costly social marketing campaigns.

The authors note that more studies on the effect of fortified seasoning powder are needed, including assessments of anthropometric status.

Acknowledgements

We thank all the children and patients participating in the survey. We also thank the health care workers in Banan Healthy Center for Women and Children of Chongqing, China, particularly Tian Weiming, Wang Wuli and Liu Guanjun, for their diligent assistance. This study was supported by a grant from SIGHT AND LIFE.

References

1. Mehansho H, Mellican RI, Hughes DL, Compton DB, Walter T. Multiple-micronutrient fortification technology development and evaluation: from lab to market. *Food Nutr Bull* 2003;24:111–9.

2. Liu ZH. <http://scholar.ilib.cn/A-zgspjj2002020202.html> Mandarin.(General situation on development of enhancing nutrition). <http://scholar.ilib.cn/P-tgspjj.html> *China Food Additives* 2002; 2:3–8.
3. Chavasit V, Tontisirin K. Triple fortification of instant noodles in Thailand. *Food Nutr Bull* 1998;19:164–16.
4. West KP, Jr, Gernand AD, Sommer A. Vitamin A in nutritional anemia. In: Kraemer K, Zimmermann MB, eds. *Nutritional Anemia*. Basel: SIGHT AND LIFE Press, 2007:133–53.
5. Graham JM, Haskell MJ, Pandey P, Shrestha RK, Brown KH, Allen LH. Supplementation with iron and riboflavin enhances dark adaptation response to vitamin A-fortified rice in iron-deficient, pregnant, night blind Nepali women. *Am J Clin Nutr* 2007;85: 1375–84.
6. Makola D, Ash DM, Tatala SR, Latham MC, Ndossi G, Mehansho H. A micronutrient-fortified beverage prevents iron deficiency, reduces anemia and improves the hemoglobin concentration of pregnant Tanzanian women. *J Nutr* 2003;133:1339–46.
7. Muslimatun S, Schmidt MK, Schultink W, et al. Weekly supplementation with iron and vitamin A during pregnancy increases hemoglobin concentration but decreases serum ferritin concentration in Indonesian pregnant women. *J Nutr* 2001;131:85–90.
8. Winichagoon P, McKenzie JE, Chavasit V, et al. A multimicronutrient-fortified seasoning powder enhances the hemoglobin, zinc, and iodine status of primary school children in North East Thailand: a randomized controlled trial of efficacy. *J Nutr* 2006;136:1617–23.



Children participating in field trial



Measurement of weight and height

Recent advances in vitamin A absorption and transport

Editor's note: Nuttaporn Wongsiriroj received a travel grant from SIGHT AND LIFE to participate in the Micronutrient Forum in Turkey 2007

Nuttaporn Wongsiriroj

Institute of Molecular Biology and Genetics, Mahidol University, Salaya, Nakhonpathom, Thailand

William S. Blaner

Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, USA

Correspondence: William S. Blaner, Department of Medicine, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York, NY 10032, USA

Email: wsb2@columbia.edu

Introduction

Vitamin A deficiency (VAD) remains a public health problem causing morbidity and mortality in infants throughout much of the world (1). To correct VAD, a large dose of preformed vitamin A (retinol) is administered (2). Although it has long been clear that this approach is an effective one for treating and preventing VAD, only recently have the molecular processes and factors responsible for facilitating vitamin A absorption in the intestine and transport in the circulation begun to be understood fully at the molecular level. This review will focus on recent advances in our understanding of the molecular processes and biochemical factors that are responsible for the uptake of dietary vitamin A by the intestine and its transport in the blood.

Overview

Humans as well as other animal species have no capacity for *de novo* vitamin A synthesis. All vitamin A present in the body must be

acquired from the diet. There are two forms of vitamin A available in the diet, preformed vitamin A and provitamin A carotenoids. Preformed vitamin A consists primarily of retinol and retinyl esters that have been consumed in animal food products. Provitamin A carotenoids such as β -carotene, α -carotene and β -cryptoxanthin are found in dark green and yellow fruits and vegetables (mangoes, papaya, carrots, dark green leafy vegetables and red palm oil are some rich dietary sources of provitamin A carotenoids). The different dietary vitamin A forms are processed in the intestine (see **Figure 1** and below for more details) to retinyl esters, and the retinyl esters are packaged along with other dietary lipids into newly synthesized chylomicrons. These nascent chylomicrons are secreted into the lymphatic system for uptake into the general circulation and delivery to the liver and other tissues (3, 4). Approximately 75% of chylomicron (dietary) vitamin A is taken up by hepatocytes in the liver, the major organ for vitamin A storage in the body. The remainder of postprandial vita-

min A is taken up by other organs, including the eye and adipose tissue. Vitamin A stored in liver and adipose tissue is mobilized and delivered to target tissues for vitamin A action by retinol-binding protein (RBP or RBP4) (4, 5). (Although the older literature has referred consistently to this vitamin A-binding protein as RBP, investigators recently have started to use a version of its genetic nomenclature, *Rbp4*, to describe the protein as RBP4.)

Within tissues, retinol is converted to its biologically active metabolites. The active form of vitamin A needed to support vision is 11-*cis*-retinaldehyde. All other actions of vitamin A within the body are thought to involve retinoic acid and its effects on regulating gene expression. All-*trans*-retinoic acid can bind to each of the three retinoic acid nuclear receptors (RAR α , RAR β , and RAR γ) and each of three retinoic X receptors (RXR α , RXR β , and RXR γ), whereas 9-*cis*-retinoic acid binds only the RXRs. After binding, these nuclear receptors become activated

and can then regulate (increase or decrease) gene expression in the nucleus of cells. Vitamin A has an important role in regulating the actions of other hormone and nutrient-dependent genes because the RXRs are able to form protein-protein complexes with vitamin D nuclear receptors (VDRs), thyroid hormone nuclear receptors (TRs), and peroxisome proliferators-activated nuclear receptors (PPARs). Through these interactions, vitamin A and the RXRs can regulate a broad spectrum of hormonally and nutrient-responsive genes that are

needed to support reproduction, cell proliferation and differentiation, and immunity (5).

Intestinal absorption of vitamin A

The intestinal absorption of vitamin A can be thought of as occurring in four stages. These are: 1) The processing of dietary vitamin A in the lumen of the intestine and uptake into the enterocyte (also known as intestinal mucosa cells); 2) The intracellular metabolism of the different dietary forms

to retinol; 3) The conversion of retinol to retinyl ester; and 4) Retinyl ester incorporation into nascent chylomicrons for secretion along with other dietary lipids into the lymphatic system. These processes are summarized in **Figure 1**. The proteins that are mentioned in this review that are known to be involved in the intestinal absorption of vitamin A are listed in **Table 1**.

1. Luminal processing and cellular uptake

The major sources of vitamin A present in the diet are retinol, retinyl ester and provitamin A carotenoids. Retinol is absorbed as such from the intestinal lumen into the mucosal cells. Retinyl esters must be hydrolyzed to retinol prior to intestinal absorption either within the intestinal lumen by pancreatic triacylglycerol lipase (PTL) or at surface of the enterocyte by brush border retinyl ester hydrolase (REH). At present, it is unclear which enzyme is primarily responsible for this process. Another enzyme long proposed to be important for catalyzing luminal retinyl ester hydrolysis, carboxyl ester lipase (CEL), appears to not be essentially involved in the intestinal absorption of vitamin A. However, studies of CEL-deficient mice indicated that this enzyme is not needed to assure uptake of dietary vitamin A. Other enzymes present in the lumen of the intestine or on the enterocyte surface may also participate in the hydrolysis of dietary retinyl esters (6). Enzyme assays in CEL-deficient mice showed that PTL exhibits both pancreatic triacylglycerol lipase activity and retinyl ester hydrolase activity, suggesting that PTL may be the main retinyl ester hydrolase in the intestinal lumen. However, a third unidentified retinyl ester hydrolase, neither CEL

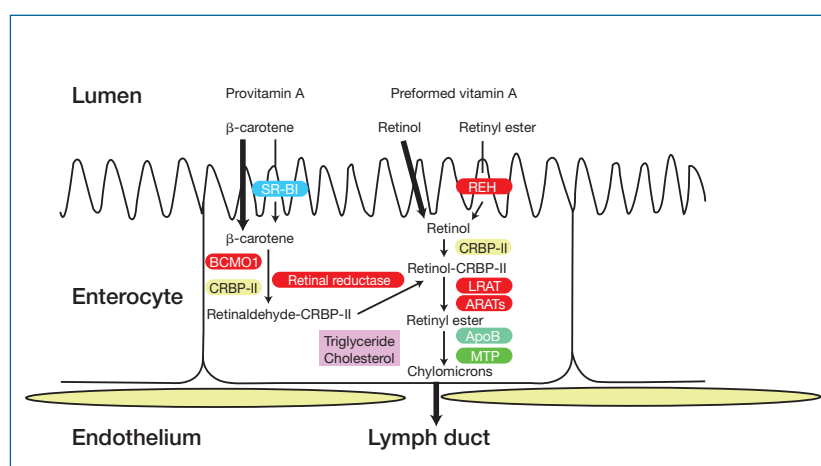


Figure 1: Vitamin A arrives from the diet in the intestinal lumen in two forms, provitamin A carotenoids (e.g., β-carotene) and preformed vitamin A (retinol and retinyl esters). Provitamin A carotenoids; like β-carotene are absorbed both passively and via facilitated diffusion involving the brush border membrane receptor SR-BI. Preformed vitamin A arriving as retinyl ester from the diet must undergo hydrolysis prior to its uptake into the enterocyte via the action of a retinyl ester hydrolase (REH). Several luminal retinyl ester hydrolases and a brush border retinyl ester hydrolase have been proposed to have important roles in this process. Dietary vitamin A arriving as retinol is absorbed directly into the enterocyte. Upon entry of the retinol into the enterocyte, it immediately binds to CRBP-II. Within the enterocyte, β-carotene is acted upon by carotene cleavage enzyme (CCE) and converted to retinaldehyde, which then also binds CRBP-II. Retinaldehyde bound to CRBP-II is subsequently reduced to retinol via the actions of a retinal (retinaldehyde) reductase. LRAT then catalyzes the esterification of CRBP-II bound retinol to retinyl ester, which is incorporated into newly synthesized chylomicrons. Some retinyl ester is likely formed from retinol through the actions of an acyl-CoA-dependent enzyme (ARAT) in a manner that becomes progressively more significant as the amount of retinol being consumed in the diet or administered pharmacologically increases. The assembly of newly synthesized chylomicrons is dependent on the presence of apoB, MTP, and dietary triacylglycerols and cholesterol

Table 1: Proteins important for facilitating vitamin A absorption in the intestine

Pathway	Protein(s)	Role(s)
1. Cellular uptake into the enterocyte	Retinyl ester hydrolases (pancreatic triacylglycerol hydrolase [PTL], brush border retinyl ester hydrolase)	Hydrolyze retinyl ester arriving from the diet to retinol
	Enterocyte receptor scavenger receptor class B, type I (SR-BI)	SR-BI is needed to facilitate intestinal carotenoid uptake across the enterocyte brush border membrane
	Unknown membrane receptors	As yet to be identified transporters may facilitate provitamin A and preformed vitamin A uptake from the intestinal lumen into the enterocyte
2. Enterocyte metabolism of provitamin A carotenoids to vitamin A	Carotene cleavage enzyme (BCMO1)	Cleaves β -carotene symmetrically into two molecules of retinaldehyde
	Retinaldehyde reductase	Intestinal retinaldehyde reductase remains to be identified
	Cellular retinol-binding protein, type II (CRBP-II)	Binds retinol and retinaldehyde and serves as a substrate for esterification; is found only in the intestine in the adult
3. Retinol esterification within the enterocyte	Lecithin-retinol acyltransferase (LRAT)	Primary enzyme responsible for retinyl ester formation in the intestine
	Diacylglycerol acyltransferase 1 (DGAT-1)	An enzyme that catalyzes triacylglycerol synthesis from diacylglycerol and fatty acyl-CoA. Able to catalyze retinyl esterification in a fatty acyl-CoA dependent manner. Acts in response to both physiologic and pharmacologic doses of retinol
	Acyl-CoA:retinol acyltransferases (ARATs)	Active under pharmacological (high dose) of retinol by unknown ARATs
4. Chylomicron formation	Apolipoprotein B (apoB)	ApoB48 is synthesized in the intestine and essential for chylomicron formation
	Microsomal triacylglycerol transfer protein (MTP)	Plays an important role in the transfer of lipid during lipoprotein assembly. Lack of this protein (in abetalipoproteinemia patients) leads to an inability to produce chylomicrons and very low density lipoproteins, and impairs vitamin A uptake

nor PTL, is present in the lumen (7). Regardless of enzymatic origin, the free retinol formed from retinyl ester hydrolysis appears to be taken up by the intestinal mucosal cells by both passive diffusion and facilitated diffusion. The proteins involved in facilitated retinol uptake remain to be determined.

The uptake of provitamin A carotenoids by enterocytes has long been thought to occur via passive diffusion, similar to other dietary lipids. However, recent studies suggest that some provitamin A carotenoid uptake may be mediated by a specific membrane transporter (i.e., scavenger receptor class B, type I [SR-BI]) and possibly other enterocyte transporters. Studies of SR-BI-deficient mice indicated that SR-BI can facilitate the absorption of β -carotene and may be important for β -carotene absorption, at least in mice fed a high-fat diet (8). Once inside the enterocyte, provitamin A carotenoids can be cleaved centrally at the 15, 15' bond to yield two molecules of retinaldehyde by the actions of carotene cleavage enzyme.

2. Intracellular metabolism converging on retinol

Within the enterocyte, newly absorbed retinol or retinaldehyde formed through carotenoid cleavage is bound to cellular retinol-binding protein, type II (CRBP-II). This protein is expressed solely in the small intestine. CRBP-II plays a very important role in facilitating vitamin A uptake in the intestine, since mice lacking CRBP-II show an impaired capacity of vitamin A absorption especially when dietary vitamin A amounts are low, suggesting that CRBP-II has a role in intestinal absorption but is not essentially needed for this process (9). Retinaldehyde bound to CRBP-II is subsequently reduced to retinol. Many enzymes are able to catalyze this reaction, including short-chain and medium-chain alcohol dehydrogenases as well as members of the aldo-keto reductase enzyme family. Until now, no unique intestinal retinaldehyde reductase has been identified as being responsible for catalyzing conversion of retinaldehyde to retinol. The retinol formed through either retinaldehyde reduction or from retinyl ester hydrolysis (upon uptake of preformed vitamin A) also binds CRBP-II where it serves as a good substrate for reesterification by the enzyme lecithin-retinol acyltransferase (LRAT).

3. Retinol esterification

The literature suggests that CRBP-II facilitates retinyl ester formation from newly absorbed retinol and that LRAT is the key enzyme involved in catalyzing retinyl ester synthesis in the small intestine. However,

the literature also suggests that an as yet to be identified acyl-CoA:retinol acyltransferase (ARAT) activity also may play a role in this process, especially when very high doses of vitamin A are ingested (10). The molecular identity of this ARAT has long remained elusive. Recently, three independent *in vitro* studies suggested that diacylglycerol acyltransferase, type 1 (DGAT-1) is able to esterify retinol to retinyl ester in an acyl-CoA-dependent manner and thus able to act as an ARAT *in vitro* (11–13). DGAT-1 was originally identified as an enzyme capable of triacylglycerol biosynthesis from diacylglycerol and fatty acyl-CoA and is expressed in many tissues, including the intestine. This suggests that DGAT-1 may act physiologically in the intestine to catalyze fatty acyl-CoA-dependent retinol esterification and may have a role in facilitating the processing of dietary vitamin A in the intestine.

4. Chylomicron formation and secretion into the lymphatic system

Upon retinol esterification, the resulting retinyl esters are incorporated into newly synthesized chylomicrons. Chylomicrons consist of triacylglycerols, phospholipids, cholesterol, retinol, retinyl esters and several specific apolipoproteins (apoB48, apoA-I, apoA-IV and apoCs). Chylomicron synthesis occurs within the enterocyte and requires apoB48. Additional proteins, including microsomal triacylglycerol transfer protein (MTP), is required for chylomicron assembly (14). In abetalipoproteinemia patients, intestinal chylomicron and hepatic very low density lipoprotein (VLDL) synthesis and secretion are absent due to a genetic defect of MTP. This results in the malabsorption of dietary fat and fat-soluble vitamins, including vitamin A. These patients show an impaired ability to absorb vitamin A and develop retinal degeneration in spite of long-term vitamin A supplementation (15). Within 6 to 10 hours after consumption of a meal containing vitamin A, the dietary vitamin A is taken into the body as retinyl esters in chylomicrons for tissue uptake. However, small amounts of free retinol may also be absorbed in chylomicrons or secreted into portal circulation where it may bind intestinally synthesized high density lipoprotein (HDL) or possibly apo-RBP4 that may be present in the circulation. Support for this possibility comes from the observation that abetalipoproteinemia patients absorb some dietary vitamin A (16). It has been postulated that these patients absorb retinol on either intestinal HDL or apo-RBP4 present in the portal circulation.

Vitamin A transport in the circulation

As mentioned above, after consuming a vitamin A-rich meal, vitamin A can be present in the circulation at relatively high concentrations as retinyl esters in chylomicrons and chylomicron remnants. In addition, vitamin A is present in the circulation in other forms. The major form of vitamin A present in the fasting circulation is retinol bound to RBP4. However, the fasting circulation also contains low amounts of retinoic acid bound to albumin, low amounts of retinyl esters bound either to VLDL or low density lipoprotein (LDL), as well as water soluble glucuronides of retinol and retinoic acid. In addition, provitamin A carotenoids may be present in the circulation bound to VLDL and LDL. The different forms of vitamin A present

in the circulation are summarized in **Figure 2**.

Retinol is transported in the blood bound to RBP4 (17). RBP4 is primarily synthesized and secreted from the liver, where the majority of the body's vitamin A is stored (18, 19). However, RBP4 is also synthesized and secreted in lesser amounts by adipose tissue (20). RBP4 forms a one-to-one protein-protein complex with another blood protein, transthyretin (TTR), and this prevents renal clearance of the retinol-RBP4 by the glomerulus (21). In well-nourished humans and animal models, fasting blood amounts of all-*trans*- and 13-*cis*-retinoic acid bound to albumin are approximately 0.1–0.4% of those of retinol-RBP4 during fasting (3). Yet, this circulating retinoic acid can contribute significantly to tissue pools of retinoic acid in well-nourished animals and presumably

this is the case in humans as well (22). Retinyl esters are normally secreted at low concentrations (1–2% of those of retinol-RBP4) from the liver bound to newly synthesized VLDL (3). The physiologic significance of VLDL retinyl ester has not been systematically investigated but, invoking similarities between VLDL and chylomicron metabolism, it seems likely that retinyl ester contained within VLDL is destined for uptake by extrahepatic tissues. The circulation also contains low amounts of retinol- β -glucuronides and retinoyl- β -glucuronides (amounts similar to those of all-*trans*- and 13-*cis*-retinoic acid) that are fully water soluble (3). The body may use these β -glucuronides of vitamin A to satisfy tissue vitamin A needs, because they can be readily hydrolyzed to retinol and retinoic acid (3); however, this hypothesis has not been experimentally proven. It is important to note that β -glucuronides of vitamin A metabolites are routinely eliminated from the body.

RBP4 and type 2 diabetes

Until the recent publication of work by Kahn and colleagues (23), the sole known physiologic action of RBP4 was the mobilization of retinol from tissue stores. Kahn and colleagues reported data that indicate RBP4 synthesized and secreted by adipocytes has an important role in regulating systemic insulin sensitivity and glucose homeostasis in humans, as well as in animal models (23). Serum RBP4 amounts were shown to be significantly increased in several mouse models of obesity and insulin resistance, thus suggesting RBP4 is an adipocyte-derived signal that can impair insulin sensitivity and hence modulate glucose homeostasis. Studies in humans also support a role for RBP4 in the

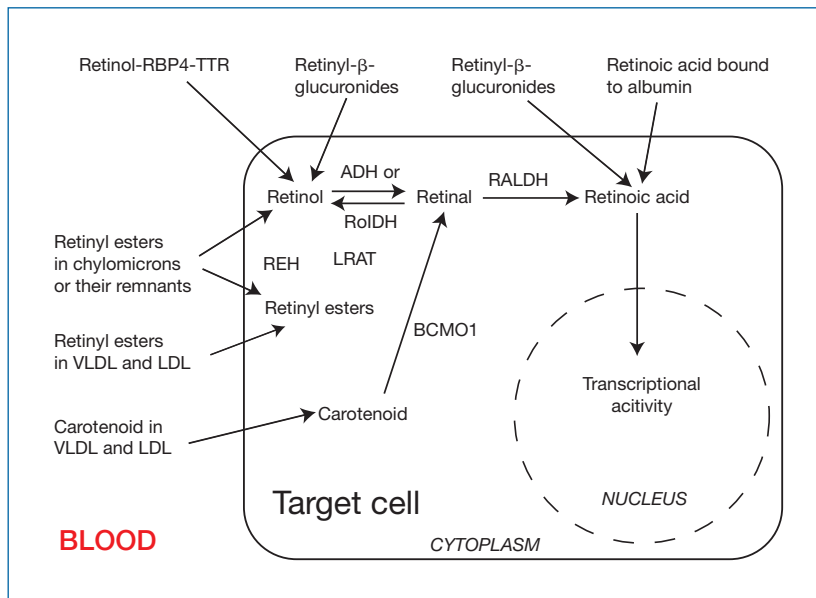


Figure 2: Vitamin A is present in the circulation in many forms. In the fasting circulation, retinol bound to RBP4 is the major vitamin A form in the blood. Also present in the fasting circulation, albeit in much lower amounts than retinol-RBP4, are all-*trans*- and 13-*cis*-retinoic acids bound to albumin, retinyl esters present in VLDL and LDL and β -glucuronides of both retinol and retinoic acid. In addition, provitamin A carotenoids are also present in VLDL and LDL and this provitamin A carotenoid may be converted within tissues to vitamin A. The abbreviations given for enzymes catalyzing metabolic conversions are the same as in **Figure 1**

development of insulin resistance and type 2 diabetes and provide a causal basis for known linkages between obesity, where RBP4 secretion would be elevated due to an increase in adipocyte number, and the development of type 2 diabetes (24). Human studies have shown statistically significant positive correlations between serum RBP4 amounts and the magnitude of insulin resistance in obese patients experiencing impaired glucose tolerance and type 2 diabetes as well as in non-obese, non-diabetic subjects with a strong family history of type 2 diabetes (24). These exciting findings provide a new level of understanding of relationships between vitamin A transport and the development of insulin resistance and raise the possibility of a new therapeutic intervention to lower serum RBP4 concentrations as an anti-diabetic therapy.



References

1. Sommer A, West KP Jr. Vitamin A deficiency: health, survival, and vision. New York and Oxford: Oxford University Press, 1996.
2. WHO, UNICEF, IVACG Task Force: Vitamin A supplements. In: A guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia. 2nd ed. Geneva: World Health Organization, 1997.
3. Blaner WS, Olson JA. Retinol and retinoic acid metabolism. In: Sporn MB, Roberts AB, Goodman DS, eds. The retinoids: biology, chemistry and medicine. 2nd ed. New York: Raven Press, 1994.
4. Harrison EH. Mechanisms of digestion and absorption of dietary vitamin A. *Annu Rev Nutr* 2005;25:87–103.
5. Wongsiriroj N, Wasantwisut E, Blaner WS. Vitamin A deficiency in children. In: Glew R, Rosenthal M, eds. Clinical studies in medical biochemistry. 3rd Ed. New York and Oxford: Oxford University Press, 2006.
6. Weng W, Li L, van Bennekum AM, et al. Intestinal absorption of dietary cholesteryl ester is decreased but retinyl ester absorption is normal in carboxyl ester lipase knockout mice. *Biochemistry* 1999;38:4143–9.
7. van Bennekum AM, Fisher EA, Blaner WS, Harrison EH. Hydrolysis of retinyl esters by pancreatic triglyceride lipase. *Biochemistry* 2000;39:4900–6.
8. van Bennekum AM, Werder M, Thuahnai ST, et al. Class B scavenger receptor-mediated intestinal absorption of dietary beta-carotene and cholesterol. *Biochemistry* 2005;44:4517–25.
9. E X, Zhang L, Lu J, et al. Increased neonatal mortality in mice lacking cellular retinol-binding protein II. *J Biol Chem* 2002;277:36617–23.
10. Ong DE, Newcomer ME, Chytil F. Cellular retinoid-binding proteins. In: Sporn MB, Roberts AB, Goodman DS, eds. The retinoids: biology, chemistry and medicine. 2nd ed. New York: Raven Press, 1994.
11. O'Byrne SM, Wongsiriroj N, Libien J, et al. Retinoid absorption and storage is impaired in mice lacking lecithin: retinol acyltransferase (LRAT). *J Biol Chem* 2005;280:35647–57.
12. Yen CL, Monetti M, Burri BJ, Farese RV. A human skin multifunctional O-acyltransferase that catalyzes the synthesis of acylglycerols, waxes, and retinyl esters. *J Lipid Res* 2005; 46:1502–11.
13. Orland MD, Anwar K, Cromley D, et al. Acyl coenzyme A dependent retinol esterification by acyl coenzyme A: diacylglycerol acyltransferase 1. *Biochim Biophys Acta* 2005;1737:76–82.
14. Hussain MM, Fatma S, Pan X, Iqbal J. Intestinal lipoprotein assembly. *Curr Opin Lipidol* 2005;16:281–5.
15. Chowdhury I, Banin E, Merin S, Cooper M, Granot E. Long-term assessment of combined vitamin A and E treatment for the prevention of retinal degeneration in abetalipoproteinaemia and hypobetalipoproteinaemia patients. *Eye* 2001;15:525–30.
16. Berriot-Varoqueaux N, Aggerbeck LP, Samson-Bouma M. [Microsomal triglyceride transfer protein and abetalipoproteinemia.] *Ann Endocrinol (Paris)* 2000;61:125-9.
17. Kanai M, Raz A, Goodman DS. Retinol-binding protein: the transport protein for vitamin A in human plasma. *J Clin Invest* 1968;47:2025-44.
18. Blomhoff, R, Rasmussen M, Nilsson A, et al. Hepatic retinol metabolism. Distribution of retinoids, enzymes, and binding proteins in isolated rat liver cells. *J Biol Chem* 1985;260:13560–5.
19. Blaner WS, Hendriks HF, Brouwer A, et al. Retinoids, retinoid-binding proteins, and retinyl palmitate hydrolase distributions in different types of rat liver cells. *J Lipid Res* 1985;26: 1241–51.
20. Soprano DR, Blaner WS. Retinol-binding protein. In: Sporn MB, Roberts AB, Goodman DS, eds. The retinoids: biology, chemistry, and medicine. 2nd Ed. New York: Raven Press, 1994.
21. Peterson PA. Studies on the interaction between prealbumin, retinol-binding protein, and vitamin A. *J Biol Chem* 1971;246: 44–9.
22. Kurlandsky SB, Gamble MV, Ramakrishnan R, Blaner WS. Plasma delivery of retinoic acid to tissues in the rat. *J Biol Chem* 1995;270: 17850–7.
23. Yang Q, Graham TE, Mody N, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 2005; 436:356–62.
24. Graham TE, Yang Q, Blüher M, et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. *N Engl J Med* 2006;354: 2552–63.

Applying behavior change research to promote micronutrients

Dorothy Foote

3 Pickering Street #02-36, Nankin Row, China Square Central,
Singapore 048660

Email: dorothyfoote@gmail.com

Introduction

What motivates people to change? Why do they choose the foods that they do? How can public health programs influence people to make healthy choices? These were some of the main questions addressed by scientists and nutrition practitioners at the Symposium on Understanding and Influencing Consumer Food Behaviors for Health, organized by the International Life Sciences Institute (ILSI) in Singapore on July 18–20, 2007.

Many countries are now facing the double burden of malnutrition: overnutrition and undernutrition coexist within the same regions, cities, neighborhoods, and even households. The determinants of food security have been described as availability, accessibility and choice. However, the relative contribution of these determinants varies across and within country settings (1).

For middle to higher income segments of a population, most foods are relatively available and accessible. Among these groups, influencing consumer choices is the main challenge for public health communications. In this context, 'healthier-choice' products must compete with less healthy commercial alternatives on the traditional four P's of marketing (product, price, placement and promotion). Among poorer segments of a population, choices are more limited, based on the availability and accessibility of products.

So although the relative contribution of choice as a determinant of food behavior varies widely across the spectrum of development, it can be observed that in all contexts knowledge alone is not enough to change practice. Eating is a complex behavior that is influenced by social, cultural, economic, and psychological factors. Continuing efforts to reduce



Consumer research aims to understand the various factors that can predict food choices. This diagram is from the presentation, "Overview of consumer science and consumer food behavior" by Dr Adam Drewnowski

poverty and increase the availability and accessibility of food among the poor, market research to understand the mind of the consumer, and creative strategies to remove barriers and enable new behaviors are all needed to 'sell' healthy products and healthy behaviors.

The primary focus of the ILSI Symposium was behavior change as a means to address the rising levels of obesity and chronic disease in the Asian region. However, the theories and various approaches that were described are also relevant for promoting micronutrients to address undernutrition. Case

studies from China, Indonesia, and Singapore demonstrated how programs are working to increase the availability and accessibility of micronutrients, and to change consumer behaviors for healthier choices.

Consumer science – know your audience

Dr. Adam Drewnowski, of the University of Washington, gave an overview of consumer science and consumer food behavior. The purpose of applying consumer science and research methods is to understand the mind of the consumer – the ‘what, when, why, where, and how often of eating.’ Understanding these factors opens the door to successful marketing. What is the socioeconomic position of the target group? (I.e. what cost can they afford?) What is the geographic comparison of where people live and work, where they eat, and what kinds of foods are available? (I.e. markets, supermarkets, street vendors, fast-food, etc.?) And importantly, what do they most like to eat? (I.e. what does the consumer think and feel about the taste of the food, the benefits, the concerns, and how the food fits into their lifestyle, etc.?) All of these factors contribute to food choices and ultimately to health outcomes.

The issue of food preference was explored in more detail in another presentation by Dr. Drewnowski, Biological, social, cultural, and psychological influences on food choice. He described the concept of ‘Time Poverty’ – a social phenomenon that plays an increasingly important role in food choices:

“Urbanization, a major global trend, has placed severe constraints on the food distribution systems. The urban consumer is many stages away from the sources of food production and the food supply. Foods and beverages delivered to city dwellers need to be nutritious, affordable, and safe. Another societal trend – the entry of women into the work force – has limited the amount of time traditionally given to the purchasing and preparing of food. ‘Time Poverty’ is a new social phenomenon”(2).

Marketing strategies – learning to listen

In a market where many similar products compete for the consumer’s choice, marketing strategies have had to adapt quickly to rapidly changing consumer preferences. The methods and tools that modern marketers have developed to listen to consumers can also benefit social marketing and nutrition promotion.

Dr. Howard Moscowitz, of Moscowitz Jacobs Inc., described the method of Rule-Developing Experimentation (RDE, www.mji-designlab.com), a method for understanding the ‘mind’ of the consumer in an ongoing, disciplined, and archival fashion. RDE uses a rapid survey of respondents’ preferences (i.e. what product characteristics they like, or which messages and visual elements on a poster or package design appeal to them the most). The data on consumers’ preferences, along with their basic sociodemographic information, is then used to dissect the various preference segments that exist within the population.

Theories of behavior change

The process by which people are led to adopt new behaviors has been described in various ways over the years. Dr. John Foreyt, of Baylor University, gave an overview of some of the most influential theories of behavior change.

The Stages of Change model (1) describes six stages of “readiness” that an individual can move through toward adopting a new behavior. The stages are pre-contemplation, contemplation, preparation, action, maintenance, and relapse. By identifying where individuals – or the majority of the target population – are on this continuum, nutrition messages can be directed appropriately to help people move toward action and the maintenance of healthy behaviors, such as consuming micronutrients. The case study from Singapore described in this article is an excellent example of applying the Stages of Change model.

The Health Belief Model (2) considers behavior change as a function of the individual’s perceived vulnerability to illness (perceived susceptibility and

severity) and the perceived effectiveness of the new behavior to prevent or treat the illness. The individual must be convinced that the new behavior is effective, and have confidence to perform the new behavior.

Social Cognitive Theory (3) describes behavior as a reciprocal interaction between a person and his/her environment. Two central constructs of this theory include self efficacy, which is a person’s belief in their ability to change, and outcome expectation, which is the degree to which a person believes that a specific course of action will lead to an expected outcome.

1. Prochaska, J.O. & DiClemente, C.C. (1983). Stages and processes of self-change in smoking: Toward an integrative model of change. *Journal of Consulting and Clinical Psychology*, 51;3:390–95.
2. Becker, M. H., ed. (1974). *The Health Belief Model and Personal Health Behavior*. Health Education Monographs, 2:324–473.
3. Bandura, A. (1986). *Social foundations of thought and action: A social cognitive theory*. Prentice-Hall, Englewood Cliffs, N.J.

Researchers can then identify which combinations of elements are most attractive and motivating for each segment. This is a knowledge-based approach that helps program planners learn how to motivate target groups to choose healthier products or behaviors.

The importance of this and similar methods is to ensure that program planners systematically listen to the reactions and preferences of the target audience. Pre-testing messages and materials is an essential step in designing any health promotion program.

Case studies of practical application

Three case studies illustrated the three main approaches to combating micronutrient malnutrition – fortification, supplementation, and dietary diversification. They elaborated the application of behavior change theories, consumer science, and marketing principles for promoting micronutrients in large-scale public health programs.

Marketing of iron fortified soy sauce in China

– Dr. Junsheng Huo, Chinese Centre for Disease Control and Prevention

The case study on iron-fortified soy sauce in China provided an excellent example of a public health program working with industry and local markets to make a needed product available and accessible (i.e. affordable) to consumers while targeting messages that motivate consumers to choose the iron-fortified product over competing products on the market.

Recognizing iron deficiency and iron deficiency anemia (IDA) as key public health problems, China

adopted food fortification as an important strategy for improving iron nutrition, and soy sauce was selected as one of the vehicles. In the first phase of the project (2003–2007), the fortified soy sauce reached over 50 million consumers in seven provinces, including about 33 million of the at-risk population (women and children). Among this population, anemia prevalence was reduced by 30%, with 80% of people becoming aware of the health benefits of iron-fortified soy sauce. How did the program achieve these results?

The Food Fortification Office (FFO) of the China Center for Disease Control and Prevention (CDC) takes a ‘two wheels run simultaneously’ approach, meaning that the CDC and soy sauce manufacturers work together to move the program forward. Other partners include local governments, industry associations, inspection institutes, and mass media partners. Importantly, the FFO established 22 sentinel sites to monitor knowledge and use of the fortified product and bioeffectiveness. Producing the fortified soy-sauce was just one step in making it ac-

cessible to the population. Another important step was engaging retailers, including two major supermarkets in China – Su Guo and Carrefour – to carry and promote the fortified product. To reach poor rural areas, one food company produces and distributes 400 mL plastic sachets of fortified soy sauce to local markets and retail outlets at a reduced – hence more affordable – cost for consumers.

To raise people’s awareness about the health benefits of iron and create demand for the fortified product, a broad social marketing campaign was launched with simple messages that iron is good for health, improves vitality, and is especially good for women. The message of ‘vitality’ was targeted to appeal to the desired health effects of the working class population.

The mass media campaign was launched via the press, television, radio, internet, consultations and lectures, and a wide range of print media. Activities that were suitable to each local area were organized: free anemia testing and health consultation in public areas raised



In China, iron-fortified soy sauce is promoted to “give vitality” and is sold at an affordable cost

people's awareness of their personal susceptibility to anemia; village doctors, who are trusted sources of health information, conducted training sessions in their villages; information about the program was disseminated on buses and through television programs broadcast in the buses, as well as through the post, to reach people on their daily routes.

Program monitoring data from the sentinel sites revealed impressive success in the first years of the program. The general public in the program areas is now more aware of iron deficiency and IDA. Specifically, they are more aware of the symptoms, and adverse health effects of anemia. They are more likely to take action if they know they are anemic, and the majority of those taking action said that they would choose and use iron-fortified soy sauce to avoid anemia.

Social marketing of vitamin A supplementation in Indonesia

– Dorothy Foote, MPH, nutrition and health consultant

Indonesia has a long and successful history in conducting research and programs to combat vitamin A deficiency. In the wake of the Asian economic crisis, purchasing power and therefore access to micronutrient-rich foods decreased. The need to strengthen the national vitamin A supplementation program for children under five years of age was recognized as urgent.

Helen Keller International (HKI) and the Indonesian Ministry of Health (MOH) worked together from 1999–2004 to implement an accelerated national social marketing campaign to promote twice-yearly vitamin A supplementation for children aged 6–59 months. The promoted behavior was relatively simple – mothers had to take their children to receive a free vitamin A capsule twice a year.

To motivate mothers, it was essential for the campaign to communicate the key information – What? Vitamin A capsule. Why? For healthy eyes and strong body. When? February and August. Where? At the Posyandu (integrated health post) or Puskesmas (com-

munity health center) How much? Free. For whom? Blue capsules for children aged 6–11 months, red capsule for children aged 12–59 months. The campaign media were colorful, festive, and simple. Print media (posters, bumper stickers, banners, brochures, etc.) and electronic media (radio and television spots) were distributed nationwide, and special community promotion events were organized around the campaign months of February and August.

During the same period (1999–2003), HKI, in collaboration with the Government of Indonesia, conducted household-based surveys once every three months through the Nutrition and Health Surveillance System (NSS) among ~36,000 households (representing 70% of Indonesia's rural population and urban poor in the country's four major cities). This made a population-based evaluation of the social marketing campaign possible. NSS data showed increased knowledge about vitamin A supplementation in the target population, and increased vitamin A capsule coverage in urban poor and rural areas – from 28% to 81% (urban poor), and 41% to 77% (rural) among 6–11 month olds; and from 48% to 84% (urban poor), and 65% to 81% (rural) among 12–59 month olds. The MOH and UNICEF ensured that vitamin A capsule supply (availability) during this period was not a barrier to increased coverage.

This case study demonstrated that a well-designed and well-positioned social marketing campaign can have a positive impact on health behaviors. Reliable monitoring systems are essential to documenting the reach and impact of such programs. Sustaining successful vitamin A supplementation requires resources not only for capsules (to ensure supply), but also for social marketing to create and sustain demand for this life-saving intervention.



The social marketing campaign for vitamin A supplementation in Indonesia conveyed the key messages: What? Vitamin A capsule. Why? Healthy eyes and strong body. How much? Free. When? February and August. Where? Health Post or Health Center. For whom? Blue capsule for 6–11 month olds, red capsule for 12–59 month olds

From knowledge to practice – application of consumer research to promote fruit and vegetable consumption in Singapore

– Dr Annie Ling, Singapore Health Promotion Board

In Singapore, the consumption of fruits and vegetables is on the rise following a widespread campaign across the city-state to promote the message: '2+2 a Day' (meaning the consumption of two fruits and two vegetables daily). Dr Annie Ling of the Singapore Health Promotion Board reported on how consumer

research was used to develop the communication messages and outreach strategies.

A cross-sectional study was designed based on the ‘Stages of Change’ behavior change model. The study investigated the stages of readiness (pre-contemplation, contemplation, preparation, action, and maintenance) among Singaporean adults to consume adequate daily portions of fruits and vegetables. The findings were used to identify which kinds of messages and interventions would be most likely to move people to the next stage of change in adopting and maintaining the behavior of consuming ‘2+2 a Day.’

People in the contemplation and preparation stages, who represented 61.1% of Singaporean adults, were selected as the primary target audience. This meant they were “intending to take action within the next six months” (contemplation) or “intending to take action within the next 30 days and had already taken some behavioral steps (preparation).”

Intervention strategies were based on further research on where people eat – National Nutrition Surveys (NNS) in Singapore in 1998 and 2004 showed that the frequency of eating at hawker centers increased from 37.1% and 49.9% over the period. The ‘2+2 a Day’ Program therefore targeted outreach strategies to these venues, deploying ‘Fruit Ladies’ at food courts, and distributing labels at hawker stalls encouraging consumers to “Ask for More Vegetables” and “Have a Serving of Fruit at Every Meal.”

An evaluation of the program showed that knowledge of the recommended daily servings of fruits



Outreach strategies for ‘2+2 a Day’ in Singapore promote fruits and vegetables in places where people normally eat (hawker centers and food courts)

and vegetables increased from 7.1% to 31.8% from 2001 to 2004. NNS data from 1998 and 2004 also showed that the proportion of Singaporean adults eating ‘2+2 a Day’ increased from 5.0% to 14.0%. The program illustrates how consumer-based, behavior change research can be integrated with professional judgment and creativity to successfully motivate consumers towards healthy choices.

Conclusion

Across the various strategies to promote micronutrients (fortification, supplementation, dietary diversification), and across different program settings, the relative influence of availability, accessibility, and choice varies. A good understanding of these determinants through research and common sense about the context is essential to planning effective policies and programs.

While supplementation remains a key intervention for combating micronutrient malnutrition, food fortification with micronutrients and other dietary interventions are becoming an increasingly appropriate intervention as globalization opens markets and shifts the structure of where and how people access food. In this context, nutrition program planners will face increasing challenges in under-

standing the complex factors that influence consumer food choices. For all micronutrient program strategies, understanding what motivates the choices of the target population is essential. Another key element for successful programs is to have monitoring systems to evaluate program impact and provide ongoing feedback about the appropriateness of interventions.

More detailed information from the ILSI Symposium on Understanding and Influencing Consumer Food Behaviors for Health can be obtained by email from: ilsisea@singnet.com.sg.

References

1. Helen Keller International/Asia-Pacific. *Homestead Food Production – A Strategy to Prevent Malnutrition and Poverty*. Jakarta, Indonesia: Helen Keller International, 2001.
2. Drewnowski, A (2007). Abstract of the presentation, Biological, Social, Cultural, and Psychological Influences on Food Choice. ILSI Symposium on Understanding and Influencing Consumer Food Behaviors for Health, Singapore, 18–20 July 2007.

10th Asian Congress of Nutrition

Taipei, Taiwan, September 9–13, 2007

Noel W. Solomons

Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM), 17a Avenida 16–80, Zona 11, Guatemala City, Guatemala
Email: cessiam@guate.net.gt

The 10th Asian Congress of Nutrition (ACN) was literally held in the shadow of the world's tallest office building – the Taipei 101. The Taipei International Convention Center was the venue for the three-and-a-half-day program of plenary lectures (5), dialogues (3), symposia (21), and workshops (6) at this quadrennial scientific event. Moreover, there was a permanent poster session throughout the event, nestled near the exhibition area. The attendance of 1,400 delegates from 30 nations made this the largest gathering in the history of the ACN.

The local hosts were the Nutrition Society of Taiwan. On a related note, the Federation of Asian Nutrition Societies convened its regular meeting and selected Singapore as the site for the 11th ACN in 2011. The Council of the International Union of Nutritional Sciences (IUNS) also held its meeting in Taiwan to prepare for the 2009 International Congress of Nutrition in Bangkok; each of its members presented at least one invited talk in a symposium and moderated a session of the ACN.

Plenary program

The plenary program included hour-long talks by five renowned scientists from the USA, Chile, Japan, India and Australia, distributed between the first and last days' morning sessions. Dr Walter C. Willett's presentation, "Overview and perspectives in human nutrition," centered on dietary patterns and their associations with a reduced risk of chronic diseases. The Nurses' Health Study found that alcohol intake increased the risk of breast cancer, but that this risk was eliminated by a high intake of folic acid and dietary folates. On the other hand, fruits and vegetables were found to reduce the risk of cardiovascular disease (CVD), but had no influence on overall cancer risk.

Dr Ricardo Uauy's presentation, "Tackling the burden of disease with a common agenda," highlighted the persistence of nutrient deficiencies and their consequences on mortality, morbidity, and impaired function as well as demographic, epidemiological, and nutritional transitions. The key message was that it is neither logical nor sufficient to address one or the other poles of the problem; rather, we should find ways to address both with a common agenda.

Dr Hisanori Kato's presentation, "Nutrigenomics: the cutting edge and the Asian perspective," covered the recent advances in and the remaining limitations of the analytical methods in proteomics and metabolomics. Dr Kato emphasized that both the total diet and specific nutrients can influence the expression of genes, and postulated an eventual contribution of genomics to individualized nutrition. Dr Nita Bhandari presented "The new growth standard of the 21st century," a perspective on the 2006 World Health Organization (WHO)



Banner at the entry of the conference centre

growth curves, which discussed the data collection that was implemented to cover the ethnic and geographic spectrum of the planet. Dr Bhandari highlighted that all previous growth curves were *references* to normative populations as they

existed, whereas the 2006 growth curves represent a *standard* for how growth should occur.

Dr Mark L. Wahlqvist ended the sequence with his discourse on “The new Nutrition science in practice.” The theoretical basis for nutrition science came out of the 2003–2007 Task Force on Eco-Nutrition of the IUNS, suggesting that nutritional science not only develops on the biomedical front, but also in the societal and environmental dimensions of nutrition. The presentation illustrated the convergence of these dimensions with concrete examples, such as the issue of land use for food crops versus biofuels.

Free-paper sessions

Over 490 free papers were listed in the ACN program. Several of the best in each category were presented orally within the symposia. A total of 268 abstracts were presented in the poster session. **Table 1** provides a breakdown of the number of posters on different topic areas. The range of topics is illustrative of the emerging research priorities among students and

young investigators in the Asian region. The free papers on vitamin and mineral nutrition were the fourth most abundant among the topics, representing 8.5% of all posters. Interestingly, issues related to chronic disease, long-term function, and health comprised the top three free-paper topics, constituting over 50% of all programmed submissions.

The traditional hallmark interests of SIGHT AND LIFE have always been micronutrients and micronutrient malnutrition. This was recently updated to include the double-burden of nutrition and the extent to which vitamins and minerals play a role in either acute deficiencies or chronic diseases. For economy of space, however, this report focuses primarily on the explicit reports and observations in the area of micronutrient nutrition in its classic context of requirements and deficiencies.

In the vitamin and mineral nutrition section, two posters that caught people’s attention were “Biological activities of banana peel” and “An apple a day, with or without the skin: vitamin content in parts of



Prof. Nevin S. Scrimshaw, Emeritus Institute Professor of the MIT, and President of the International Nutrition Foundation

apple fruit.” In terms of assessments, the paper on “Estimation of dietary selenium intakes of Taiwanese by a self-constructed food selenium content database” was intriguing. There were many papers on unique sources of pro-vitamin A carotenoids in Asian plants and algae, on the role of vitamins in the regulation of gene transcription of active proteins, and on toxic trace elements such as aluminum and arsenic.

Dialogue sessions

A series of three debates between two speakers with divergent views on a central topic were part of the program. Within the context of Asian culture, which generally favors harmony over confrontation, the debates were re-christened dialogues. Two of these sessions had specific relevance to micronutrient nutrition.

Dialogue D2 had as its topic “National fortification policy.” Two observers, who were not native to Asia, provided their perspectives on fortification programs at the national level in the region. Dr Noel W. Solomons, from Guatemala, framed his remarks

Table 1: Overview of topics and number of posters of the free papers included in the 10th ACN program

Topic area	No of posters
Dietary bioactive compounds and functional foods	105
Diet, nutrition and chronic disease	97
Nutritional epidemiology	42
Vitamin and mineral nutrition	40
Energy nutrient metabolism	37
Nutrition education	30
Diet, nutrition and immune function	28
Nutrition through the life cycle	21
Nutrition and food processing	19
Clinical nutrition	15
Community and public health	14
Diet, nutrition and physical activity	12
Gastrointestinal function	8

under the title “Balanced advocacy.” His counterpart, Dr Wahlqvist, from Australia, chose the title “Policy in evolution.” A point of contention was whether it was feasible or desirable for Asian populations to make major changes in their dietary patterns for the sake of consuming nutrients from nutrient-dense foods. The former speaker favored fortification of staples or condiments, whereas the latter favored food-based approaches. Both speakers found common ground in the emerging promise of the bio-fortification of staple crops, such as rice and wheat, to increase their micronutrient content.



Prof. Mark L. Wahlqvist of Australia

Dialogue D3 was on the topic “Current calcium recommendations,” which initiated a discussion on calcium intake in early life and its implications for the accretion of skeletal bone mass and mineralization throughout life. Dr Connie Weaver, from the US, led the dialogue with her chosen topic, “Current calcium recommendations in North America for children and adolescents.” Dr Warren Tak Keung Lee, from the UK (formerly from Hong Kong), addressed the topic of “Calcium requirements for Asian children and adolescents.” The discussion focused on the reality of ethnic discrepancies in bone

Table 2: Selected symposia of relevance to micronutrient nutrition at the 10th ACN

S3 Dietary pattern, health and total well-being
S4 Agricultural food production
S5 Approaches to combat double burdens: micronutrient deficiencies and complex diseases
S6 Nutrient-gene interactions
S7 Diet, nutrition and bone health
S13 GMO foods
S17 Assessment and evaluation of diet in Asian region

retention at equivalent levels of calcium intake; studies show that black adolescents, particularly females, retain and deposit more calcium in their bones than their white peers. Asian girls, whether living in the US or in East Asia, are also more efficient in the bony utilization of dietary calcium. The fulcrum issue remained whether the level of adequate intake recommended by the US Dietary Reference Intake is appropriate for ethnic groups other than North American Caucasians.

Symposia program

A total of 21 symposia were conducted during the morning and afternoon sessions of the second and third days of the Congress. Many of the symposium themes were outside our central area of interest, with only seven being of selected relevance to micronutrients. These are listed in **Table 2**.

The “Dietary pattern, health and total well-being” (S3) symposium was remarkable in its explicit exploration and promotion of “dietary quality.” This perspective on healthful eating goes beyond just satisfying energy needs; it also takes nutrient density, pattern of foods, and beneficial constituents into consideration. The symposium touched on ways to define and measure dietary quality, and even assess it with biomarkers.

The “Agricultural food production and public health” (S4) symposium included two topics of relevance to micronutrient nutrition. These included the development of rice varieties that improve human nutrition and a global perspective of plant-based health food from an agricultural point of view.

The “Approaches to combat double burdens: micronutrient deficiencies and complex diseases” (S5) symposium best embodied and exemplified the paradigm that SIGHT AND LIFE announced in September of 2006. The keynote address in this symposium by Dr Lindsay Allen, from the US, addressed the question, “To what extent can food-based approaches improve micronutrient status?” Dr Allen concluded that foods of animal origin could close some of the gap, but that fortification or bio-fortification is needed for full micronutrient security. Case-study discussions from Thailand, Vietnam, and Malaysia confirmed the difficulty of achieving a nutrient-dense diet and, at the same time, the rise of overweight and chronic diseases in each Southeast Asian state.

An international panel in the “Nutrient-gene interactions” (S6) symposium explored the topic of Nutrigenomics, which touched on modern analytical capacity in genomic dissection, and the re-

sponse of organisms to nutrient availability and food consumption. The diverse interaction of energy-restricted diets, berries, folic acid, phytochemicals, and essential fatty acids with genetics and the genome were discussed.

The “Diet, nutrition and bone health” (S7) symposium was led by a keynote address by Dr Weaver on the role of nutrition in optimizing peak bone mass. Other talks within the symposium looked at calcium-isoflavone interactions in bone metabolism and the resurgence of the importance of vitamin D in bone health.

The “GMO foods” (S13) symposium was almost entirely devoted to issues of safety in relation to biotechnology products in the human and animal food chain. The discussion covered perspectives on safety, aspects of detection of genetic modification, and regulation and labeling issues.

The “Assessment and evaluation of diet in the Asian region” (S17) symposium included two topics of central relevance to micronutrient nutrition. These included how to adapt and apply the US Dietary Reference Intake approach to Asian countries, and a commentary on the limitations and resolution of dietary assessments for micronutrient intake.

Workshop sessions

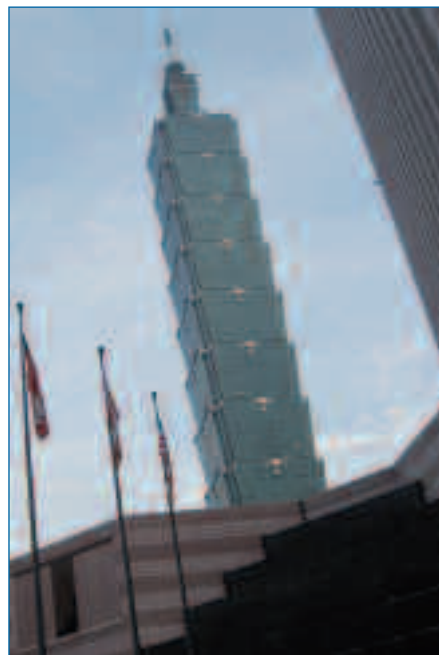
Six workshops were offered, covering practical areas related to policy issues, institutional feeding programs, nutrition education through the mass media, metabolic and nutritional aspects of glutamate, innovation in food science, and improving nutrition research. Within these, two presentations emerged as highly relevant to SIGHT AND LIFE’s readers. Dr Patanee Winichagoon, of the Institute of Nutrition at the Mahidol University in Bangkok, presented on the “Co-existence of micronutrient malnutrition: implication for nutrition policy and programs in Asia.” Dr Winichagoon noted that multiple nutrients are often deficient in persons or populations; whether formulation of multiple micronutrient supplements or concerted food-based strategies are more feasible and appropriate is a regional policy question. Dr Eileen Kennedy, dean of the Tufts University Friedman School of Nutrition Science and Policy in the US, presented on “Public-private sector collaborations,” which looked at the opportunities for

forming partnerships or alliances between industry and public sector entities. Dr Kennedy outlined four areas of contention that need to be addressed: 1) Lack of mutual trust; 2) Advertising to children; 3) Academics paid as consultants; and 4) Biases, transparency and conflict of interest.

Closing remarks

The Asian region has two nations with over a billion inhabitants each (China and India) and, overall, constitutes almost half of the world’s population. With Taiwan being the site of the 10th ACN and Singapore selected as the venue for the next Congress, it is not surprising that issues of chronic disease and long-term health are beginning to dominate the scientific agenda of the region’s scientists, given the highly urbanized settings and rising prosperity of these fast-growing economies.

However, it is also clear that there remain great economic, social, and environmental disparities between the countries of this region, and there will be increasing stresses from the double burden of under and over-nutrition as the disparities widen. This is a region where the spectrum of nutritional disorders and chronic as well as infectious diseases will likely affect the greatest numbers of people. Looking forward, these problems look set to be further exacerbated by the nutrition and health impacts of progressive climate change.



Impressions from Taipei

SIGHT AND LIFE continues to support the fight against micronutrient malnutrition by nurturing the skills and knowledge that can make a difference in communities the world over, and providing programmatic and other support to relevant interventions. This report is part of this ongoing support to our network of stakeholders around the world, to help connect us to the latest thinking in our field and make our work stronger.

Inside SIGHT AND LIFE

Hua Jing is a PhD student at the Department of International Health – Human Nutrition, Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. From 18 June to 17 August 2007, she worked as an intern in the SIGHT AND LIFE team in Kaiseraugst, Switzerland.

In the first of a new series, Inside SIGHT AND LIFE, Hua Jing describes her impressions of working with the Kaiseraugst team – shortly after arriving in Switzerland and shortly before returning to the USA two months later.



Hua Jing

The view from outside (June 2008)

SIGHT AND LIFE (SAL): Hua Jing, welcome to Switzerland and welcome to SIGHT AND LIFE! Let me start by asking what made you want to work in the field of nutritional science?

Hua Jing (HJ): I simply want to use my knowledge of medicine and public health, and of laboratory techniques too, to help people who are suffering the effects of poor nutrition in developing countries. My first degree was a Bachelor of Medicine from Peking University Health Science Center, which I followed with Master of Medical Science from the Department of Food Science and Nutrition at the School of Public Health at Peking University. I then embarked on a Master of Science

degree in Nutritional Sciences at the University of Wisconsin-Madison. If what I've learned in the course of my studies can help victims of malnutrition in some way, I'll be very happy.

SAL: You currently have a DSM Fellowship in Micronutrient Research at Johns Hopkins University. What does this involve?

HJ: At the University of Wisconsin-Madison from July 2004 to July 2006 I conducted research into the bioavailability of pro-vitamin A carotenoids, and these studies sparked my interest in the subject of public health. It was also at Wisconsin that I received intensive training in analytic laboratory techniques such as HPLC (high-performance liquid chromatography). At Johns Hopkins, where I've been since August 2006, I'm applying these techniques and also going a stage further, for I'm receiving intensive academic training as a research assistant from Professor Keith West. My focus is on identifying micronutrient levels in serum and processing the accompanying data. Next year I shall commence my own research into micronutrient deficiency, working towards a PhD.

SAL: So what will you be doing in the SIGHT AND LIFE team for the next two months?

HJ: As I'm sure you're aware, SIGHT AND LIFE receives many requests to fund work in the field of micronutrition. Writing an appropriately formulated proposal can be very challenging, however – and so can trying to evaluate proposals that don't meet the funding criteria. It was therefore decided to develop standard guidelines for submitting proposals and also a standard approach to evaluating these. My tasks within SIGHT AND LIFE include drawing up an evaluation grid to facilitate the process, evaluating individual proposals, and developing the criteria and format for proposals to be submitted in 2008. Our hope is that by giving people better instructions as to how to meet our criteria, we'll encourage a general improvement in the quality of proposals submitted, which will result in more proposals achieving their aim of receiving funding.

SAL: What are your first impressions of the SIGHT AND LIFE team? Have you settled well into your new working environment?

HJ: I have indeed settled in well, and I'm thoroughly enjoying the

Hua Jing BM, MMS. Honors and awards

1996	Beijing Medical University Academic Excellence Scholarship
1997	Beijing Medical University Academic Excellence Scholarship
1999	Peking University Academic Excellence Scholarship
2000	Peking University Guanghua Scholarship (topmost)
2000	Peking University Outstanding Student Honor (super honor)
2006	Johns Hopkins School of Public Health Adele Diaz Scholarship
2007	Johns Hopkins School of Public Health DSM Fellowship

Publications

Hua Jing, Yong Li. Effects of ethanol on mouse embryonic brain development and heat shock protein 73 expression. *Toxicology In Vitro*. 2004 Oct; 18(5): 601–7.

Hua Jing, Mingxi Zang, Yong Li. Effects of ethanol on mouse embryonic brain development: an in vitro study. *China Reproductive Health*. 2004, 15(2): 107–110.

Zang, MX, Li, Y, Xue, LX, Jia, HT, **Jing, H**. Cooperative activation of atrial natriuretic peptide promoter by Dhand and MEF2C. *J Cell Biochem*. 2004 Dec; 93(6):1255–66.

Christopher Davis, **Hua Jing**, Julie A.Howe, Torbert Rocheford, and Sherry A. Tanumihardjio. Cryproxanthin from supplements or biofortified maize enhances liver vitamin A in mongolian gerbils more than or equal to carotene supplements. (submitted)

experience of applying my academic training to real-life situations. Although small, the SIGHT AND LIFE team is embedded within DSM and therefore enjoys global leverage. We collaborate with major global institutions such as the World Food Program, so it's a very stimulating working environment to be in. The team has all been very welcoming and helpful – and they're passionately committed to fighting micronutrient deficiencies in developing countries.

SAL: You come from China, you've been studying in the USA and are now working in Switzerland. How do you manage to cope with the cultural differences between these countries?

HJ: At the beginning I did experience some culture shocks, I must confess, but I've found inspiration in the words of Stephan Tanda, the member of DSM's Managing Board with responsibility for DSM's Nutrition cluster. He says, "Think local, leverage global." So wherever I live, I strive to live and think global. This allows me to incorporate positive elements of the new cultures that I encounter into my own culture – which helps me to develop personal global leverage.

SAL: Chinese medicine is growing increasingly popular in the Western world; Chinese food has long been so. What, in your view, can the West learn from China's understanding of the relationship between nutrition and health? And what can China learn from the West?

HJ: Chinese medicine looks at people holistically, balancing various factors such as food intake, sleep and emotional state. Western medicine focuses by contrast on curing individual symptoms, especially acute disease. I think the two approaches have much to learn from each other. Chinese medicine could benefit from the rigor of the Western approach, while Western medicine could benefit from the all-encompassing view taken by Chinese medicine. That said, my qualifications are in Western medicine, not Chinese!

The view from inside (August 2008)

SAL: Hua Jing, we first spoke almost two months ago, just after you had joined the SIGHT AND LIFE team as an intern. That period has now come to an end. Were your expectations of the internship fulfilled?

HJ: Very much so. My time here gave me the opportunity to apply my university learning to an industrial context and to greatly broaden my general understanding of industry.

SAL: So you had plenty to do?

HJ: Oh, I was kept very busy! I completed the new document standard as planned, developed grant application guidelines for use in 2008, participated in the editorial work of the SIGHT AND LIFE team, supported the dissemination of the SIGHT AND LIFE Nutritional Anemia Guidebook for review by special-

ist journals, and had the chance to meet various experts in the field of nutritional science.

SAL: What were your impressions of DSM, the sponsor of SIGHT AND LIFE?

HJ: What impressed me most was the diversity of the company, not just within the SIGHT AND LIFE team but throughout the organization. It was inspiring to see so many people from such widely differing cultural backgrounds working so closely together.

SAL: Did you experience any problems during your stay in Switzerland?

HJ: I did have some problems with the local languages – not at work, where everyone spoke English, but in daily life outside. I remember having terrible difficulty trying to ask for hair conditioner in a particular shop: no-one seemed to understand the term! So I would advise prospective interns to learn some of the local languages before coming here. I did pick up a few words myself, of course: gruezi, guten Tag, bonjour, merci, voilà and ciao.

SAL: Is there one experience that sums up your sojourn with SIGHT AND LIFE?

HJ: Yes, it was my last day in Kaiseraugst. Everyone from the SIGHT AND LIFE team gathered together to bid me farewell, which was very touching. We had

got along very well for a period of two months and had achieved a great deal together during that time. I found myself beginning to miss my SIGHT AND LIFE colleagues even before leaving them! I must confess that I'd been looking forward to returning to the USA, but in the end I found it extremely difficult to say goodbye to my new colleagues in Switzerland.

SAL: What will be the focus of your work in Baltimore next year?

HJ: I'll take more classes in how to develop proposals and will also sit various exams so that I can commence my own research and embark on the associated field work in June 2008. My topic hasn't been defined as yet, but I'm currently exploring various ideas together with my supervisors. Dr Klaus Kraemer's input here has also been extremely helpful.

SAL: Hua Jing, Many thanks for talking with SIGHT AND LIFE MAGAZINE, and the best of luck with all you do.

HJ: Thank you. Having the chance to crystallize my thoughts in this way is a very satisfying conclusion to an important phase in my professional and personal development.

Interview by Jonathan Steffen

SIGHT AND LIFE is a humanitarian initiative of DSM covering a wide range of activities in collaboration with global and local partners and cooperating with leading universities. To ensure a sustainable and significant improvement in human nutrition and health, SIGHT AND LIFE encourages partnerships, the exchange of scientific information and the creation of networks. For more information please visit www.sightandlife.org

DSM Nutritional Products

DSM Nutritional Products is the world's leading supplier of vitamins, carotenoids and other fine chemicals to the feed, food, pharmaceutical and personal care industries. The business has sales of over EUR 2 billion and a long tradition as a pioneer in the discovery of new products, new formulations and attractive applications for all industry segments. For further company information please visit www.dsmnutritionalproducts.com

UNLIMITED RESPONSIBILITY

SIGHT AND LIFE IS A HUMANITARIAN INITIATIVE OF DSM

DSM

DSM creates innovative products and services in life sciences and materials sciences, contributing to the quality of life. DSM's products and services are used globally in a wide range of markets and applications, supporting a healthier, more sustainable and enjoyable way of living. End markets include human and animal nutrition and health, personal care, pharmaceuticals, automotive, coatings and paint, electrics & electronics, life protection and housing. The company strategy, *Vision 2010 – Building on Strengths*, focuses

on accelerating profitable and innovative growth of the company's specialties portfolio. The key drivers of this strategy are market-driven growth and innovation, an increased presence in emerging economies and operational excellence. DSM has annual sales of almost EUR 9 billion and employs some 22,000 people worldwide. The company is headquartered in the Netherlands, with locations in Europe, Asia, the Americas, Africa and Australia. More information about DSM can be found at www.dsm.com

DSM Nutritional Products Ltd.
P.O. Box 3255, CH-4002 Basel
Switzerland

Unlimited. DSM



Multiple micronutrient literature

David I. Thurnham

University of Ulster, Northern Ireland Centre for Food and Health,
Coleraine Northern Ireland, UK
Email: di.thurnham@ulster.ac.uk

Vitamin A

Prevalence and causes of childhood blindness in camps for displaced persons in Khartoum: results of a household survey. Zeidan Z, Hashim K, Muhit MA, Gilbert C. *East Mediterr Health J* 2007;13:580–5. (Department of Community Medicine, Faculty of Medicine, University of Khartoum, Khartoum, Sudan. Email: drziedan61@hotmail.com)

The prevalence and causes of visual impairment and blindness were determined in 29 048 children < 16 years in all households of 5 camps for internally displaced people in Khartoum State, Sudan. After house-to-house visits by trained health care workers, 916 children received further assessment, 2.7% of whom were found to be blind, 1.6% to be severely visually impaired and 5.5% to be visually impaired, according to WHO criteria. The prevalence of blindness in children in the camps was estimated as 1.4 per 1000 children. The leading causes of blindness were found to be corneal opacities (40.0%), mainly due to vitamin A deficiency, followed by amblyopia (32.5%)

Causes and temporal trends of childhood blindness in Indonesia: study at schools for the blind in Java. Sitorus RS, Abidin MS, Prihartono J Br J Ophthalmol 2007;91:1109–13. (Department of Ophthalmology, Faculty of Medicine, University of Indonesia. Jakarta. Salemba 6, Jakarta-10430. Indonesia. Email: ritasito@yahoo.com)

From a total of 504 students in schools for the blind in Java, 479 were examined using a modified WHO Prevention of Blindness (WHO/PBL) procedure. Authors found a majority of the students (95%) were blind (BL) and 4.6% were severely visually impaired (SVI). The major anatomical site of BL/SVI was whole globe in 35.9%, retina in 18.9%, lens in 16.4%

and cornea in 16.1%. The major underlying etiology of BL/SVI was undetermined in 32.7%, hereditary factors in 31.9% (mainly retinal dystrophies), and childhood disorders in 28.5%. Avoidable causes of BL/SVI accounted for 59.9% of the total students (measles-related 23.1%; cataract (15.5%) and glaucoma (8.2%)). Comparisons of trends of SVI/BL among <16 y and \geq 16 y, suggested that childhood disorders and corneal factors have declined, while hereditary disorders have increased. Optic nerve disorder, although not counted as a major cause of blindness, seems to be on the increase. Conclusions: The temporal changes could reflect improved vitamin A supplementation, measles vaccination and socioeconomic development in Indonesia.

Out-of-home food intake is often omitted from mothers' recalls of school children's intake in rural Kenya. Gewa CA, Murphy SP, Neumann CG. *J Nutr* 2007;137:2154–9. (Department of Community Health Sciences, School of Public Health, University of California, Los Angeles, CA 90095, USA. Email: cgewa@mednet.ucla.edu)

The objectives of this study were to describe the types and composition of foods consumed outside the home (OH) by rural school-aged Kenyan children, to assess their contribution to the daily intake of the child, and to evaluate the ability of the mother to estimate intake of OH foods. To capture any seasonal differences, the study was conducted twice, once during a food shortage season (FSS) and again during the subsequent harvest season (HS). OH foods contributed 13 and 19% of daily energy intake in the FSS & HS, respectively, but mothers missed 77 and 41% of the OH energy intake. Nutrients most likely to be under-reported on the mothers' recalls were vitamin C (59 and 26% was missed in the FSS & HS, respectively) and vitamin A (~22% was missed in both seasons). To ensure that all

food intake is recalled, it is important that school children be included in dietary assessment interviews about their own intakes.

Improved vitamin A supplementation regimen for breastfed very low birth weight infants.

Aurvåg AK, Henriksen C, Drevon CA et al. *Acta Paediatr* 2007;96:1296–302. (Department of Pediatrics, Akershus University Hospital and Akershus Faculty Division, University of Oslo, Norway. Email: anne.aurvaag@ahus.no)

Authors observed that preterm infants usually have low retinol concentrations at birth and at discharge from hospital and report a new protocol designed to raise plasma retinol in very low birth weight infants (VLBW: birth weight < 1500 g). An open intervention trial was conducted on 53 VLBW infants in which a daily dose of vitamin A was given mixed with human milk instead of as a bolus and varied according to bodyweight. Blood samples were collected at inclusion and discharge from hospital, and plasma retinol was analyzed using HPLC. At discharge from hospital, the reference group had lower median plasma retinol concentrations compared to the modified group (0.30 vs. 0.49 mmol/L, $p = 0.008$). Fewer infants in the modified group had plasma retinol levels below 0.35 mmol/L compared to infants in the reference group (44% vs. 69%, $p = 0.04$). [DIT: Infants are born with low concentrations of serum retinol (<1.0 mmol/L) but the values in VLBW infants are particularly low even at discharge. It would be interesting to know whether the intervention group achieved normal values more quickly than the reference group.]

Vitamin D

Vitamin D in defense of the human immune response.

Adams JS, Liu P, Chun R et al. *Ann N Y Acad Sci* 2007; 26 July, ahead of print. (Cedars-Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, California, USA. Email: adamsj@schc.org)

Defensin is a generic name reserved for an endogenously synthesized antimicrobial agent. The authors reviewed a series of discoveries that led to the proposal that 25-hydroxylated metabolite of vitamin D is a key intracellular regulator of the synthesis and action of naturally occurring defensin molecules against bacterial antigens. Key elements of the discussion include (1) the basic element of the human immune response that is responsive to vitamin D, (2) describe work relevant to the extrarenal expression of the vitamin D-1-hydroxylase (CYP27b1) in the macrophage as an initiator of the

innate immune response, and (3) describe recent work on the relevance of the vitamin D intracrine-autocrine-paracrine system in a model of a common and devastating human disease, tuberculosis. Authors suggest that there is a long history of studies that show that host-defenses against *Mycobacterium tuberculosis* is dependent on serum 25-OHD levels of the host and not on the action of 1-25(OH)2D.

Vitamin D deficiency. Holick MF. *New Engl J Med* 2007;357:266–81. (Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, the Vitamin D, Skin, and Bone Research Laboratory, Boston University Medical Center, Boston, MA 02118, USA. Email: mholick@bu.edu)

A useful general review on what is currently known of the metabolism of vitamin D. The author believes that vitamin D deficiency is more common than generally recognized. His cut-off for deficiency is 75 nmol/L for serum 25-OHD concentrations – a threshold the author maintains is necessary for anti-fracture efficiency in post-menopausal women. A lower threshold of 50 nmol/L may be sufficient for the immunomodulatory actions of 25-OHD. The author associated poor vitamin D status with osteoporosis, chronic disease and some common cancers. Readers will be aware however that low concentrations of 25-OHD found in patients with cancer may well be a consequence of the condition rather than a cause. However, the author describes evidence to suggest that persons with better vitamin D status may be better able to exert local control on cancer cell growth, so delaying development of the disease. The author emphasizes the need for sunlight to promote vitamin D synthesis in the skin and provides details on vitamin D supplements needed where sunlight sources are poor.

Vitamin D and prevention of breast cancer. Welsh J. *Acta Pharmacologica Sinica* 2007;28:1373–82. (Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556, USA. Email: jwelsh3@nd.edu)

Epidemiologic data have demonstrated that breast cancer incidence is inversely correlated with indices of vitamin D status, including ultraviolet exposure, which enhances epidermal vitamin D synthesis. The vitamin D receptor (VDR) is expressed in mammary epithelial cells, suggesting that vitamin D may directly influence sensitivity of the gland to transformation. Consistent with this concept, in vitro studies have demonstrated that the VDR ligand, 1,25-dihydroxyvitamin D (1,25D), exerts negative growth regulatory effects on

mammary epithelial cells that contribute to maintenance of the differentiated phenotype. Furthermore, deletion of the VDR gene in mice alters the balance between proliferation and apoptosis in the mammary gland, which ultimately enhances its susceptibility to carcinogenesis. In addition, dietary supplementation with vitamin D, or chronic treatment with synthetic VDR agonists, reduces the incidence of carcinogen-induced mammary tumors in rodents. Collectively, these observations have reinforced the need to further define the human requirement for vitamin D and the molecular actions of the VDR in relation to prevention of breast cancer.

Vitamin E

Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. Willers SM, Devereux G, Craig LCA et al. *Thorax* 2007;62:772–8. (Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, P O Box 80178, 3508 TD Utrecht, The Netherlands. Email: S.Willers@iras.uu.nl)

Because maternal vitamin E, vitamin D and zinc intakes during pregnancy have been associated with asthma, wheeze and eczema in 5-year-old children, the authors investigated maternal intake during pregnancy by food frequency questionnaire (FFQ) in a longitudinal cohort study. 1253 cohort children participated at 5 y and maternal FFQ data were available for 1212. No consistent associations were found between childhood outcomes and maternal intake of the analyzed foods except for apples and fish. Maternal apple intake was beneficially associated with wheeze (odds ratio [OR] highest vs lowest tertile 0.63), asthma (OR 0.54) and doctor-confirmed asthma (OR 0.47) in the children. Maternal fish consumption was beneficially associated with doctor-confirmed eczema (OR ≥ 1 /week vs never 0.57). Conclusion: Consumption of apples and fish during pregnancy may have a protective effect against the development of childhood asthma and allergic disease.

Nutritional antioxidants and age-related cataract and maculopathy. Chiu C, Taylor A. *Exp Eye Res* 2007;84:229–45. (The Laboratory for Nutrition and Vision Research, USDA Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111, USA. Email: allen.taylor@tufts.edu)

Age-related cataract (ARC) and maculopathy (ARM) are two major causes of blindness worldwide. There

are important functional, surgical and financial reasons to study relationships between risk for ARC/ARM and nutrition, particularly given the rapidly growing elderly segment of our population. It is clear that oxidative stress is associated with compromises to the lens and retina and over 70 studies have attempted to relate antioxidant intake to risk for ARC and ARM. This article reviews epidemiological literature about ARC and ARM with emphasis on roles for vitamins C and E and carotenoids. Since glycation and glycooxidation are major molecular insults which involve an oxidative stress component, the authors also review new literature that relates dietary carbohydrate intake to risk for ARC and ARM. To evaluate dietary effects as a whole, several studies have tried to relate dietary patterns to risk for ARC. Authors note that data from the observational studies generally support a protective role for antioxidants or supplements but results from intervention trials are less encouraging with respect to limiting risk for ARC/ARM prevalence. Likewise it is difficult to determine why the various types of studies are not yielding similar results. The authors speculate that there are many common insults and mechanistic compromises that are associated with aging, and proper nutrition early in life may address some of these compromises and provide for extended youthful function later in life. Whether it is possible to identify an effective nutritional strategy to prevent or delay the development and progress of ARC/ARM and the age when the supplementation should begin needs further study.

Vitamin E: inflammation and atherosclerosis. Singh U, Devaraj S. *Vitam Horm* 2007;76:519–49. (Department of Pathology, Laboratory for Atherosclerosis and Metabolic Research, UC Davis Medical Center, Sacramento, California 95817, USA. Email: uma.singh@ucdmc.ucdavis.edu)

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the western world with its incidence increasing lately in developing countries and evidence suggests inflammation is involved in its etiology. The authors report recent emerging data on α -tocopherol as well as gamma-tocopherol and tocotrienols especially with regards to their effect on inflammation as it relates to CVD. Authors point out that vitamin E is a potent antioxidant and comprises eight different isoforms. The anti-inflammatory properties of α -tocopherol have been assessed in terms of decreasing C-reactive protein (CRP) and proinflammatory cytokines especially at high doses. They also discuss work showing gamma-tocopherol decreases reactive nitrogen species and also appears to have anti-inflammatory properties; however, there are scanty

data examining pure gamma-T preparations. They suggest that tocotrienols (alpha and gamma) may prevent CVD but the data are conflicting. [DIT: There is still much to learn about vitamin E and its functions in the body. However readers may also want to consult the paper below and others in the literature that find no benefits of vitamin E supplements against CVD.]

A randomized factorial trial of vitamins C and E and β -carotene in the secondary prevention of cardiovascular events in women: Results from the Women's Antioxidant Cardiovascular Study (NCT00000541). Cook NR, Albert CM, Gaziano JM et al. *Arch Intern Med* 2007;167:1610–8. (Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Ave E, Boston, MA 02215, USA. Email: ncook@rics.bwh.harvard.edu)

Randomized trials have largely failed to support an effect of antioxidant vitamins on the risk of cardiovascular disease (CVD). Few trials have examined interactions among antioxidants, and, to our knowledge, no previous trial has examined the individual effect of vitamin C on CVD. The Women's Antioxidant Cardiovascular Study tested the effects of vitamin C (500 mg/d), vitamin E (600 IU every other day), and β -carotene (50 mg every other day) on the combined outcome of myocardial infarction, stroke, coronary revascularization, or CVD death among 8171 female health professionals at increased risk, in a 2 x 2 x 2 factorial design. Participants were \geq 40 years with a history of CVD or 3 or more CVD risk factors and were followed up for a mean duration of 9.4 y, from 1995–1996 to 2005. A total of 1450 women experienced 1 or more CVD outcomes. There was no overall effect of vitamin C (relative risk [RR], 1.02; [P=0.71]), vitamin E (RR, 0.94; [P=0.23]), or β -carotene (RR, 1.02; [P=0.71]) on the primary combined end point or on the individual secondary outcomes of myocardial infarction, stroke, coronary revascularization, or CVD death. A marginally significant reduction in the primary outcome with active vitamin E was observed among the pre-specified subgroup of women with prior CVD (RR, 0.89; 95% CI, 0.79–1.00 [P=0.04]; P value for interaction, 0.07). There were no significant interactions between agents for the primary end point, but those randomized to both active vitamins C and E experienced fewer strokes (P value for interaction, 0.03). There were no overall effects of vitamins C and E or β -carotene on cardiovascular events among women at high risk for CVD.

Vitamin K

Vitamin K status in the elderly Booth SL. *Curr Opin in Clin Nutr Metabol Care* 2007;10:20–3. (Vitamin K Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111, USA. Email: sarah.booth@tufts.edu)

Poor vitamin K nutrition has recently been linked to several chronic diseases associated with abnormal calcification in the elderly. To understand the impact of vitamin K nutrition on healthy aging it is necessary to assess both the determinants and the adequacy of vitamin K nutritional status. Recent work suggests elderly persons consume more vitamin K than young adults: however, a subgroup of the elderly population does not meet the current recommended dietary intakes. The first meta-analysis evaluating the data on the role of vitamin K and bone health concluded that increased intakes of vitamin K are warranted to reduce bone loss and fracture risk among the elderly. Other work suggests that non-dietary determinants of vitamin K status need to be factored into any discussion on the adequacy of nutritional status of the elderly and a promising area of research is the interrelationship between estrogen and vitamin K. Thus some elderly persons may benefit from increased intakes of vitamin K to reduce bone loss and fracture risk but much more research is required to identify non-dietary determinants of vitamin K status, and their impact on the elderly.

HPLC method for plasma vitamin K1: effect of plasma triglyceride and acute-phase response on circulating concentrations. Azharuddin MK, O'Reilly DS, Gray A, Talwar D. *Clin Chem* 2007; 53:1706–13. (Scottish Trace Element and Micro-nutrient Reference Laboratory, Department of Clinical Biochemistry, Royal Infirmary, Glasgow, UK. Email: dtalwar@gri-biochem.org.uk)

The plasma concentration of vitamin K1 (K1, phylloquinone) is the most reliable index for assessing vitamin K status. Authors validated an HPLC method to quantify plasma K1 and examined the effect of plasma triglyceride concentration on the K1 reference interval and any effects of inflammation using C-reactive protein (CRP) on K1 concentration in plasma. K1 was extracted from fasting plasma samples by deproteinization and C18 solid-phase extraction, separated by reversed-phase HPLC, and detected fluorometrically after postcolumn reduction with a platinum catalyst using a novel internal calibrator, docosyl naphthoate. The recovery of K1 was $>$ 90%. Between-run imprecise-

sion was 8.7%–9.0%, and within-run imprecision was 3.8%–7.0%. The linearity was up to 44.8 nmol/L, limit of detection 0.08 nmol/L, and limit of quantification 0.14 nmol/L. The correlation between plasma K₁ and triglyceride concentrations was $r = 0.7$ in the reference population. The 95% reference interval for the K₁:triglyceride ratio was 0.20 to 2.20 nmol/mmol. After surgery, plasma concentrations of CRP were significantly increased, whereas triglyceride and K₁ but not the K₁:triglyceride ratio were transiently decreased > 50%. K₁ population reference intervals should be expressed as a ratio of the triglyceride concentration. K₁ concentrations in plasma are decreased by inflammation and, unless corrected for plasma triglyceride concentration, are unlikely to be a reliable index of vitamin K status. [DIT: This work adds yet another nutrient to the growing list of micronutrients that are influenced by inflammation.]

B vitamins

Trends in blood folate and vitamin B 12 concentrations in the United States, 1988–2004. Pfeiffer CM, Johnson CL, Jain RB et al. *Am J Clin Nutr* 2007;86:718–27. (National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA. Email: cpfeiffer@cdc.gov)

Monitoring the folate status of US population groups over time has been a public health priority for the past 2 decades especially since the implementation of a folic acid fortification program in the mid-1990s. Authors measured blood indicators of folate and vitamin B12 status pre-fortification in ~23 000 participants in NHANES III (1988–1994) and post-fortification in ~8000 participants in 3 NHANES periods (1999–2004). Serum and RBC folate concentrations increased substantially (by 119–161% and 44–64%, respectively) in each age group in the first post-fortification survey period and then declined slightly (by 5–13% and 6–9%, respectively) in most age groups between the first and third post-fortification survey periods. Serum vitamin B12 concentrations did not change. Prevalence estimates of low serum and RBC folate concentrations declined in women of childbearing age from before to after fortification (from 21% to < 1% and from 38% to 5%, respectively) but remained unchanged thereafter. Prevalence estimates of high serum folate concentrations increased in children and older persons from before to after fortification (from 5% to 42% and from 7% to 38%, respectively) but decreased later after fortification. Conclusions: The small fall-off in folate concentrations post-fortification does not raise concerns about inadequate status.

Folate and vitamin B 12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Morris MS, Jacques PF, Rosenberg IH, Selhub J. *Am J Clin Nutr*. 2007;85:193–200. (Jean Mayer US Department of Agriculture, Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111, USA. Email: martha.morris@tufts.edu)

Vitamin B12 deficiency causes pernicious anemia and affects many seniors. Historic reports on the treatment of pernicious anemia with folic acid (FA) suggest that high-level FA fortification delays the diagnosis of or exacerbates the effects of vitamin B12 deficiency. This idea is controversial, however, because observational data are few and inconclusive. Furthermore, experimental investigation is unethical. Authors examined the relations between serum folate and vitamin B12 status relative to anemia, macrocytosis, and cognitive impairment (i.e., Digit Symbol-Coding score < 34) in senior participants in the 1999–2002 US National Health and Nutrition Examination Survey. The subjects had normal serum creatinine concentrations and reported no history of stroke, alcoholism, recent anemia therapy, or diseases of the liver, thyroid, or coronary arteries ($n = 1459$). Low vitamin B12 status was defined as a serum B12 < 148 pmol/L or a serum methylmalonic acid concentration > 210 nmol/L – the maximum of the reference range for serum vitamin B12-replete participants with normal creatinine. After control for demographic characteristics, low versus normal vitamin B12 status was more likely to be associated with anemia (2.7 x), macrocytosis (1.8 x), and cognitive impairment (2.5 x). In addition, in those with a low vitamin B12 status, a high serum folate (> 59 nmol/L – 80th percentile) was more likely to be associated with anemia (3.1 x) and cognitive impairment (2.6 x). The authors concluded that in seniors with low vitamin B12 status, high serum folate was associated with anemia and cognitive impairment. However when vitamin B12 status was normal, high serum folate was found to be associated with protection against cognitive impairment (0.4 x).

Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Dolinoy DC, Huang D, Jirtle RL. *Proc Natl Acad Sci USA* 2007;104:13056–61. (Department of Radiation Oncology and University Program in Genetics and Genomics, Duke University, Durham, NC 27710, USA. Email: jirtle@radonc.duke.edu)

The hypothesis of fetal origins of adult disease suggests that early developmental exposures involve epigenetic modifications, such as DNA methylation, that influence adult disease susceptibility. In utero or neonatal exposure to bisphenol A (BPA), a high-production-volume chemical used in the manufacture of polycarbonate plastic, is associated with higher body weight, increased breast and prostate cancer, and altered reproductive function. BPA has been detected in 95% of human urine samples of a reference population of adults in the USA. Authors describe a study in which adult pregnant mice were exposed to BPA and a gene (*agouti*) that determines coat color was monitored. In wild-type mice, coat color is predominantly black but hypomethylation of the *agouti* gene by exposure of the mice to BPA shifted the distribution of coat color and produced yellow offspring. However, maternal dietary supplementation, with either methyl donors like folic acid or the phytoestrogen genistein, negated the DNA hypomethylating effect of BPA. Thus, the authors present compelling evidence that early developmental exposure to BPA can change offspring phenotype by stably altering the epigenome, an effect that can be counteracted by maternal dietary supplements.

Folic acid supplementation lowers blood arsenic.

Gamble MV, Liu X, Slavkovich V et al. *Am J Clin Nutr* 2007;86:1202–9. (Departments of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY. Email: mvg7@colombia.edu)

Chronic arsenic exposure currently affects >100 million persons worldwide. Authors investigated whether *in vivo* metabolism by folate-dependent one-carbon metabolism, would detoxify ingested inorganic arsenic (InAs) by methylation to monomethylarsonic (MMAs) and dimethylarsinic (DMAs) acids to facilitate urinary arsenic elimination. In a randomized, double-blind, placebo-controlled trial, 130 arsenic-exposed Bangladeshi adults with low plasma folate (< 9 nmol/L) were supplemented with folic acid. Blood InAs, MMAs, and DMAs were measured before and after 12 wk of supplementation with folic acid (400 mg/d) or placebo. MMAs in blood were reduced by a mean (SE) of 22.2% (2.9) in the folic acid group and by 1.2% (3.6) in the placebo group ($P < 0.0001$). There was no change in blood DMAs but rapid excretion was indicated by an increase in urinary DMAs ($P = 0.0099$). Total blood arsenic was reduced by 13.6% in the folic acid supplementation group and by 2.5% in the placebo group ($P = 0.0199$). Folic acid supplementation acted primarily by decreasing blood MMAs and

increasing urinary DMAs. The implications of this study need to be explored to determine if folate supplementation as a public health strategy in countries where arsenic intake is a problem can prevent arsenic-induced illnesses.

Very low oral doses of vitamin B-12 increase serum concentrations in elderly subjects with food-bound vitamin B-12 malabsorption.

Blacher J, Czernichow S, Raphaël M et al. *J.Nutr* 2007; 137:373–8. (INSERM U 258, Hôpital Paul Brousse, Villejuif, France. Email: jacques.blacher@htd.aphp.fr)

The BOSSANOVA study, a randomized double-blind trial, was designed to determine the amount of oral vitamin B12 that would increase the serum vitamin B12 concentration by 37 pmol/L (50 ng/L) and determine whether there was a dose response. The authors also aimed to quantify the most efficient dose to be added to flour in addition to folic acid (flour co-fortification with vitamin B12 and folic acid). Sixty-seven patients were randomly assigned to 1 of 6 groups receiving various daily oral doses of vitamin B12 (i.e., 2.5, 5, 10, 20, 40 or 80 mg/d) for 30 d. The dose response was tested for different biological variables using a mixed model, taking into account the variable's initial value (between-subject effect), a linear log-dose effect, and a linear log (dose x time) interaction, where time was d 15 or d 30. Significant between-subject effects were found for serum vitamin B12, plasma homocysteine, and methylmalonic acid concentrations, but a log-dose effect was found only for serum vitamin B12 ($P < 0.001$). The slope of the line tended to be higher ($P = 0.07$) at d 30 than at d 15. For a mean serum vitamin B12 increase of 37 pmol/L, a dose of 5.9 (95% CI, 0.9–12.1) $\mu\text{g}/\text{d}$ was needed. Authors concluded that very low oral doses of vitamin B12 increased serum vitamin B12 concentrations in elderly subjects with sub-clinical vitamin B12 deficiency, following a log-dose pattern, and the results should assist the design of public health program for safe flour co-fortification with folic acid.

Vitamin C

Old world meets modern: a case report of scurvy.

Wang AH, Still C. *Nutr Clin Pract* 2007; 22:445–8. (Department of Gastroenterology and Nutrition, Geisinger Medical Center, 100 N. Academy Ave., Danville, PA 17822, USA. Email: alanwang97@yahoo.com)

Authors describe a case of scurvy (vitamin C deficiency) in a 65-year-old man. The patient reported heavy

alcohol abuse over the last several years. He also reported that his diet consisted of cheese pizzas only. On physical examination, he was noted to have spontaneous ecchymosis (bruises) of his lower extremities (denying any history of trauma); poor dentition; and corkscrew hairs on his chest, abdomen, and legs, with associated perifollicular petechia (small hemorrhages at the base of hair follicles). Punch biopsy of his skin lesions revealed perivascular lymphohistiocytic inflammation, with some focal perifollicular erythrocyte extravasation. Serum ascorbic acid concentration was $< 7 \mu\text{mol/L}$ ($< 1.2 \text{ mg/L}$) (normal range, $11\text{--}80 \mu\text{mol/L}$). The patient was successfully treated with 1 g/d vitamin C for the first 5 d, followed by a dose of 500 mg/d . [DIT: I agree with the authors that scurvy is rarely seen in modern times but it does still occur. I have found that the hemorrhages and unusual dietary habits are almost always present.]

Oxidative stress in sepsis in children. Cherian S, Jameson S, Rajarajeswari C et al. *Indian J Med Res* 2007;125:143–8. (Departments of Biochemistry, Kasturba Medical College & Hospital, Manipal 576104, India.)

Authors assessed the levels of certain antioxidants in blood of children with sepsis to investigate oxidative damage. Thirty-eight children with sepsis (1 to 5 y) and 39 age- and sex-matched controls were admitted to a tertiary care hospital. Red cell glutathione (GSH), superoxide dismutase (SOD) and thiobarbituric acid reactive substance (TBARS) and plasma vitamin C were estimated by standard techniques. There was no significant differences in erythrocyte GSH, SOD and TBARS levels in children with sepsis when compared to controls. However, plasma vitamin C levels were significantly lower in the patients. The authors suggest that active phagocytosis may reduce vitamin C due to its role as a free radical scavenger. The authors suggest that children affected by sepsis probably adapt to the free radical toxicity induced by this condition. [DIT: It has been known for many years that there is an active uptake of vitamin C from plasma by leukocytes emerging from the bone marrow with the onset of infection. Whether the process is primarily to boost antioxidant protection within the leukocytes or reduce the concentrations of a potential pro-oxidant in the plasma or both is not clear. If vitamin C is not removed from damaged tissues, it can react with iron to produce ferrous iron which may promote tissue damage by Fenton chemistry.]

Efficacy of topical vitamin C derivative (VC-PMG) and topical vitamin E in prevention and treatment of UVA suntan skin. Puvabanditsin P, Vongtongsri R. *J Med Assoc Thai* 2006;89:S65–S68. (Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Rama IV Rd, Bangkok 10330, Thailand. Email: fmedphp@md2.md.chula.ac.th)

Exposure of the skin to ultraviolet radiation (UVA) is known to induce reactive oxygen species and cause tissue damage and inflammation. In 20 volunteers, the authors tested whether two well-known antioxidants (topical 10% vitamin C derivative (VC-PMG) and topical 5% vitamin E) would inhibit these mediators and reduce UVA-induced skin reaction. Prior to 30 Joules UVA exposures, volunteers were asked to apply both agents twice daily for 3 days. Treatments had no effects on the melanin index measured immediately after irradiation using the Maxemeter. After continuing the cream application for 12 weeks, there were also no bleaching effects observed after 2, 4, 6, 8, 10 and 12 weeks compared to the placebo. The treatment was found to have no effects on prevention or treatment of effects of UVA irradiation.

Minerals

Distribution of anemia associated with micronutrient deficiencies other than iron in a probabilistic sample of Mexican children. Villalpando S, Pérez-Expósito AB, Shamah-Levy T, Rivera JA. *Ann Nutr Metab* 2006;50:506–11 (Center for Research on Nutrition and Health, Instituto Nacional de Salud Pública, Cuernavaca, Mexico. Email: svillalp@insp.mx)

The workers explored the associations among anemia (Hb and percent transferrin saturation (PTS)) and vitamins A, C, and folate deficiencies in a probabilistic sample of 0.5–11 y ($n = 1770$) Mexican children from the National Nutrition Survey (1999). Overall, 16.6% of children were anemic and of these 62% were iron deficient ($\text{PTS} < 16$). Vitamin A deficiency was more frequent in children with iron deficiency (ID) than non-ID children both with (40.6 vs. 16%) and without anemia (27.7 vs. 11.9%, both $p < 0.05$). In addition non-anemic, ID children had lower hemoglobin folate (11.5 vs. 22%, $p < 0.05$) than their non-ID counterparts. Mean concentrations of serum iron ($p < 0.01$), folate ($p < 0.001$) and retinol ($p < 0.0001$), but not ascorbic acid ($p < 0.6$), were significantly lower in anemic than in non-anemic children. In a linear regression model, 15% of hemoglobin variation in children

was explained by retinol, folate and PTS, but not vitamin C ($p < 0.0001$). Authors concluded anemia was mostly associated with iron deficiency and with a lesser proportion of folate and vitamin A deficiencies. Interventions aimed to reduce anemia in this population must consider interactions between those micronutrients in designing strategies. [DIT: 14% of the probabilistic sample was excluded with CRP >3 mg/L; the hemoglobin folate value was determined from whole blood folate and hemoglobin measured in dried blood spots and expressed as μg folate/L erythrocytes.]

Sex differences in prevalence of anaemia and iron deficiency in infancy in a large multi-country trial in South-East Asia. Wieringa FT, Berger J, Dijkhuizen MA et al. *Br J Nutr.* 2007;98:1070–1076. (University Medical Center Nijmegen, The Netherlands, and Nutrition Research and Development Centre, Bogor, Indonesia. Email: wieringa@tiscali.nl)

Biochemical data from 4 parallel, randomized, double-blind trials with Fe and/or Zn supplementation in infants (n 2452) in Indonesia, Thailand and Vietnam was pooled to evaluate effects of Fe supplementation and sex on the prevalence of anemia and Fe status in infants in SE Asia. At recruitment (5 mo of age), Hb concentrations were slightly but significantly lower in boy infants compared with girl infants (108.7 v. 111.4 g/L, $P = 0.04$). At 11 mo of age, boy infants not receiving Fe had significantly lower Hb (106.2 v. 111.0 g/L, $P < 0.001$) and lower serum ferritin concentrations (14.3 v. 21.1 mg/L, $P < 0.001$) than girl infants not receiving Fe. Consequently, boy infants had a higher relative risk of anemia (1.6, 95 % CI 1.3, 2.1) and of Fe-deficiency anemia (3.3, 95 % CI 2.1, 5.0) than girl infants. Fe supplementation significantly increased Hb concentrations in both boys and girls and there was no sex difference in Fe status in infants receiving Fe for 6 mo. Authors suggest that standard infant feeding practices in SE Asia do not provide sufficient Fe to meet requirements and that Fe requirements for boy infants are ~ 0.9 mg/d higher than for girl infants especially in the second half of infancy.

Sodium iron(III) ethylenediaminetetraacetic acid synthesis to reduce iron deficiency globally. Loots D, van Lieshout M, Lachmann G. *Eur J Clin Nutr* 2007;61:287–9. (Department of Nutrition, School of Physiology, Nutrition and Consumer Sciences, North-West University, Potchefstroom, South Africa. Email: vgedtl@puk.ac.za)

Although there is much interest in using sodium iron (III) ethylenediaminetetraacetic acid (EDTA) in food fortification programs to tackle the global problem of iron deficiency and its anemia, the authors found that synthesis methods of stable isotope-labeled sodium iron (III) EDTA for use in human bioavailability studies are incomplete, incorrect or totally lacking. To meet this need, the authors devised a simplified and optimized synthesis of sodium iron (III) EDTA from a block of isotopically enriched iron metal that can be easily and cheaply reproduced using simple basic laboratory apparatus. The resulting product is of high purity (99.9%), and may be used for human stable isotope bioavailability studies. The authors argue that the simplicity of the method allows workers to perform their own syntheses and that greater uniformity in this synthesis will reduce the variation observed between studies.

Iron status of inner-city African-American infants. Lozoff B, Lu Angelilli M, Zatakia J et al. *Am J Hematol.* 2007;82(2):112–21. (Center for Human Growth and Development, University of Michigan, Ann Arbor, Michigan 48109, USA. Email: blozoff@umich.edu)

The Fe status of African-American infants continues to be subject to debate. Authors characterized the Fe, lead and inflammation status of 198 9-mo inner-city infants (94% fed Fe-fortified formula). The proportion with Fe deficiency was calculated based on three approaches (≥ 2 abnormal iron measures with or without anemia for MCV model; NHANES II, ferritin model and NHANES III, or Sweden/Honduras study) and a promising new measure – body iron, calculated from ferritin and transferrin receptor (TfR). There were no sex differences for any iron measure. Hb < 110 g/L was observed in 25%; Hb ≤ 105 g/L in 10.1%. Free erythrocyte protoporphyrin (FEP) values were elevated without elevated lead concentrations or an inflammatory response: mean FEP = 866 mg/L red blood cells (75.5 $\mu\text{mol/mol}$ heme); 52.3% were > 800 mg/L (1.42 $\mu\text{mol/L}$), almost half of whom had a second abnormal Fe measure. The estimated prevalence of Fe deficiency was 14.4, 5.3, and 2.5% for the MCV, ferritin, and Sweden/Honduras models, respectively, and 4.1% for body Fe < 0 mg/kg. Regulation of iron storage is immature at < 1 year of age, making estimates of Fe deficiency that depend on ferritin, including body Fe, suspect in this age period. Thus, the "true" prevalence of Fe deficiency could not be established with confidence and functional indicators of poor Fe status in young infants are urgently needed.

Sensory characteristics and iron dialyzability of gluten-free bread fortified with iron. Kiskini A, Argiri K, Kalogeropoulos M et al. *Food Chem* 2007;102: 309–316. (Laboratory of Engineering, Processing and Preservation of Foods, Department of Food Science and Technology, Agricultural University of Athens, Iera Odos 75, Athens 11855, Greece. Email: kapsok@aua.gr)

The objectives of the present study were (a) to produce gluten-free bread, fortified with Fe (GFB-Fe), using selected Fe compounds (ferric pyrophosphate, ferric pyrophosphate with emulsifiers, NaFeEDTA, electrolytic iron, ferrous gluconate, ferrous lactate and ferrous sulfate), (b) to test sensory characteristics of the GFB-Fe (feel-mouth texture, crumb color, aroma and taste), and (c) to compare iron dialyzability of various iron compounds in GFB-Fe. The most acceptable products were those fortified with ferric pyrophosphate with emulsifiers and ferric pyrophosphate. Ferrous dialyzable iron (ferrous iron with molecular weight lower than 8000 Da, an index for prediction of Fe bioavailability) was measured under simulated gastrointestinal conditions. Ferrous dialyzable iron in GFB-Fe fortified with ferric pyrophosphate with emulsifiers, NaFeEDTA, ferrous bis-glycinate, ferrous gluconate or ferrous sulfate was higher than that in GFB-Fe fortified with electrolytic iron, ferrous lactate or ferric pyrophosphate ($P < 0.05$). These results are promising for the development of GFB-Fe products in the future.

Molecular control of iron transport. Ganz, T. *J Am Soc Nephrol.* 2007;18:394–400. (Departments of Medicine and Pathology, David Geffen School of Medicine, 10833 Le Conte Avenue, CHS 37-055, University of California, Los Angeles, CA 90095-1690, USA. Email: tganz@mednet.ucla.edu)

The Fe-regulatory hormone hepcidin is a 25-amino acid peptide that is synthesized in hepatocytes. Hepcidin binds to the cellular Fe export channel ferroportin and causes its internalization and degradation and thereby decreases Fe efflux from Fe exporting tissues into plasma. By this mechanism, hepcidin inhibits dietary Fe absorption, the efflux of recycled Fe from splenic and hepatic macrophages, and the release of Fe from storage in hepatocytes. Hepcidin synthesis is stimulated by plasma Fe and Fe stores and is inhibited by erythropoietic activity, ensuring that extracellular plasma Fe concentrations and Fe stores remain stable and the erythropoietic demand for Fe is met. During inflammation, increased hepcidin concentrations cause Fe sequestration in macrophages, resulting in hypoferrremia and eventually anemia of inflammation.

Hepcidin deficiency plays a central role in most Fe-overload disorders. The role of hepcidin abnormalities in anemias that are associated with renal disease and in resistance to erythropoietic therapies remains to be elucidated.

Nutritional iron deficiency: an evolutionary perspective. Denic S, Agarwal MM. *Nutrition* 2007; 23:603–14. (Faculty of Medicine & Health Sciences, UAE University, Al Ain, Abu Dhabi, United Arab Emirates. Email: s.denic@uaeu.ac.ae)

Iron deficiency, with or without Fe-deficiency anemia, is so ubiquitous that it affects all populations of the world irrespective of race, culture, or ethnic background. Despite all the latest advances in modern medicine, improved nutrition, and the ready availability of cheap oral Fe, there is still no good explanation for the widespread persistence of Fe deficiency. It is possible that the Fe deficiency phenotype is very prevalent because of many factors other than the commonly cited causes such as a decreased availability or an increased utilization of Fe. Several thousand years ago, human culture changed profoundly with the agrarian revolution, when humans turned to agriculture. Their diet became Fe deficient and new epidemic infections emerged due to crowding and lifestyle changes. There is convincing evidence that Fe deficiency protects against many infectious diseases such as malaria, plague, and tuberculosis as shown by diverse medical, historical, and anthropologic studies. Thus, this change of diet increased the frequency of Fe deficiency, and epidemic infections exerted a selection pressure under which the Fe deficiency phenotype survived better. Multiple evolutionary factors have contributed in making Fe deficiency a successful phenotype. Authors analyze some of the recent findings on Fe metabolism, the theories explaining excessive menstruation in human primates, the unexplained relative paucity of hemochromatosis genes, the former medical practice of “blood-letting,” and other relevant historical data to fully understand the phenomenon of Fe deficiency. They suggest that, due to a long evolutionary persistence of Fe deficiency, efforts at its prevention will take a long time to be effective.

Effect of zinc supplementation on child mortality. Lazzarini M. *Lancet* 2007;370:1194–5. (Dept of Pediatrics, Institute of Child Health, IRCCS Burlo Garofolo, Trieste, Italy. Email: lazzarini@burlo.triest.it)

Author comments on the accompanying article by Tielsch and colleagues and suggests that when exam-

ining the results of intervention trials, readers should look at the confidence intervals (CI) of potential benefits. She suggests that although the overall result may not reach statistical significance, “if the upper boundary of the CI includes an important benefit, the possibility that treatment still might be worthwhile has not been ruled out”. In other words the investigators might have missed a true treatment effect and the stronger the non-significant trend in favor of the experimental treatment, the more likely the investigators missed a true treatment effect and that zinc can reduce mortality in children over 12 mo. She accepts however that establishing the size of the effect and the influence of malaria may now be difficult to investigate as inclusion of a placebo group in future trials would be ethically questionable, at least in areas with malaria.

Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial.

Tielsch JM, Khatry SK, Stoltzfus RJ et al. *Lancet* 2007;370:1230–9. (Dept of Intl Health, Johns Hopkins University, Baltimore, MD, USA.

Email: jtielsch@jhsph.edu)

Zinc supplementation can reduce subsequent morbidity in children recovering from diarrhea and respiratory illness in developing countries. Authors assessed the effect of daily zinc supplementation on morbidity and mortality in children in southern Nepal. The trial comprised a community-based, cluster-randomized, double-masked, placebo-controlled, 2x2 factorial trial in children aged 1–35 mo (NCT00109551). Treatment groups were placebo, Fe and folic acid, Zn, and Fe and folic acid with Zn (12.5 mg Fe, 50 mg folic acid and 10 mg Zn). All children received vitamin A supplementation twice per year. Only the Zn arm of the study was reported in the manuscript. 41 276 children (placebo n=20 308 or Zn n=20 968) were followed-up for 60 636.3 person-years. The primary outcome was child mortality but daily reports of common morbidities in stratified random subsamples of children were assessed every week for 12 mo. Authors reported that total mortality of children receiving zinc supplementation was not significantly different from that of children receiving placebo. Further data are needed from other populations with endemic Zn deficiency to confirm a potential beneficial effect in children over 12 mo (135 Zn vs 165 placebo; 0.80, 0.60–1.06). The frequency and duration of diarrhea, persistent diarrhea, dysentery, and acute lower respiratory infections did not differ between the groups.

A mathematical model of zinc absorption in humans as a function of dietary zinc and phytate.

Miller LV, Krebs NF, Hambidge KM. *J Nutr* 2007; 137:135–41. (Section of Nutrition, Department of Pediatrics, University of Colorado Health Sciences Center, Denver, CO 80262, USA.

Email: leland.miller@uchsc.edu)

The quantities of zinc and phytate in the diet are the primary factors determining zinc absorption. A mathematical model of zinc absorption as a function of dietary zinc and phytate can be used to predict dietary zinc requirements and, potentially, enhance our understanding of zinc absorption. Authors described a model relating total zinc absorption to total dietary zinc and total dietary phytate, fitted it to 21 mean data from whole day absorption studies using nonlinear regression analysis and found it to have an R-squared of 0.82. The model was judged to be valid and of immediate value for studying and predicting absorption. A version of the model incorporating a passive absorption mechanism was not supported by the available data.

Plant breeding to control zinc deficiency in India: how cost-effective is biofortification?

Stein AJ, Nestel P, Meenakshi JV et al. *Pub Hlth Nutr* 2007;10:492–501. (Division of International Agricultural Trade and Food Security, University of Hohenheim (490b), 70593 Stuttgart, Germany.

Email: astein1@uni-hohenheim.de)

The survey aimed to estimate the potential impact of Zn biofortification of rice and wheat on public health in India and to evaluate its cost-effectiveness compared with alternative interventions and international standards. The burden of Zn deficiency (ZnD) in India was expressed in disability-adjusted life years (DALYs) lost. Current Zn intakes were derived from a nationally representative household food consumption survey (30-day recall) and attributed to household members based on adult equivalent weights. Using a dose-response function, projected increased Zn intakes from biofortified rice and wheat were translated into potential health improvements for pessimistic and optimistic scenarios. After estimating the costs of developing and disseminating the new varieties, the cost-effectiveness of Zn biofortification was calculated for both scenarios and compared with alternative micronutrient interventions and international reference standards. From representative household survey data (n = 119 554) authors calculated the annual burden of ZnD in India is 2.8 million DALYs lost. Zn biofortification of rice and wheat may reduce this burden by

20–51% and save 0.6–1.4 million DALYs each year, depending on the scenario. The cost for saving one DALY amounts to \$US 0.73–7.31, which is very cost-effective by the standards of the World Bank and the WHO, and is lower than that of most other micronutrient interventions.

Interaction of lead with some essential trace metals in the blood of anemic children from Lucknow, India. Ahamed M, Singh S, Behari JR et al. *Clin Chim Acta* 2007;377:92–7. (Analytical Toxicology Division, Industrial Toxicology Research Centre, P.O. Box 80, M.G. Marg, Lucknow-226 001, India. Email: Ahamed1123@rediffmail.com)

Lead inhibits heme synthesis, can cause anemia and may affect the absorption and metabolism of essential trace metals. There is little information from northern India on high blood lead levels ($\geq 100 \mu\text{g/L}$) and anemia in children. A cross-sectional study recruited 75 children from Lucknow aged 1–7 y (50 anemic ($\text{Hb} \leq 80 \text{ g/L}$) and 25 non-anemic ($\text{Hb} > 80 \text{ g/L}$)) to evaluate the association of blood lead levels $\geq 100 \mu\text{g/L}$ with anemia. In addition, blood levels of lead, iron, zinc, copper, and calcium, hemoglobin (Hb), hematocrit, ascorbic acid and delta-aminolevulinic acid dehydratase (delta-ALAD) were measured. Children were categorized into those with blood lead $\geq 100 \mu\text{g/L}$ (6.89 ± 2.44 ; $n=19$, GI) and those with blood lead $>100 \text{ mg/L}$ (21.86 ± 7.58 ; $n=56$, GII). After adjustment for child's age, sex, and area of residence, children with blood lead levels $\geq 100 \mu\text{g/L}$ were 2.87 (95% CI: 1.60–2.87) times as likely to have anemia as children with blood lead levels $<100 \text{ mg/L}$. The differences of the adjusted mean values of Hb, delta-ALAD, and hematocrit were significantly lower in children from the GII group when compared to children from the GI group ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively). Among essential trace metals, adjusted mean levels of blood iron, zinc, and calcium were significantly lower in GII as compared to GI ($P < 0.05$ each). There were significant negative correlations of blood lead levels with delta-ALAD ($r = -0.612$, $p < 0.01$), hematocrit ($r = -0.427$, $p < 0.05$), iron ($r = -0.552$, $p < 0.05$) zinc ($r = -0.427$, $p < 0.05$), and calcium ($r = -0.324$, $p < 0.05$). Conclusion: Results indicate that elevated blood lead levels ($\geq 100 \mu\text{g/L}$) in children were significantly associated with risk of anemia and that blood lead levels also influenced the status of essential trace metals.

Prevalence of iron deficiency and anemia among healthy women of reproductive age in Bhaktapur, Nepal. Chandyo RK, Strand TA, Ulvik RJ et al. *Eur J Clin Nutr* 2007;61:262–9. (Department of Child Health, Institute of Medicine, Tribhuvan University, Kathmandu, Nepal. Email: tor.strand@cih.uib.no)

This cross-sectional study used a cluster sampling procedure to randomly recruit 500 apparently healthy women of reproductive age (13–35 years) to explore associations between markers of Fe status and Fe intake. Plasma concentration of hemoglobin (Hb), ferritin and transferrin receptors was measured. Dietary information was obtained by a food frequency questionnaire and two 24-h dietary recalls. The prevalence of anemia (Hb concentration $< 120 \text{ g/L}$) was 12% ($n = 58$). The prevalence of depleted Fe stores (plasma ferritin $<15 \mu\text{g/l}$) was 20% ($n = 98$) whereas the prevalence of Fe deficiency anemia (anemia, depleted Fe stores with elevated transferrin receptor (tfr) i.e. $> 1.54 \text{ mg/l}$) was 6% ($n = 30$). Seven percent ($n = 35$) of women had Fe-deficient erythropoiesis (depleted Fe stores and elevated transferrin receptor but normal Hb). Out of the 58 anemic women, 41 (71%) and 31 (53%) also had elevated plasma tfr and depleted Fe stores, respectively. 54% of the women ate less than the recommended average intake of Fe. The main foods contributing to dietary Fe were rice, wheat flour and green and dry vegetables. The prevalence of anemia in our study was substantially lower than the national figure for non-pregnant women. Only about half of the women with anemia also had depleted Fe stores, suggesting that other causes of anemia may be prevalent in this population.

Plasma carotenoid levels and cognitive performance in an elderly population: results of the EVA Study. Akbaraly NT, Faure H, Gourlet V et al. *Gerontol A Biol Sci Med Sci* 2007;62:308–16. (NSERM U888, Hôpital La Colombière, 39 Avenue Charles Flahault, BP 34493, 34093 Montpellier, Cedex 5, France. Email: akbaraly@montp.inserm.fr)

The authors hypothesized that because carotenoids have antioxidant properties, they may have a role in preventing cognitive impairment. In a cross-sectional analysis on a healthy elderly population (the EVA, “Etude du Vieillissement Artériel,” study; $n = 589$, age = 73.5 ± 3 years), the relationships between cognitive performance (assessed by the Mini-Mental State Examination, Trail Making Test Part B, Digit Symbol Substitution, Finger Tapping Test, and Word Fluency Test) and different plasma carotenoid concentrations (lutein, zeaxanthin, β -cryptoxanthin, lycopene, α -caro-

tene, and *trans*- β -carotene and *cis*- β -carotene) were examined. Logistic regression showed that participants with the lowest cognitive functioning (< 25th percentile) had a higher probability of having low levels of specific plasma carotenoids (< 1st quartile): lycopene and zeaxanthin. For zeaxanthin, odds ratios ranged from 1.70 to 1.97 for the different tests and for lycopene, from 1.64 to 1.93. The authors recognized that there is no way of knowing if the low levels of carotenoids precede or are a consequence of cognitive impairment but suggest further research is needed to investigate their observations.

Multi-micronutrient supplements

A multiple-micronutrient-fortified beverage affects hemoglobin, iron, and vitamin A status and growth in adolescent girls in rural Bangladesh. Ziauddin Hyder SM, Haseen F, Khan M et al. *J Nutr* 2007;137:2147–53. (Department of Public Health Sciences, University of Toronto and Research Institute, the Hospital for Sick Children, Toronto, Canada M5G 1X8. Email: ziauddin.hyder@sickkids.ca)

The authors tested whether a multiple-micronutrient-fortified beverage given 6d/wk for 12 mo could improve hemoglobin (Hb) concentrations, micronutrient status, and growth among adolescent girls in rural Bangladesh. A total of 1125 girls (Hb \geq 70 g/L) enrolled in a randomized, double-blind, placebo-controlled trial and were allocated to either a fortified or non-fortified beverage of similar taste and appearance. The fortified beverage increased Hb, serum ferritin (sFt) and retinol concentrations and had greater increases in weight, MUAC, and BMI at 6 mo ($P < 0.01$). Consuming the beverage for an additional 6 mo did not further improve the Hb concentration, but the sFt level continued to increase ($P = 0.01$). The use of a multiple-micronutrient-fortified beverage can contribute to the reduction of anemia and improvement of micronutrient status and growth in adolescent girls in rural Bangladesh

Effects of maternal vitamin supplements on malaria in children born to HIV-infected women. Villamor E, Msamanga G, Saathoff E et al. *Am J Trop Med Hyg* 2007;76:1066–71. (Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA. Email: evillamo@hsph.harvard.edu)

The effects of maternal multivitamin supplementation on the risk of malaria in children are unknown. Authors examined the impact of providing multivita-

mins or vitamin A/ β -carotene supplements during pregnancy and lactation to HIV-infected women on their children's risk of malaria up to 2 years of age, in a randomized, placebo-controlled trial. Tanzanian women (N = 829) received one of four daily oral regimens during pregnancy and after delivery: 1) vitamins B, C, and E (M); 2) vitamin A and β -carotene (VA/BC); 3) multivitamins including VA/BC (M+VA/BC); or 4) placebo. After 6 mo, all children received 6-mo oral VA supplements irrespective of treatment arm. The incidence of childhood malaria was assessed through 3-mo blood smears and at monthly and interim clinic visits from birth to 24 mo of age. Compared with placebo the incidence of clinical malaria was 71% lower ($P < 0.02$) in group M, 43% ($P = 0.04$) lower in M+VA/BC and 63% ($P = 0.06$) lower in VA/BC. The effects did not vary according to the children's HIV status. Supplementation of pregnant and lactating HIV-infected women with vitamins B, C, and E might be a useful, inexpensive intervention to decrease the burden of malaria in children born to HIV-infected women in sub-Saharan Africa. [DIT: It seems unlikely that nutritional status would influence the frequency of being bitten by mosquitoes suggesting that better nutritional status may help children to recover more quickly.]

Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: Effects on growth and motor development. Adu-Afarwuah S, Lartey A, Brown KH et al. *Am J Clin Nutr* 2007;86:412–20. (Program in International Nutrition and Community Nutrition, University of California, Davis, CA 95616–8669, USA. Email: khbrown@ucdavis.edu)

A low micronutrient content of complementary foods is associated with growth faltering in many populations. A potential low-cost solution is the home fortification of complementary foods with Sprinkles (SP) powder, crushable Nutritabs (NT) tablets, or energy-dense (108 kcal/d), fat-based Nutributter (NB). Authors investigated whether multiple micronutrients added to home-prepared complementary foods would increase growth and if the effect would be greatest in the presence of added energy from fat. Ghanaian infants (n = 313) were randomly assigned to receive SP, NT, or NB containing 6, 16, and 19 vitamins and minerals, respectively, daily from 6 to 12 mo of age. Anthropometric status; micronutrient status; motor development; and morbidity were assessed at intervals. Infants (n = 96) not randomly selected for the intervention (non-intervention; NI) were assessed at 12 mo. The groups did not differ significantly at baseline,

except that the NB group had a higher proportion of boys and weighed slightly more. The dropout rate (15/313) was low. At 12 mo, after control for initial size, the NB group had a significantly greater mean weight-for-age z score (WAZ) (-0.49) and length-for-age z score (LAZ) (-0.20) than did the NT group (WAZ: -0.67; LAZ: -0.39) and the NT and SP groups combined (WAZ: -0.65; LAZ: -0.38); the difference with the NI group (WAZ: -0.74; LAZ: -0.40) was not significant. A lower percentage of the NI infants (25%) than of the intervention groups (SP: 39%; NT: 36%; NB: 49%) could walk independently by 12 mo. All 3 supplements had positive effects on motor milestone acquisition by 12 mo compared with no intervention, but only NB affected growth.

Efficacy of daily and weekly multiple micronutrient food-like tablets for the correction of iodine deficiency in Indonesian males aged 6–12 mo. Wijaya-Erhardt M, Untoro J, Karyadi E et al. *Am J Clin Nutr.* 2007 85:137–43. (SEAMEO-TROPED Regional Center for Community Nutrition, University of Indonesia, Jakarta, Indonesia. Email: mwijaya@seameo-rccn.org)

Infants are highly vulnerable to iodine deficiency, and little data exist on the effect of multiple-micronutrient supplementation on their iodine status. Authors compared the efficacy of daily and weekly multiple micronutrient food-like tablets (foodLETs) to increase iodine status in infants. In a double-blind, placebo-controlled trial, 133 Indonesian males aged 6–12 mo were randomly assigned to 1 of 4 groups: a daily multiple-micronutrient foodLET providing the Recommended Nutrient Intake (RNI)(DMM), a weekly multiple-micronutrient foodLET providing twice the RNI (WMM), a daily 10-mg Fe foodLET (DI), or placebo. Urinary iodine (UI) concentrations were measured at baseline and at 23 wk. At baseline, the average UI concentration (1.37 $\mu\text{mol/L}$) was within the normal range but 30.8% of subjects had iodine deficiency (UI < 0.79 $\mu\text{mol/L}$). At 23 wk, initial UI correlated inversely with the changes in UI ($P < 0.001$) but after baseline adjustment, the changes in UI were not significantly different between the 4 groups ($P = 0.39$). The DMM group appeared to be the most effective in reducing iodine deficiency and avoiding iodine excess, but the differences were not significant. Daily consumption of a

multiple-micronutrient foodLET providing the RNI during infancy may be one strategy to improve iodine status.

Non-provitamin A carotenoids

The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study: Age-Related Eye Disease Study Research Group. AREDS Report No. 22. *Arch Ophthalmol* 2007;125:1225–32. (The EMMES Corporation, 401 N Washington St, Ste 700, Rockville, MD 20850-1707. Email: aredspub@emmes.com)

Relationships between dietary carotenoids, vitamin A, alpha-tocopherol, and vitamin C and prevalent age-related macular degeneration (AMD) in the Age-Related Eye Disease Study (AREDS) were assessed using logistic regression analyses. Stereoscopic color fundus photographs were used to categorize 4519 AREDS participants aged 60 to 80 years at enrolment into 4 AMD severity groups and a control group (participants with < 15 small drusen). Nutrient intake was estimated from a self-administered semi-quantitative food frequency questionnaire at enrolment. Intake values were energy adjusted and classified by quintiles. Dietary lutein/zeaxanthin intake was inversely associated with neovascular AMD (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.45–0.93), geographic atrophy (OR, 0.45; 95% CI, 0.24–0.86), and large or extensive intermediate drusen (OR, 0.73; 95% CI, 0.56–0.96), comparing the highest vs lowest quintiles of intake, after adjustment for total energy intake and non-nutrient-based covariates. Other nutrients were not independently related to AMD. In conclusion higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having neovascular AMD, geographic atrophy, and large or extensive intermediate drusen.

Experiences of SIGHT AND LIFE

Alumni in Community Eye Health at the International Centre for Eye Health

Editor's note: Since 1991, SIGHT AND LIFE has been supporting training of students – with a special interest in vitamin A and nutrition – in Community Eye Health at the International Centre for Eye Health (ICEH) at the London School of Hygiene and Tropical Medicine. We were interested to hear from the alumni – most of them returned to their home countries after the course – about what the course has meant to their professional life and daily work. We are very grateful to Mrs Adrienne Burrough of ICEH who went back to the files and tracked down most of the former students to obtain their comments. Here we publish a selection of responses of more than 40 students from more than 20 different nations.

Dr Felix Ezepue, 1991

Qualifications: Ophthalmologist
Country: Nigeria

I am a member of the National Advisory Committee on Micro-nutrient Deficiency. I am also a member of the National Committee for the Prevention of Blindness. I have conducted and supervised others in the conducting of blindness and low vision surveys. In all these, the knowledge and skills gained on the course were found to be very useful.

Mr Michael Bassu, 1993

Qualifications: Ophthalmic Nurse
Country: Tanzania

It is true that the course changed our approach to eye care. The improved quality of eye care attracted more patients to our clinics and the number of surgical cases went up. Many school children were screened at their school health clinics and educated on vitamin A deficiency and other diseases.

Dr Do Seiha, 1994

Qualifications: Ophthalmologist
Country: Cambodia

I am currently working in the Preah Ang Duong Eye Hospital in Phnom Penh. I am the Coordinator for the National Prevention of Blindness & VISION 2020 in Cambodia.

Mrs Hilda Kazembe, 1995–1996

Qualifications: Ophthalmic Nurse
Country: Malawi

Since my return from training at ICEH, I have continued to teach and coordinate the ophthalmic

training program at the Malawi College of Health Sciences in Lilongwe, Malawi. The training program has been upgraded to diploma level. Future plans include introducing other programs aimed at addressing the human resource component of VISION 2020: The Right to Sight. The programs being targeted are cataract surgery, ophthalmic nursing, and refraction. These are going to be offered at advanced diploma level.

I will always be very grateful to SIGHT AND LIFE, this great organization that has dedicated itself to eradicating blindness caused by VAD, for funding my training.

Mr Bakary Ceessay, 1995–1996

Qualifications: Cataract surgeon
Country: The Gambia

Since completing the course, I have been promoted to Deputy Program Manager (DPM) for the National Eye Care Program of the Gambia. I go to hospitals or secondary units



Mrs Hilda Kazembe



Mr Bakary Ceesay examining a patient

to operate on cataract patients or to see eye patients.

The course in Community Eye Health has assisted me a great deal. It has made my work easier and I am now able to apply the skills gained during the training. In the Gambia, receipt of vitamin A is now recorded in the infant and welfare card given to children during their visits. We also have a monitoring unit checking on the nutritional status of infants.

Dr Dipak Kumar Nag, 1996–1997
Qualifications: Ophthalmologist
Country: Bangladesh

When I look back 10 years, I recall that terms such as ‘avoidable blindness’ and ‘community eye care’ were not a part of my day-to-day conversations. Completing the M.Sc. course in Community Eye Health in 1997 changed my vocabulary and my life.



Dr Dipak Kumar Nag

In addition to my present job in the government sector, I am currently attached to the University of South Asia as a course coordinator for the Master of Public Health in Ophthalmology (MPHO). I enjoy sharing my knowledge and views with students who also want to follow careers in blindness prevention in Bangladesh.

I thank all the staff at the ICEH for the fantastic time I had during my stay in London, and especially for the scholarship provided by SIGHT AND LIFE, without which I would not have come to ICEH to study.

Dr Mansur Rabiu, 1998–1999
Qualifications: Ophthalmologist
Country: Nigeria



Dr Mansur Rabiu

Presently, I am heading the Nigerian National Blindness and Low Vision Survey Project. This is a three year multi-million dollar project that involves conducting a population-based survey on blindness, visual impairment, normative parameters, socioeconomic, and qualitative measures across Nigeria. The result of the survey is expected to be applicable to most parts of West Africa.

I have indeed benefited immensely from the Master’s course in Community Eye Health. The course has prepared me to be able to head the above-mentioned project. Since completing the course, I have become more of a community ophthalmologist than a clinical

ophthalmologist in Nigeria and the whole of West Africa.

Mr Momodou Bah, 1999–2000
Course: Master of Science (M.Sc.) in Community Eye Health,
Country: The Gambia



Mr Bah about to board a dug-out canoe in Guinea Bissau

Since my return home from studies, I have been engaged in blindness prevention activities in the Gambia, Guinea-Bissau, Senegal and Guinea-Conakry.

I am the project officer for Sight Savers International’s Gambia country office. My Master’s in Community Eye Health has adequately prepared me for the tasks and challenges I now face in bringing eye care to underserved and poor communities.

Dr Mohammad Muhit, 1999-2000
Qualifications: Ophthalmologist
Country: Bangladesh

The Master’s in Community Eye Health program has helped me to re-orient myself from clinical ophthalmology to a Community Eye Health approach, and also provided me with the necessary skills and knowledge to practice Community Eye Health to help solve the problem of blindness in developing countries. Since then, I have continued to focus my work on childhood blindness in Bangladesh. The



Dr Muhit with a patient

Community Eye Health course also taught me how to translate research into policy and programs in developing countries.

My training at ICEH on Community Eye Health enabled me to develop a public health approach for prevention of blindness among children and I am continuously using those skills in my work to achieve the goals of VISION 2020.

Mr Jib Acharya, 2001–2002

Qualifications: Ophthalmic Assistant
Country: Nepal



Mr Jib Acharya

Firstly, I would like to convey my sincere thanks to SIGHT AND LIFE for funding my Masters in Community Eye Health at the International Center for Eye Health (ICEH) in London in 2001. I was the first person with this qualification in Nepal in the field of preventive ophthalmology. The course at ICEH has equipped me as an expert in the field of Community Eye Health.

Since completing the course in 2002, I have worked for the Nepal Red Cross Society and Shri Janaki Eye Hospital, Janakpur (in collaboration with the Swiss Red Cross). We work in four districts in Nepal and three districts in India. The populations we serve number approximately 2.8 million in Nepal and 3 million in India.

Dr Kuldeep Dole, 2002–2003

Qualifications: Ophthalmologist
Country: India

I am currently working as a community ophthalmologist at H.V. Desai Eye Hospital in Pune, India. This job involves working at outpatient clinics and conducting operations.



Dr Kuldeep Dole

I am also involved in project planning and implementation. Currently, we are working on a project for pediatric eye care services for this region in collaboration with ORBIS International. Since it began in March 2004, I have been a technical consultant to this project. This job involves leading a team of health workers to accomplish set objectives, coordinating with partner NGOs, reporting, developing strategies, controlling the budget, and undertaking public relations. This work is possible because of the training that I received at the London School of Hygiene and Tropical Medicine through support from SIGHT AND LIFE.



Dr Kuldeep Dole examining a child

Dr Mansyur Syumarti, 2003–2004

Qualifications: Ophthalmologist
Country: Indonesia

Before undertaking the Masters course, I had no idea about Community Eye Health and only treated patients with eye problems individually, without a community perspective of the problem.

On returning to Indonesia after completing the Master's in Community Eye Health, I worked as a program coordinator in the community ophthalmology unit of Cicendo Eye Hospital. In this job, I have been involved in various activities to develop community eye care programs in Indonesia. I am able to carry out these activities because of what I learned on the Community Eye Health course.



Dr Syumarti in the field, conducting a survey

Dr Funmi Bankole, 2003–2004
Qualifications: Ophthalmologist
Country: Nigeria



Dr Funmi Bankole beside the project vehicle during a survey

The course afforded me the opportunity to acquire skills in designing, analyzing and carrying out field work in population-based research. This has helped me in building my career in preventive ophthalmology in my country.

I am presently back in Lagos State in Nigeria with the State Prevention of Blindness program, where I take part in planning and implementing free eye screening



Dr Funmi Bankole at the registration point, where she participated in supervising an enumerator

programs and surgical expeditions to various communities in Lagos State, focusing on the less privileged people.

Dr Kahaki Kimani, 2003–2004
Qualifications: Ophthalmologist
Country: Kenya

What I learned during the Masters in Community Eye Health course at the London School of Hygiene and Tropical Medicine has proven to be immensely useful in my career as well as in my daily work. The post-graduate students in our department of Ophthalmology, University of Nairobi, have also benefited from the Community Eye Health modules and I am sure this will be very useful to them once they qualify and go to work in their own countries.



Dr Kimani operating

I hope to publish the work I did on the vitamin A situation in children's homes in Nairobi for my dissertation during the course.

Dr Perpetua Odugbo, 2004–2005
Qualifications: Ophthalmologist
Country: Nigeria

An area in which I am involved is monitoring of the food fortification program, which includes assessing the availability of vitamin A-fortified foods in selected markets in the study area, and the percentage

of these products that meets the specified levels of vitamin A.

Given this opportunity to connect with the wide range of SIGHT AND LIFE's readership, I would like to request assistance, in checking the level of vitamin A in locally available grains, which are used for preparing semi-solid food for children being weaned off breast milk. This forms the staple food for most children from around the age of 4 months to 2 years or more.



Dr Kimani and colleagues with a patient

Dr Lutful Husain, 2005–2006
Qualifications: Ophthalmologist
Country: Bangladesh

I am currently working at the Centre for Women and Child Health (CWCH), an NGO-based clinical and research organization in Dhaka with the aim of improving maternal and child health at the community level through nutrition, clinical, and research activities.

My plans for the future are to initiate a school-based screening program to detect refractive error and other eye diseases at the community level, and to carry out research to detect subclinical vitamin A deficiency among pregnant women living in the vicinity of CWCH by measuring serum retinol levels.



Centre for Women and Child Health, where vitamin A capsules, oral polio vaccine, and anthelmintic drugs were distributed to children on National Immunization Day in 2006

Dr Khumbo Kalua, 2005–2006

Qualifications: Ophthalmologist
Country: Malawi



Dr Kalua examining a child with cornea disease

I am currently in the process of establishing a resource centre for our region here in Blantyre and hope to send out a proposal for possible funding assistance from ICEH or any of the donors, including SIGHT AND LIFE, that sponsored me for the training. I would like to focus more on childhood blindness and conduct more research in the area.

I have just received news that I have been awarded funding from the British Council for the Prevention of Blindness to pursue a Ph.D. on Key Informant Methods in Africa for identifying blind chil-

dren. This is an extension of my MSc dissertation. I will be taking this up in London with ICEH at the London School of Hygiene and Tropical Medicine in September 2007.

Prof. Iftikhar Hussain, 2006–2007

Qualifications: Public Health Doctor
Country: Bangladesh



Prof. Iftikhar Hussain

My aim in joining the Diploma Course in Community Eye Health at the London School of Hygiene and Tropical Medicine was to acquire the skills to develop a course curriculum for the Master of Public Health in Community Ophthalmology at the University of South Asia School of Public Health and Life Sciences in Dhaka, Bangladesh.

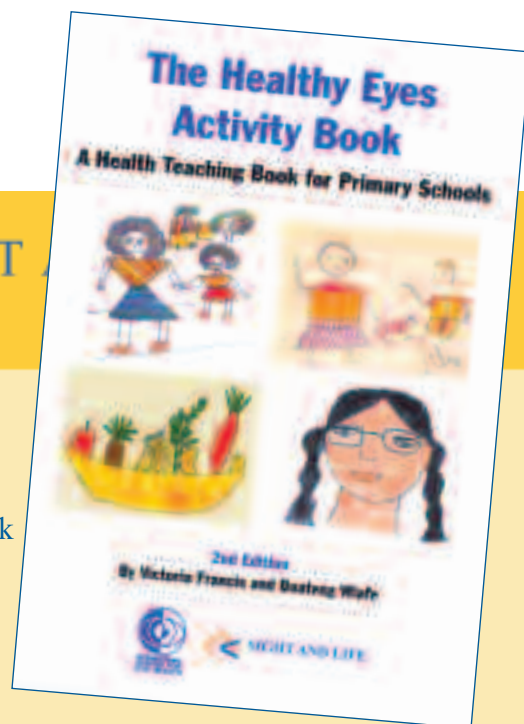


Teaching population based survey methods with our MPH students

My training in Community Eye Health has given me the opportunity to take a close look at the course and address the issues regarding community eye care. We started our course in June 2006, after my return from London, and six students have enrolled for the MPH in Ophthalmology. In the current session, Spring 2007, 12 more students have enrolled, including three students from Nepal.



The Healthy Eyes Activity Book can be ordered from SIGHT AND LIFE, www.sightandlife.org



News

Sprinkles Workshop

Quality criteria for multi-micronutrient powders



Participants of the workshop

Quality criteria for multi-micronutrient powders was the only agenda item of a workshop hosted by the Sprinkles Global Health Initiative (SGHI) on September 27–28, 2007 in Toronto. Representatives from UN agencies (World Food Programme, UNICEF), donors (US Agency for International Development), NGOs (Micronutrient Initiative, Global Alliance for Improved Nutrition), the private sector (DSM Nutritional Products, Fortitech), private initiatives (Sprinkles Global Health Initiative, Heinz Company Foundation, SIGHT AND LIFE) and academia (Tufts University, Hospital for Sick Children) reviewed quality criteria for the composition, manufacturing, packaging and labeling of multi-micronutrient powders (Sprinkles™ and Sprinkles™-type products), and proposed guidelines for their wide-scale production and distribution.



Micronutrient malnutrition is common among people in resource-poor countries who live largely on grain-based diets with no or little access to animal-derived or fortified food. Young children, pregnant and lactating women and schoolchildren are particularly vulnerable to micronutrient malnutrition. Nutritious foods with adequate amounts of micronutrients help children grow and develop normally and ward off fatal infectious

diseases. But the provision of a nutritionally complete diet also has long-term health benefits, including improving cognitive development and reducing the risk of chronic diseases.

Multi-micronutrient powders packed into individual sachets (Sprinkles™) are a new solution to fortify foods with essential vitamins and minerals in an effective way. Multi-micronutrient powders have been used for 10 years in a number of trials and are proven to reduce anemia and improve the micronutrient status of children. The content of a sachet (containing 1 RNI of most vitamins and trace elements) is usually added by the mother or caregiver to the porridge of a child at home, and is thus called “in-home” or “point of use” fortification. Although the quality of the original Sprinkles™ is controlled through a technology transfer agreement with a limited number of licensed manufacturers, other formulations of uncertain quality are also available on the market. There is hence a need to agree on quality criteria for production of all multi-micronutrient powders.

According to the organizers of the workshop, Stanley Zlotkin (SGHI) and Martin Bloem (World Food Programme), the meeting went far beyond sharing knowledge, expertise and experiences; it raised several issues regarding the durability of some of the more sensitive micronutrients in their powdered form in the harsh climatic conditions of many developing countries. The outcomes of the deliberations will be made public and published in a peer-review scientific journal.

Healthy Eyes Activity Book (HEAB), 2nd edition in Hindi and Telugu

SIGHT AND LIFE gave a generous grant to the Central Audio Visual Unit at LV Prasad Eye Institute, India, for the translation and printing in Hindi and Telugu of 9,000 copies of the 2nd edition of 'Healthy Eyes Activity Book (HEAB) – A Health Teaching Book for Primary Schools.' HEAB is authored by Dr Victoria Francis and Dr Boateng Wiawe and published jointly by the International Centre for Eye Health, London and SIGHT AND LIFE.

The Hindi version of HEAB was released on October 11, 2007 in Bhubaneswar, Orissa, by India's Union Minister of State for Health Mrs Panabaaga Lakshmi in the presence of the President of the International Agency for the Prevention of Blindness (IAPB) Dr Gullapalli Nageswara Rao. Dr Rao, who is also the Founder-Chairman of LV Prasad Eye Institute (LVPEI) in Hyderabad, India, was keen to have the Hindi HEAB book released at national level to mark World Sight Day (WSD). Significantly, WSD, which is observed every year on the second Thursday of October, is dedicated this year to the eye care of children.



From left to right: Dr Somasheila Murthy, Consultant, LV Prasad Eye Institute; Mr Ashish Vohra, Head of Commercial Mass Market, Fullerton India Credit Company Ltd. (FICCL); Upcoming Telugu film star Navadeep; Mr Ramesh Prasad, Managing Director, Prasad Media Corporation Ltd.; Dr V S Sangwan, Associate Director, LV Prasad Eye Institute; Samuel J Balasundaram, Administrator, LV Prasad Eye Institute

Marking WSD in Hyderabad, the Telugu HEAB was released jointly by up-and-coming youth icon and film actor Navdeep (of the box-office hit Telugu movie Chandamama fame) and Mr Ramesh Prasad, Chairman of Prasad Film Laboratories and Prasad's Group, India, at the inauguration of an eye care exhibition arranged by LV Prasad Eye Institute in Prasad's IMAX in the heart of Hyderabad. Introducing the book at the book release function, Mr Sam J Balasundaram, Public Relations Officer and Administrator of LVPEI, highlighted the role of SIGHT AND LIFE in making the book translations and printing possible.



Mr Ramesh Prasad, Managing Director, Prasad Media Corporation Ltd, releases the new Telugu HEAB during the World Sight Day in Hyderabad

Our heartfelt thanks go to SIGHT AND LIFE for reaching out to serve the Indian population through the book translation and bulk printing of HEAB.

To receive copies of the HEAB in Hindi and Telugu please contact Mrs Shobha Mocherla, Central Audio Visual Unit at LV Prasad Eye Institute, Hyderabad 500 034, A.P., India
E-mail: mshoba@lvpei.org

Highlights from India's third National Family Health Survey

The report of the third National Family Health Survey (NFHS-3) conducted in India during 2005–2006 was released on October 11, 2007. The NFHS-3, carried out 7 years after the NFHS-2, was conducted in 29 states including the three new states of Jharkhand, Uttaranchal and Chhattisgarh of India. The sample comprised households selected to be representative nationally as well as by state. A total of about 199,000 married women aged 15–49 years and, for the first time, men aged 15–54 years and unmarried women were interviewed. Nutritional status assessment is an important component of the NFHS providing valuable data and trends in the prevalence of wasting and stunting malnutrition in young children and women as well as the extent of micronutrient deficiencies such as that of vitamin A and iron. The NFHS-3 included nutritional status assessment of men for the first time. Also worth noting was the addition of HIV-1 testing among more than 100,000 women and men during the household survey in seven high HIV-1 prevalent states of the country. A few highlights related to the nutritional status from the report are described below.

India harbors one of the highest rates of anemia in young children and women of reproductive age, especially during pregnancy. Data from NFHS-3 reveals continuing high rates of anemia in these populations and a small but clear increase in the prevalence of anemia in both women and children from the previous survey. The overall prevalence of anemia among children and women of reproductive age¹ increased from 74% and 52%, respectively, in NFHS-2 (conducted in 1998–99) to 79% and 56%, respectively, in NFHS-3. At least half of these cases of anemia may be attributable to iron deficiency. India is one of the few countries that has a policy for iron supplementation in children. However, data collected during NFHS-3 reveal a dismally low national coverage of 5%, providing in part an explanation for the continuing and even increasing rates of anemia in this population group. Similarly,

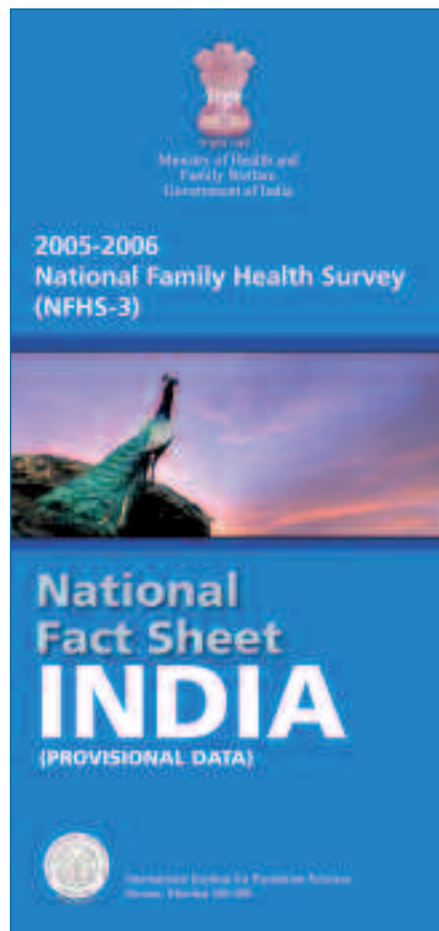
antenatal iron supplement use is low, with only 23% of women on average reporting having consumed 90 or more iron-folate tablets during a previous pregnancy. The mean prevalence of anemia among men² was 24%. While lower than that in children and women, this rate may be higher than in other settings, although comparable nationally representative data on this are scant.

A national vitamin A supplementation program calls for a large dose of vitamin A to be delivered to children from nine months to three years of age once every six months. NFHS-3 found a modest increase in vitamin A supplementation coverage from 17% in NFHS-2 to 25% in NFHS-3. This level of coverage is far below being universal and is unlikely to impact on either the prevalence of xerophthalmia or lead to reductions in child mortality. A 25% reduction in the prevalence of night blindness among pregnant women was noted (from 12% in NFHS-2 to 9% in NFHS-3).

The NFHS-3 estimates of the prevalence of underweight (<-2 z-score weight for age), wasting (<-2 z-score weight for height) and stunting (<-2 z-score, height for age) malnutrition among children under 5 years were based on the new WHO reference

standards³. Approximately half were stunted, 43% were underweight, and 20% were wasted. The NFHS-3 report also provides tables on secular trends using data from the previous survey which were collected only among under three year olds. After applying the new WHO reference standards to the previous data, the prevalence of stunting and underweight was found to have reduced from 51% to 45% and 43% to 40%, respectively. However, the prevalence of wasting increased by 3%, from 20% to 23%, in part due to the decline in stunting.

The NFHS-3 data also reveal the dual burden of malnutrition faced by the Indian population, a trend likely to continue to increase with the ongoing nutrition transition occurring on the subcontinent, unless strong preventive action is taken. Wasting undernutrition among women



defined as thinness (BMI<18.5 kg/m²) increased from 21% in NFHS-2 to 28% in NFHS-3. Twenty seven percent of men were also thin (BMI<18.5 kg/m²). Although the mean body mass index (BMI) was similar among men and women (20.2 and 20.5 kg/m²), 15% of men and 21% of women were overweight or obese (BMI≥25 kg/m²). Among women this rate was higher than the 17% found during NFHS-2.

Overall, the new NFHS data reveal that despite some modest improvements in child malnutrition there is a growing burden of micronutrient deficiencies and under as well as overnutrition among adults.

A copy of the report is available at:

http://www.nfhsindia.org/nfhs3_national_report.html

Communicated by Veena Singh and Parul Christian, Johns Hopkins School of Public Health, Baltimore, USA, E-mail: pchristi@jhsph.edu

¹ Defined as hemoglobin <11 g/dL for pregnant and <12 g/dL for non-pregnant women.

² Defined as hemoglobin <13 g/dL and adjusted for altitude and smoking status.

³ WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006;450:76–85.

Flour fortification trial in reforestation areas of China is done with great success

A conference on flour fortification was organized by the Chinese Ministry of Health (MOH), the State Grain Administration (SGA), the Chinese Center for Disease Control and Prevention, and the Public Nutrition and Development Center of China in Lanzhou, Gansu Province, in Northwestern China on September 14, 2007. Representatives from DSM, UNICEF, and the local CDC and Grain Bureau of Chengde and Lanzhou attended the conference.

A flour fortification trial was launched in reforested areas of China in 2002, with support from UNICEF and implemented by the conference organizers. The purpose of the project was to assess the effectiveness of flour fortification where it was currently being done in China, and offer evidence to scale up the project nationwide. DSM and



View into the conference hall

SIGHT AND LIFE donated premix for the three-year project.

The trial data show that micronutrient deficiencies among populations consuming fortified flour have been reduced significantly. Officials from the SGA and MOH concluded that flour fortification is a cost-effective and safe way to improve micronutrient wellbeing without having to make changes to the diet.

DSM received an award as a valuable partner of the flour fortification trial.



SIGHT AND LIFE



The Nutritional Anemia book and guidebook can be ordered from SIGHT AND LIFE, www.sightandlife.org

ISBN 3-906412-33-4



Global consultation on weekly iron and folic acid supplementation for anemia prevention in women of reproductive age

organized by Dr Tommaso Cavalli-Sforza, Nutrition Adviser of WHO Regional Office for the Western Pacific and Dr Brunno de Benoist, Coordinator, Micronutrient Unit, WHO, held last 25–27 April 2007 in Manila.

The objectives of the consultative meeting were as follows:

1. Review the evidence of the efficacy, effectiveness, safety and feasibility of preventive supplementation with weekly iron and folic acid supplementation in improving iron



Participants of the global consultation on iron and folic acid supplementation

- and folate status, before, during and after pregnancy;

2. Based on the above evidence, specify the conditions under which weekly iron and folic acid supplementation could be successfully implemented as measures to prevent anemia at population level in women of reproductive age;

3. Decide on possible recommendations and guidelines to apply this approach on a large scale in order to increase the effectiveness of programs to prevent and control anemia and iron deficiency; and

4. Identify and prioritize knowledge gaps for which additional research is needed.

First regional flour fortification workshop for East and Southeast Asia

More than 70 experts from governments, international agencies, public health institutions and the flour industry gathered in Kuala Lumpur, Malaysia, on August 18–20, 2007, for the first Regional Flour Fortification Workshop for East and Southeast Asia. The objective of the workshop was to accelerate the pace of collaborations between the public and private sector toward achieving and sustaining national flour fortification.

At present, Indonesia and the Philippines are the only countries where flour fortification is mandat-



Participants of the flour fortification workshop

ed. Efficacy trials in the Philippines showed significant improvements in iron and vitamin A status as a result of consuming bread made from iron and vitamin A-fortified wheat flour.

The participants, representing 20 countries, considered strategies to achieve the full promise of flour

fortification in Malaysia, Vietnam, and Thailand. The workshop provided a platform to assess the status of current national flour fortification efforts, analyze challenges in achieving universal flour fortification, and share lessons learned from national flour fortification initiatives.

Letters to the editor

Dear Sir,

I have been regularly receiving and writing in to your Magazine for three years now and, like many of your readers, would like to express my thanks to SIGHT AND LIFE.



Children awaiting vitamin A dosing

Since I first wrote in to the magazine, I have been working at the same dispensary at Mtambo in Tanzania, where patients are brought for medical treatment and services. Underfive children are also brought in for weighing and vaccinations, and we still give deworming tablets and vitamin A drops to all children aged one year and above. This has been achieved by the excellent team work and dedication of my three full-time village health workers. I will always be grateful to my staff, the staff of SIGHT AND LIFE, and everyone in Mtambo and around the world who has supported us.

I am doing my best to help all the people around here, especially in the areas of health education, medical treatment and data management. Nonetheless, there are still many challenges and much to learn – with support from SIGHT AND LIFE, I look forward to being fully equipped to work efficiently as a community clinician.



Child receives vitamin A capsule

We truly appreciate the very useful information SIGHT AND LIFE has given us on vitamin A and other important nutrition and health topics. I hope you will continue to support me in increasing my knowledge and providing better health education so that I may help the community in Mtambo and all other Tanzanians more effectively.

Sincerely,
Almandus John Bosco
Mtambo Dispensary
Mpanda, Tanzania

Dir Sir,

On behalf of the Sunbie Project in Ghana, I would like to share with your readers how privileged we feel to be a partner of SIGHT AND LIFE. We are grateful for your assistance to this program, which aims to eradicate vitamin A deficiency (VAD) among the poor and vulnerable in the Lemu community, in Sene District – Kwame Danso.

We have so far administered vitamin A capsules over a 10 day campaign to 3,000 children aged six months to five years. This was done by first distributing the capsules to the children attending the Lemu Community Public School, then visiting the homes of children who do not go to school. The community was very excited because their children received vitamin A capsules, as did the teachers. While administering the



Esther Pegree Bayuo dosing vitamin A

vitamin A, I came across four children with serious eye problems that needed immediate attention, which was beyond my own ability to help.

I hope to continue the project to assist the people in my community to do away with vitamin A deficiency with the help of SIGHT AND LIFE. The Sunbie Project's resources, such as personnel and funding, are limited and we appeal to SIGHT AND LIFE to continue helping the project because the demand for help is overwhelming.

In future, I would like to realize my plan to extend services to the interior villages around the Lemu community, which I think may have even more serious eye problems. However, the means to reach such villages is itself a problem. I hope with your assistance I can overcome these constraints and continue to help my community.

Yours faithfully,

Esther Pegree Bayuo, Northern School of Business, PO Box 482, Tamale, Northern Region, Ghana



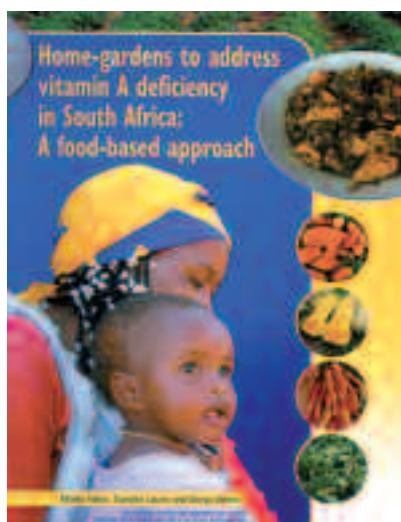
Doreen Mwintero, 6 years old, Tamale, Ghana

Publications

Editor's note: SIGHT AND LIFE presents recent publications which may be of particular interest to our readers. However, no publications other than SIGHT AND LIFE publications are available from us, nor do we have any privileged access to them.

Home-gardens to address vitamin A deficiency in South Africa: a food based approach

High rates of micronutrient malnutrition persist despite commitments made globally to reduce this serious problem. Hunger and malnutrition and their devastating consequences can be dramatically reduced through well conceived and carefully developed and implemented programs. Vitamin A deficiency is of public health significance, and affects mostly women and children in developing countries. In an attempt to address vitamin A deficiency in South Africa, the authors Mieke Faber, Sunette Laurie and Sonja Venter from the Medical Research Council (MRC) and the Agricultural Research Council developed, monitored and evaluated an integrated household food production and growth monitoring project in a rural village bordering the Valley of a Thousand



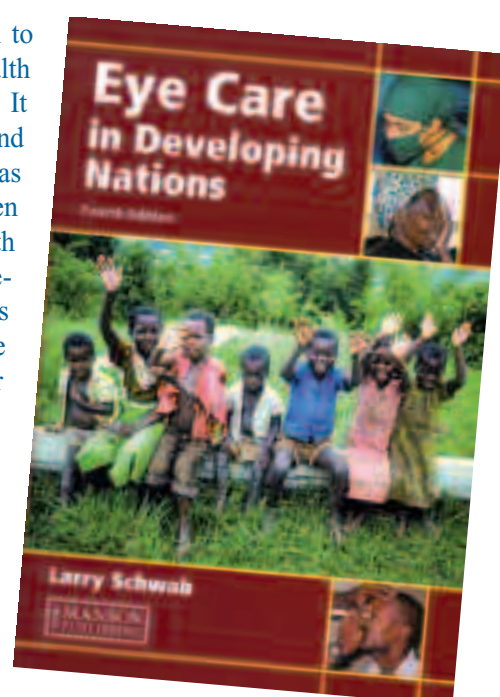
Hills in KwaZulu-Natal during the 1990s. This home-garden project, which was aimed at the production and consumption of vitamin A-rich fruits and vegetables together with nutrition education, proved to be successful in improving the vitamin A status of 2 to 5-year-old children. The home-garden approach can complement both fortification and supplementation programs and provides a sustainable means of achieving food and nutritional security. People in rural areas often have limited access to commercially available fortified foods. Rural areas will therefore benefit most from the inclusion of vitamin A-rich vegetables in gardening projects.

The purpose of this manual is to assist organizations in implementing home-garden projects to improve vitamin A status. This manual will prove to be useful, not only to those interested in food-based programs, but also to those concerned with health and nutrition education. It will also encourage and facilitate the design and implementation of effective food-based projects to improve nutrition.

For further information on the publication, please visit the website of the Agricultural Research Council of South Africa www.arc.agric.za

Eye care in developing nations

The prevention of blindness is known to be one of the most cost-effective health interventions that can be undertaken. It should start at the individual, family, and community levels. Primary eye care, as part of primary health care, has thus been strongly advocated by the World Health organization's Program for the Prevention of Blindness and Deafness in its long-standing partnership with the International Eye Foundation and other non-governmental organizations. To be meaningful, primary eye care must respond to local needs and resources and must use opportunities for community support. This book, now in its 4th edition, responds particularly well to the need for practical, innovative, and affordable solutions to bring eye care to those populations most in



need in the developing world. The most common ocular disorders and their management are described, including public health perspectives and appropriate guidelines. The book contributes greatly to increasing the access to basic eye care services in developing countries. Such services, along with appropriate public health interventions, constitute the key to eliminating unnecessary visual loss in future generations. The existence of effective public/private partnerships for the prevention of blinding diseases, along with the rapid progress of Vision 2020: the 'Right to Sight' global movement should make it possible to achieve that goal.

Alfred Sommer, Dean Emeritus and Professor, Johns Hopkins University on this book: *"It is the eye health worker's guide to delivering services to low-resource populations, whether they be pockets of poverty in otherwise affluent nations or broadly deprived populations living in the developing world. Demand for the first three*

editions has proved this book's popularity and value. We are indebted to Dr Schwab for bringing forth this expanded and updated edition."

For further information on this book please visit www.manson-publishing.co.uk

Handbook of vitamins

In keeping with the tradition of previous editions, the 4th edition of the *Handbook of Vitamins* was assembled to update and provide contemporary perspectives on vitamins. One of the of the editors' challenges (Janos Zempleni, Robert B. Rucker, Donald B. McCormick, John W. Suttie) was to maintain the clinical focus of previous editions, while addressing important concepts that have evolved in recent years owing to the advances in molecular and cellular biology as well as those in analytical chemistry and nanotechnology. The reader will find comprehensive summaries that focus on chemical,

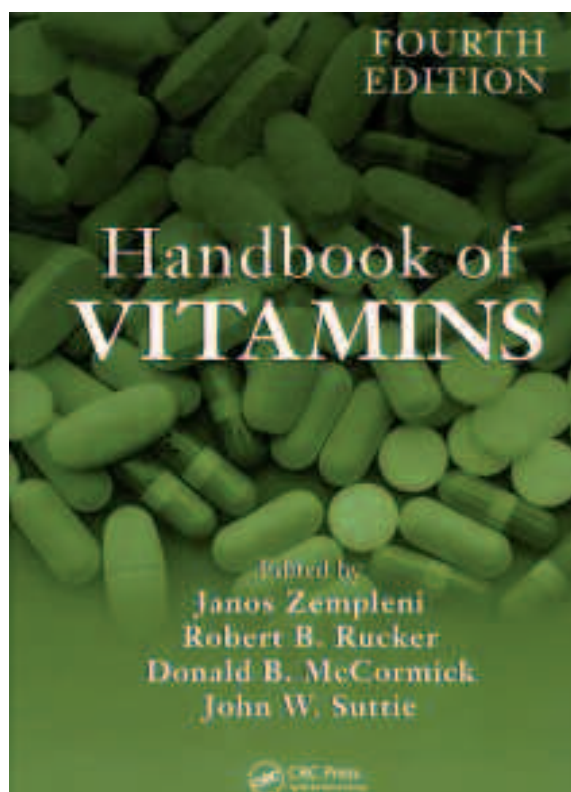
physiological, and nutritional relationships and highlights of newly described and identified functions for all the recognized vitamins. The goal was to assemble the best currently available reference text on vitamins for an audience ranging from basic scientists to clinicians to advanced students and educators with a commitment to better understanding vitamin function.

As examples, apparent vitamin-dependent modifications that are important to epigenetic events and genomic stability are described, as well as new information on the role and importance of maintaining optimal vitamin status for anti-oxidant and anti-inflammatory defense. Important analytical advances in vitamin analysis and assessment are discussed in a chapter dealing with accelerated mass spectrometry (AMS) applications.

It is also important to emphasize that much of the interest in vitamins stems from an appreciation that there regrettably remain sizable populations at risk of vitamin deficiencies. In this regard, classic examples are included along with examples of vitamin-related polymorphisms and genetic factors that influence the relative needs for given vitamins.

This volume is written by a group of authors who have made major contributions to our understanding of vitamins. Dr Janos Zempleni joins the group of editors who assembled the third edition. Dr Zempleni brings a molecular biology perspective to complement the biochemical and physiological expertise of the other editors. Dr Lawrence Machlin who was sole editor of the first two editions in this series and who died shortly after the release of the 3rd edition would be pleased with the progress and advances in vitamin research summarized in the 4th edition.

For further information on this volume please visit the website of the publisher www.crcpress.com



Community-based management of severe acute malnutrition



A joint statement by the WHO, WFP, SCN and UNICEF

Severe acute malnutrition remains a major killer of children under five years of age. Until recently treatment has been restricted to facility-based approaches, greatly limiting its coverage and impact. New evidence suggests, however, that large numbers of children with severe acute malnutrition can be treated in their communities without being admitted to a health facility or a therapeutic feeding centre.

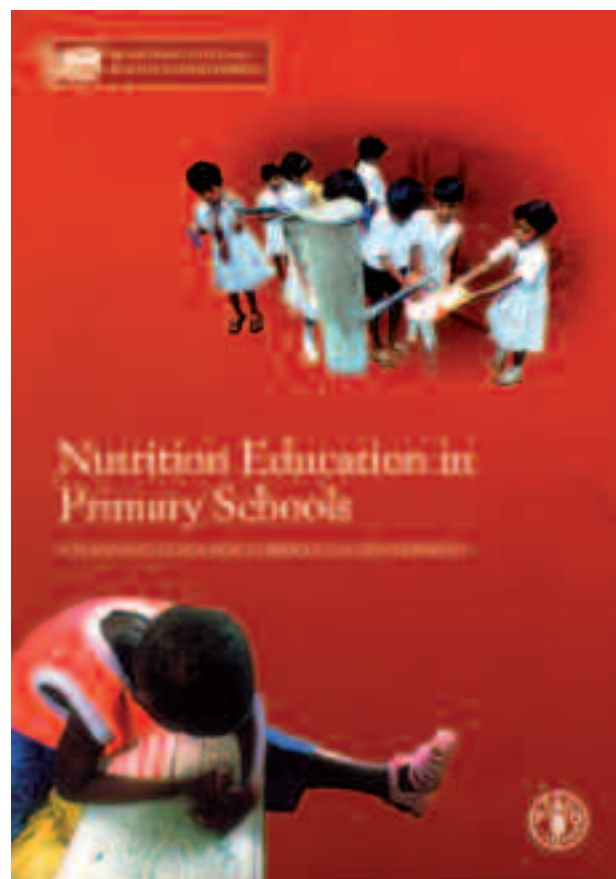
Children with severe acute malnutrition need safe, palatable foods with an energy content and adequate amounts of vitamins and minerals. Ready-to-use therapeutic foods (RUTF) are soft or crushable foods that can be consumed easily by children from 6 months without adding water. At least half of the proteins contained should come from milk. The community-based approach involves timely detection of severe acute malnutrition in the community and provision of treatment for those without medical complications with RUTF or other nutrient-dense foods at home. If properly combined with a facility-based approach for those malnourished children with medical complications and implemented on a large scale, community-based management of severe acute malnutrition could prevent the deaths of hundreds of thousands of children.

For further information please visit the WHO website www.who.int

Nutrition education in primary schools – a planning guide for nutrition education in primary schools

Educating school children in healthy nutrition is one of the most effective strategies for overcoming malnutrition and chronic diet-related diseases, but has been neglected for far too long. Chronic diet-related diseases, such as excess weight and obesity, diabetes, hypertension and cardiovascular diseases are not restricted to rich countries. They are increasing around the globe as a result of new lifestyles and eating habits. Two out of three overweight and obese people now live in low- and middle-income countries, with the vast majority in emerging markets and transition economies, according to the WHO. Certainly, hunger and undernutrition remain a major public health problem for some 820 million people in developing countries that do not have the means to buy or produce sufficient good quality food. But globalization and economic development have introduced new foods and altered dietary habits and lifestyle patterns in many developing countries as well.

It is not only the amount of food, but the quality of a diet that has a critical effect on children's growth, health and learning capacity. Eating is not just a



biological process; it depends on learned habits and perceptions, on the cultural and social environment. Good nutrition education can make children aware of how to achieve a nourishing diet with limited means; how to prepare and handle food safely and how to avoid food-related risks.

FAO has published a new comprehensive guide for curriculum development addressing nutrition education in primary schools. The new guide is aimed at ministry officials, teachers, nutrition experts, health professionals and others involved in the planning of nutrition education programs for primary schools. Although it also contains a section on the basics of healthy nutrition, the guide is not a teaching aid for nutrition education itself. It is a resource package comprising three elements: a book that explains the key ideas and processes in nutrition, health and education; a set of worksheets taking the user through the entire planning exercise; a classroom curriculum chart, providing learning objectives for nutrition education in primary schools in developing countries.

The guide is available in English and French. For further information please visit the FAO website www.fao.org

Handbook of nutrition and ophthalmology

In the last three decades, substantial progress has been made in demonstrating the importance of good nutrition to eye health. Nutrition plays a major role from early infant development through childhood and on through older age as a determinant of visual function and eye disease. The author Richard Semba has emphasized three broad themes in the *Handbook of Nutrition and Ophthalmology*. The first

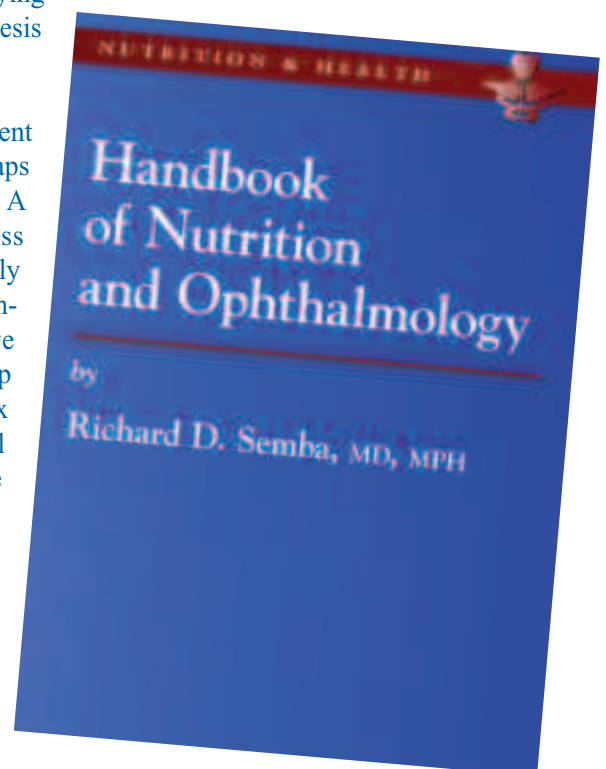
is that the adoption of a healthy diet as a major life-long habit will likely have an impact on reducing a substantial proportion of visual impairment and blindness. A major problem facing ophthalmology will be the large increase in diabetic retinopathy that is expected to follow the worldwide epidemic of type 2 diabetes and obesity. The second theme is that a historical perspective is essential to understanding current challenges in ophthalmology, medicine, and public health. Many of the eye diseases caused by nutritional deficiencies were well described when malnutrition was more highly prevalent in some parts of the world. In situations of conflict, famine, and natural disasters, the same eye diseases are seen repeatedly. Vitamin A deficiency was once a major cause of childhood blindness in developed countries and today still remains the leading cause of blindness among children in the developing world. The third theme in the handbook is that many nutrients play a role in oxidative stress and inflammation. This idea has emerged as a major underlying hypothesis in the pathogenesis of eye diseases.

Xerophthalmia is an ancient scourge and there is perhaps more known about vitamin A and nutritional blindness than is known collectively about all the other nutritional deficiencies and eye health. The relationship between the B-complex vitamins and nutritional amblyopia is complex. The role of carotenoids, antioxidant vitamins, zinc, and other nutrients in chronic eye disease, e.g. age-related macular degeneration and cataract is still evolving. The application of findings from

these studies through dietary supplementation may have great importance as the population ages and the burden of such chronic conditions increases.

Dr Semba's text covers the broad field of nutrition and ophthalmology. The content of the 12 chapters covers specific disease entities e.g., AMD and cataract, diabetic retinopathy, and inborn errors of metabolism and specific nutrients (e.g., vitamins C, E, A, and B-complex, zinc, fatty acids) and their relation to ocular disease. It is a unique text, in that all chapters were written by one author and cover a large area of material ranging from an historical overview, epidemiology, pathology and treatment of the condition. The text provides important and new authoritative information on the relation of nutrition to ocular disorders which will reward the reader with a wealth of insightful information.

For further information please visit the website of the publisher www.humanapress.com





Doreen Mwintero, 6 years old, Tamale, Ghana

Photo credits

US CDC: Cover page, 2, 7, address sheet; Tobias Vogt: page 2, 8, 10, 11

Colophon

SIGHT AND LIFE Magazine
Incorporating the Xerophthalmia
Club Bulletin

Publisher: SIGHT AND LIFE
Editor: Klaus Kraemer
Editorial team: Anne-Catherine
Frey, Svenia Sayer-Ruehmann,
Federico Graciano

Translation and language:
transparent language solutions
GmbH, Berlin

Layout and graphics:
GAS - graphic art studio,
Grenzach-Wyhlen

Printer: Burger Druck,
Waldkirch

Opinions, compilations and figures
contained in the signed articles do
not necessarily represent the point
of view of SIGHT AND LIFE and
are solely the responsibility of the
authors.

SIGHT AND LIFE
Dr Klaus Kraemer
Secretary General
PO Box 2116
4002 Basel, Switzerland
Phone: +41 61 688 7494
Fax: +41 61 688 1910
Email: info@sightandlife.org
www.sightandlife.org

ISBN 3-906412-40-7