## GLOBAL CONTROL OF MICRONUTRIENT DEFICIENCIES: DIVIDED THEY STAND, UNITED THEY FALL

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### Introduction

Aesop, in the Sixth century B.C., in his fable "The Four Oxen and the Lion", described a prowling lion in a field containing four oxen. Whenever the lion attacked, they turned their tails to one another, and he always faced the horns of one of them. But they quarreled, each went off to a separate corner of the field, and the lion then attacked them one by one and ate them. The fable's motto was "United we stand, and divided we fall".

The phrase has been used repeatedly in politics, during the founding of the US, and again to unite India during its struggle for independence. The basic idea is that, unless people are united and one people, it is easy to destroy them; thus, the maxim: 'Divide and conquer'.

I would like to argue that, until recently, this maxim, 'divide and conquer', has been the paradigm of the nutrition community's approach to micronutrient deficiencies, but it has not been an effective one.

Let's look at recent progress. In the early 1990s, the International Conference for Nutrition and the World Fit for Children boldly proclaimed new goals to reduce malnutrition in young children. They included:

- The sustained elimination of vitamin A and iodine deficiencies by 2005;
- Reduction by one-third in the prevalence of anemia, including iron deficiency, by 2010;
- Accelerated progress toward reduction of other micronutrient deficiencies.

Fifteen years later, where are we?

- Vitamin A deficiency weakens the immune system and contributes to the death of 1 million children each year;
- Iodine deficiency in pregnancy results in 18 million babies a year born mentally impaired;
- Maternal folate deficiency causes a quarter of a million severe birth defects each year;
- Zinc deficiency contributes to 5% of all child deaths;
- Maternal iron deficiency anemia results in more than 60,000 women a year dying during pregnancy and childbirth. It impairs the mental development of 40% of the developing world's children.

Micronutrient deficiencies also have profound economic costs. In 2006, the World Bank reported, "...vitamin and mineral deficiencies impose high economic costs on virtually every developing nation." According to economist Sue Horton, "micronutrient deficiencies alone cost India US\$2.5 billion annually and the productivity losses from stunting, iodine deficiency, and iron deficiency are responsible for a total loss of 2.95% of GDP."

At the 2002 UN General Assembly Special Session on Children, it was clear we were falling far short of the ambi-

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tious goals of the early 1990s: for iodine and vitamin A deficiencies, we were perhaps a little more than halfway, and there had been essentially no progress against anemia.

The traditional paradigm of the nutrition community's approach to micronutrient deficiencies, to 'divide and conquer', has hampered progress at three levels:

- Each of the individual micronutrients --vitamin A, iron, iodine and zinc- were cornered by an 'expert' group. IVACG took vitamin A, INACG iron, ICCIDD iodine, IZINCG zinc, and they each went zealously to work. There was little dialogue between them and potential interactions or combined approaches were largely ignored.
- Similarly, each of the different strategies —fortification, supplementation, and dietary diversification had their different proponents; they have rarely been integrated into combined programs. Consider iron deficiency anemia. From 1993-96, led by Unicef, 122 countries distributed nearly 3 billion iron supplements to pregnant women; 1 billion more iron-folate tablets were handed out in 1999-2000. What was the impact? The prevalence of anemia in pregnancy in South Asia and sub-Saharan Africa is still at least 50%. It has since become clear that reducing anemia will only be achieved through an integrated approach of targeted supplementation, food fortification and infection control.
- And finally, the different organizations interested in fighting micronutrient deficiencies 'did their own thing'. Industry looked for new markets and profits,

WHO promulgated policy, UNICEF and the other NGOs competed for donor money for implementation, while academia did research and, naturally, stayed above it all.

Looking back, how could we expect solid progress from such a fragmented approach?

Thus, I would like to turn Aesop's maxim on its head and suggest a new maxim of "Divided they stand, united they fall" more appropriately describes a successful future strategy for controlling micronutrient deficiencies, and perhaps holds the key to eliminating them.

This concept will help shape research programs in this new Professorship, and thus, the title of my lecture today.

This new maxim should be applied on 3 levels to control micronutrient deficiencies:

- First, at the physiological level; synergistic interactions suggest approaches that target individual micronutrient deficiencies are much less efficacious than combined approaches;
- Second, integrated programs of supplementation, fortification and dietary improvement may succeed where each alone will only be partially effective;
- And finally, innovative partnerships within academia, and at the organizational level, emphasizing public-private collaboration, are a key to success.

Let's look at each of these in more detail.

# Combined micronutrient approaches work better

First, at the physiologic level. Attacking each micronutrient deficiency individually is much less effective than attacking them simultaneously. Why? Because single micronutrient deficiencies don't occur in isolation: overlapping deficiencies of iron, vitamin A and iodine, and perhaps zinc, affect more than 50% of children and young women in developing countries. And deficiencies of one micronutrient will interfere with efforts to control the others.

These interactions are fascinating in that they can occur deep inside cell metabolism, at the level of the gene and/or enzyme.

My eminent predecessor at Wageningen, Clive West, showed adequate vitamin A is critical for optimal iron metabolism and utilization, and that the response to iron supplementation is blunted by vitamin A deficiency. Building on his work, we have recently shown this is due to vitamin A status modulating renal production of erythropoietin, an important stimulus to production of new red blood cells.

As another example, iodized salt effectively controls goiter and iodine deficiency most of the time, but not always. The effectiveness of iodine prophylaxis is dependent on the vitamin A and iron status of the target population.

#### Vitamin A and iodine

Vitamin A deficiency has multiple effects on the pituitary-thyroid axis, both in the periphery and in the brain. Studies by Morley and co-workers 3 decades ago showed vitamin A deficiency in rats increases thyroid hormone levels and thyroid size, and, conversely, large doses of vitamin A decrease them.

But the mechanism of this effect was not discovered until the mid 1990s. Normal control of TSH secretion by the pituitary involves feedback from circulating thyroid hormone. Surprisingly, vitamin A status also modulates TSH secretion by the pituitary. It turns out that both the thyroid hormoneactivated thyroid receptor and the retinoic acid-activated retinoid X receptor suppress transcription of the pituitary TSHß gene by occupying half-sites on the promoter DNA of the gene. Therefore, high doses of vitamin A and/or high circulating thyroid hormone levels will decrease transcription of the pituitary TSHß gene and TSH secretion, and thereby reduce thyroid stimulation. Conversely, vitamin A deficiency and/or low levels of circulating thyroid hormone will increase circulating TSH level, stimulating the thyroid gland.

In Zürich, Biebinger and co-workers recently investigated the effects of concurrent vitamin A and iodine deficiencies on the thyroid-pituitary axis in rats. Compared to iodine deficiency alone, expression of TSHB mRNA was much higher in the combined deficient group, and they had more goiter. These data indicate concurrent iodine deficiency and vitamin A deficiency produce more severe primary hypothyroidism than iodine deficiency alone, through effects at the level of the pituitary TSH gene.

The adverse effects of iodine deficiency are due to hypothyroidism. Could a goitrous child's vitamin A status influence his/her risk for hypothyroidism? To answer this, we studied children with concurrent iodine and vitamin A deficiencies in the mountains of northern Morocco. Increasing severity of vitamin A deficiency was a predictor of greater thyroid volume and higher concentrations of TSH; in children with vitamin A deficiency, the odds ratio for goiter was 6.5. But at the same time, it was a strong predictor of higher concentrations of thyroid hormone; the odds ratio for hypothyroidism in vitamin A deficiency was only 0.06.

The children were then given iodized salt, together with either vitamin A supplementation or placebo. The goiter rate was sharply decreased in the vitamin A group, compared to placebo.

In a follow-up study in the Limpopo region of South Africa, in children with both vitamin A deficiency and iodine deficiency, a randomized, 2x2 intervention trial was done. Children received supplements of iodine or vitamin A alone, both or neither. There was a clear effect of vitamin A supplementation, independent of iodine supplementation, on reducing TSH, thyroid volume and goiter.

Thus, vitamin A supplementation in goitrous children improves their response to iodized salt. It decreases excess TSH stimulation of the thyroid and reduces risk for goiter and its sequelae. These findings are likely mediated through the pituitary retinoid receptor and TSHß gene expression.

#### Iron and iodine

There is a similar interaction between iron and iodine. It has long been recognized that thyroid hormone metabolism is abnormal in iron deficiency anemia. In the 1990s, John Beard's group at Penn State reported that iron supplementation of anemic women increased circulating thyroid hormone.

But the mechanism by which iron deficiency impairs thyroid metabolism was unclear. Recently, we uncovered a mechanism: iron deficiency reduces activity of an iron-dependent enzyme in the thyroid, thyroid peroxidase (TPO). TPO catalyzes the two initial steps of thyroid hormone synthesis, and without enough iron, TPO cannot form thyroid hormone. The effect of iron deficiency anemia in reducing TPO activity was demonstrated in weanling rats that were fed progressively more iron-deficient diets. TPO activity was reduced by 33-56% in iron deficiency, and the rats became hypothyroid.

If iron deficiency can lower TPO activity and thereby impair thyroid metabolism, could iron deficiency block a child's ability to use the iodine in iodized salt?

This question prompted us to begin a series of studies in children in an area of endemic goitet in the mountains of western Côte d'Ivoire.

In the first study, iodine deficient children were divided into two groups: the first group consisted of goitrous children without anemia, and the second of goitrous children with iron deficiency anemia. Each child received a large dose of iodine. Followed for 6 months, TSH values were lower, and thyroid hormone levels higher, in nonanemic compared to anemic children. There was a sharp difference in goiter prevalence during follow-up, when goiter rates were 64% in the anemic children but only 12% in the nonanemic children. Thus, iodine improved both anatomic (thyroid size) and biochemical (TSH, thyroxine) measures of thyroid function in the nonanemic children compared to the children with iron deficiency anemia.

Then, each iron deficient anemic child received treatment with iron. Goiter prevalence in this group, which had plateaued at 62-64% after receiving iodine, was reduced after iron supplementation to 20%.

The final study was a controlled trial of iron supplementation in goitrous children with iron deficiency who were receiving iodized salt. This was a double-blind intervention study. One group received oral iron, and the second group received placebo. After 5 months, thyroid size decreased 2fold and the goiter rate was significantly lower in the iron supplemented group.

These studies have clarified why iodized salt will work less well in areas where vitamin A and iron deficiencies are common: both interfere with iodine metabolism. For vitamin A, the interaction occurs at a pituitary gene; for iron, at a thyroid enzyme.

This argues strongly for a combined approach, or 'united they fall': when children are deficient in several micronutrients at one time, concurrent micronutrient repletion may be necessary for optimal effect. Moreover, addition of multiple micronutrients to a single foodstuff might cost less than separate fortification programs.

## Triple-fortified salt

Because both iron and vitamin A deficiencies reduce the efficacy of iodized salt, the co-fortification of iodized salt with iron and vitamin A could be beneficial, not only to combat anemia and vitamin A deficiency, but also to improve the efficacy of iodine in the salt. Salt is often the only fortification vehicle available in rural Africa, because in poor regions of subsistence farming, salt is one of very few regularly purchased food items.

But combining multiple micronutrients together in a single food vehicle, particularly salt, creates challenges. Ferrous iron is well absorbed but colors low-grade salt yellow to brown. So we turned to ferric pyrophosphate, an iron compound with a white color that produces negligible color change when added to salt, and we ground it down to micron size to increase its absorption. Another challenge is that, in the presence of ferrous iron and moisture, losses of iodine and vitamin A from a fortified salt are high. Encapsulation could form a barrier between iron, iodine and vitamin A, and might overcome these challenges.

Therefore, to develop a triple fortified salt, we turned to food engineering, and used a novel spray-cooling process to microencapsulate iron, iodine and vitamin A in hydrogenated oil in a single processing step. A heated fat suspension is atomized with specifically designed 2-phase nozzles into partially evaporated liquid nitrogen. Smooth, tight, microspheres are formed that are 40% substrate and 60% capsule.

After testing the stability and acceptability of the triple fortified salt, we measured its efficacy in a randomized doubleblind trial in Moroccan children. It was given to households for 10 months. There was a significant decrease in the prevalence of iron deficiency anemia and vitamin A deficiency in the children receiving the triple fortified salt compared to iodized salt. Moreover, the iodine was more efficacious: goiter prevalence and the number of hypothyroid children were sharply lower in group receiving the triple fortified salt. This study showed for the first time that even lowgrade African salt can be successfully triple-fortified with microcapsules.

Within the new Professorship, in collaboration with food scientists of this University, we plan to develop innovative strategies in food technology to overcome the challenges to multiple fortification. Microencapsulation may offer new opportunities for the multiple fortification of other vehicles, e.g. flours (this is currently being tested in wheat flour in Kuwait) and extruded rice.

# Integrating strategies to control micronutrient deficiencies

## The limitations of current strategies

Moving from micronutrient interactions to the strategy level, our new maxim "divided they stand, united they fall" should guide the development of integrated programs.

For decades the three main strategies to control micronutrient deficiencies have been:

- Dietary diversification, often based on consumer education, and sometimes agriculture;
- Food fortification;
- Supplementation.

But a clear lesson drawn from the experience of the last two decades is that although each of these can contribute to the

control of micronutrient deficiencies, none can do the job alone. These individual strategies are limited in that they may provide only a fraction of the micronutrient required, work only for a specific population group, operate on a different time scale, or be the responsibility of a different government agency.

Most would agree dietary diversification is the best longterm, sustainable strategy. But progress has been slow, and in some developing countries with deteriorating economies, we need to be realistic and accept that food diversification is unlikely to significantly reduce micronutrient deficiencies in the near future. Moreover, long-term economic development and poverty reduction cannot be relied upon to eliminate micronutrient deficiencies. The children of many highincome families in the industrialized countries would lack essential micronutrients if infant foods, salt and cereals were not fortified.

Considering fortification, its success depends on finding a food that is widely eaten and yet passes through commercial processing where the micronutrient can be added. Moreover, the food must be consumed regularly and in adequate amounts by those most vulnerable to the deficiency. Universal fortification often cannot provide adequate amounts to children below two years, a group vulnerable to permanent damage from micronutrient deficiencies.

Supplementation can be effective, but is likely sustainable only when given in huge doses as depot forms at intervals of 4 to 12 months, as is done with vitamin A and iodinated poppy seed oil. Although clearly effective at reducing endpoints like mortality or cretinism, the overall safety profile of these large doses, particularly in pregnancy and early infancy, has not been rigorously tested. The logistics of daily or weekly supplementation are daunting, and, particularly for iron, compliance is often poor.

Separate application of these strategies in the past has led to disjointed, piecemeal efforts to control micronutrient deficiencies. Future success will depend on deploying not just one solution, but different combinations in a well-knit plan. A good example of an integrated approach within this new Chair is the TELFUN project that links the Division of Human Nutrition with plant scientists, food scientists, and social scientists to increase food sovereignty and nutritional status in Ecuador, India and Ghana.

Another reason for the slow progress against the micronutrient deficiencies has been too little innovation. Certainly dietary diversification, fortification, and supplementation remain important, but they often feel 'tired-out'. In any scientific field, innovation is critical to achieving real breakthroughs. In order to add innovation, we need to unite with new scientific partners. Two examples are alliances with plant sciences and genetics for biofortification, and with particle sciences for nanotechnology.

#### The cautious promise of biofortification

Long-term, sustainable control of the micronutrient deficiencies will not happen unless we include agricultural approaches. Staple crops can be enriched ('biofortified') with micronutrients using plant breeding and/or transgenic strategies that exploit enrichment traits within their genomes. This must be done without adversely affecting crop productivity. The bio-fortification of maize, millet, sorghum, yams, beans, cassava, rice and sweet potatoes is a potentially powerful weapon against micronutrient deficiencies.

But increasing the amount of a micronutrient in a food may not be enough. For trace elements like iron and zinc, the nutrients must also be bioavailable.

Take rice as an example. Worldwide, rice feeds more than half the human population, most of who live in developing countries. Rice contains small amounts of iron in the aleurone layer of the seeds, which is polished away. Consequently, iron deficiencies are widespread in monotonously rice-cating populations.

The variation in the iron content among cultivars of rice suggests selective breeding may be able to increase iron content. But although there is a range of iron content in rice of 7-23 mg/kg, most of this iron is removed during the milling process. Thus, it may be difficult to increase the absolute iron level of milled rice through plant breeding. This problem was evident when the efficacy of a rice cultivar high in iron was tested in a feeding trial in The Philippines. Because the 'high-iron' rice added only an extra  $\approx 1.5$  mg iron per day to the diet, there was no clear improvement in iron status.

Iron absorption from cereals and legumes (many have high native iron content) is low because of they have high levels of phytate and polyphenols, substances that inhibit iron absorption. In order to achieve real breakthroughs in biofortification, it is likely going to be necessary to decrease the amount of these inhibitory substances, or increase the level of enhancing substances (e.g. ascorbic acid, sulfur-containing amino acids).

Genotypes of maize, barley, and rice have been identified that are low-phytic-acid mutants, with phytic acid phosphorus content reduced by up to two thirds. However, it may be necessary to decrease phytic acid by >90% to usefully increase iron absorption from the monotonous cereal-based diets found in many developing countries.

Because of these limitations, genetic engineering may prove to be the most effective way to provide a useful amount of absorbable iron in plant foods. Working with the same plant scientists who created 'golden rice' at the ETH Zürich, a combined approach was used to modify three genes in rice in order to increase the amount of bioavailable iron.

First, a gene for the iron storage protein ferritin from the common field bean (Phaseolus vulgaris) was expressed under the control of an endosperm specific promoter in rice, increasing the iron content in the endosperm by about 3-fold. Second, a phytase (an enzyme that degrades phytate, a strong inhibitor of iron absorption) from a fungus (Aspergillus fumigatus) was expressed in the rice. Finally, the gene for a cysteine-rich metallothionine was over-expressed in the rice, increasing the cysteine content in the soluble fraction of the seed proteins is by 7-fold. Sulfur-containing amino acids like cysteine may improve iron absorption.

Thus, not only was the iron content of the endosperm increased, but the level of both an enhancer and inhibitor were adjusted to maximize absorption. This may be the method most likely to yield benefits in biofortification with iron. These preliminary studies suggest iron content can be increased in staple foods by plant breeding and, even more promising, by genetic engineering. The challenge is now to show that iron can be increased to nutritionally-useful levels and that the additional iron is bioavailable. To do this, the Chair will work closely with Harvest Plus, a global alliance formed to biofortify staple food crops.

Biofortification is an exciting new tool that may be able to reach the most vulnerable, rural poor. Within this new Chair, its ability to fight micronutrient deficiencies will be fully explored.

#### Nanotechnology may enhance trace element delivery

The central challenge in iron fortification is that water-soluble, highly bioavailable iron compounds cause adverse sensory changes in foods, while poorly soluble iron compounds, although more stable in foods, are poorly absorbed.

To overcome this, we have recently turned to nanotechnology. Reducing the particle size of poorly absorbed iron compounds to submicron size is promising because it greatly increases their bioavailability, and, thus, their nutritional value.

In medicine and pharmaceutics, nanotechnology is increasingly applied to enhance the absorption of drugs and vaccines. Also, nanosized silicon- and titanium dioxides are currently used in food and drink products; for example, nano-sized silicon dioxide is added to powders increase flowability. However, the potential of nanotechnology to enhance nutritional value is largely unexplored. Recently, with the Particle Technology Laboratory in Zürich, we developed the first iron nanoparticles for nutritional applications. We synthesized amorphous ferric phosphate nanopowders using flame spray pyrolysis. Regular-sized ferric phosphate is a poorly soluble iron compound of little nutritional value due to its low bioavailability. Flame spray pyrolysis can produce tailor-made particles with high surface area and well-defined chemical composition. It is an established, scalable technology that may prove cost-competitive for production of nanoparticles for nutritional supplementation and/or food fortification.

These ferric phosphate nanoparticles had a mean particle size of 10 nm— 10,000 of them would fit across the diameter of a human hair. They were compared to the 'gold standard' iron compound, ferrous sulfate, in vitro and in animal studies. Ferrous sulfate, although very well-absorbed, usually colors foods brown. The results showed that the nanosized ferric phosphate had remarkably high solubility and bioavailability in rats, equal to that of ferrous sulfate.

This novel approach could lead to the development of the next generation of trace element compounds for human nutrition. Poorly absorbed compounds with superior sensory qualities, when reduced to nanoscale, may become useful for human nutrition, because particle size reduction increases their absorption while retaining their sensory inertness.

Considering the clear advantage of tackling micronutrient deficiencies in a combined approach, in Zürich we are now producing atomically-mixed iron and zinc nanoparticles. Overlapping iron and zinc deficiencies are common in the developing world, and co-fortification could be beneficial, particularly since high amounts of iron inhibit zinc absorption when given as supplements but may not when given with food.

We are also investigating packaging nanosized iron and zinc in folate-containing capsules for folate-receptor targeted delivery in the duodenum. Folic acid is a B-vitamin essential for building blood cells, and its deficiency, along with iron deficiency, is a common cause of anemia. It is often supplemented along with iron to control anemia in children and pregnant women. The inclusion of folates in liposomes surrounding nanoparticles may not only deliver folic acid but also enhance iron and zinc absorption.

These examples suggest uniting traditional strategies of supplementation, fortification and diversification with innovative new technologies like genetic engineering and nanoscience may provide the breakthroughs we need to finally control the micronutrient deficiencies.

#### Uniting in public-private partnerships

Control of micronutrient deficiencies has been traditionally perceived as a problem to be dealt with by health care workers treating those with clinical signs of deficiency. But in the last 10 years, it has become clear that new alliances are needed to achieve what the public health sector alone cannot.

Since the mid 1990s, a growing international dialogue on micronutrient malnutrition has led to new coalitions that include:

- Governments and their citizens;
- The commercial sector and its market;
- Academia in developing and industrialized countries;
- International agencies, including UN and non-government organizations.

These alliances follow the new maxim, "divided they stand, united they fall", in their approach to micronutrient deficiencies. Examples of global public-private coalitions include the Global Alliance for Improved Nutrition (GAIN), and the Flour Fortification Initiative, and the Global Network for the Sustained Elimination of Iodine Deficiency.

Even the traditional strict division of the micronutrients by expert advisory groups may be changing. In April 2007, the new Micronutrient Forum brought them together under one roof, and for the first time a single major meeting specifically addressed the major micronutrient deficiencies - vitamin A, iron, zinc, folate and iodine.

# This Professorship

The movement toward alliances in nutrition leads logically to why the endowment of this Chair in Micronutrients and International Health by Unilever is so prescient, and so important. Until now, fortification, particularly to control iron deficiency, has been less successful than hoped for. Effective public-private partnerships could change this, as the public sector (with the mandate to improve public health) and the private sector (with the expertise in food development and marketing) work together. One of the main goals in this new Chair will be to clearly define the extent and impact of the micronutrient deficiencies, develop innovative technology and rigorously evaluate new fortification strategies, including bioavailability and efficacy. But it is only the private sector —such as Unilever and their Regional Nutrition and Health teams in the developing world— that can take the next step to develop, distribute and market fortified foods to whole populations.

This Chair reflects Unilever's commitment to help reduce child mortality and malnutrition worldwide. This commitment is also evident in Unilever's global partnerships with the World Food Program, GAIN and UNICEF that focus on food fortification, child nutrition, and school feeding programs. Within the Chair, Unilever has funded a Research Program focusing on mental development of children, including funding for three PhD and six MSc students. Three MSc students, from Kenya, Thailand and the Philippines, will begin their studies in September.

Under the exemplary leadership of Jo Hautvast, Clive West and Frans Kok, the Division of Human Nutrition at Wageningen has become a global leader in international nutrition. Through its longstanding collaborations with institutions in developing countries and its sandwich PhD fellowships, the Division has been hugely influential in capacity building, particularly in Asia and Africa. Currently 20 international PhD students are ongoing, and yearly about 10 international students are enrolled in the MSc programme Nutrition and Health. Strong research lines have been developed on micronutrient deficiencies, mainly deficiencies of vitamin A, iodine, iron and zinc. The efficacy trial of NaFeEDTA-fortified whole maize flour in Kenya published last month in the Lancet by Pauline Andang'o and co-workers is a fine example of a Wageningen sandwich PhD program producing groundbreaking research in the field of micronutrients.

Within the new Chair, I plan to build on these strengths of the Division, particular in the field of metabolic aspects of micronutrient malnutrition. To do this, we will develop partnerships with other groups at Wageningen, as well as at the ETH Zürich, to exploit the latest technology in stable isotopes, biofortification, nanoscience and food process engineering. The expertise of the Human Nutrition group in Zürich in stable isotopes of iron and zinc complement our Division's expertise in organic mass spectroscopy. A new project examining the interactions of heme iron and folate absorption at a shared duodenal transporter will draw on the stable isotope expertise of both groups.

One focus of the Chair will be micronutrition and mental development in children. Although controlled trials have suggested benefits of iron, iodine and perhaps zinc on cognition, the mechanism(s) remain largely unknown. Available clinical tests to assess cognition are limited by their high variability. The rapid advance of electrodiagnostic studies and functional brain imaging techniques, such as MRI and FDG-positron emission tomography, may allow us to more objectively measure and characterize cognitive changes due to malnutrition. Also, use of gene arrays, proteomics, and metabolomics will point to the cellular mechanisms that underlie a clinical response to nutritional interventions. These techniques may allow us to identify the adverse effects of marginal micronutrient deficiencies not only in childhood, but also in pregnancy. In September, two new PhD students within the Chair, one from India and one from Thailand, will begin to study the adverse affects of maternal iodine deficiency on thyroid function and neurocognitive development of the offspring, using these approaches.

At Wageningen, the Chair plans to work closely with the other groups in the Division of Human Nutrition. At the molecular level, with the group of Michael Müller, as well as the Cell Biology and Immunology Group, new functional tests using peripheral macrophages may elucidate the metabolic effects of malnutrition on immune function and inflammatory cytokines. This could provide important insight into the critical link between micronutrient deficiencies and infections common in developing countries, such as malaria, tuberculosis and HIV/AIDS.

At the population level, an area of shared research will be the effects of the so-called 'double burden' of malnutrition of both obesity and micronutrient deficiencies in transition and developing countries, and their interactive contribution to diabetes, chronic inflammation, and cardiovascular disease. Another shared interest is selenium deficiency, both its role in induction of cancer as studied by Pieter van 't Veer and his group, and its potential role in increasing the burden of infectious diseases in developing countries. Collaboration with Renger Witkamp will help bring the lessons learned from nanoparticle use in pharmaceuticals to food applications. We will turn to Kees de Graaf to help evaluate potential sensory changes in foods induced by biofortification or nanotechnology. Finally, the expertise of Lisette de Groot's group on nutrition and cognitive function in the elderly is complementary to our planned studies in children.

In teaching, a goal of the Chair will be to consolidate the lectures on micronutrients currently scattered throughout the BSc and MSc programs in Nutrition and Health, and develop one or more specific MSc-courses on micronutrient nutrition in developing countries. Also, in collaboration with Wageningen graduate schools such as VLAG, we plan to implement an intensive post-graduate course on micronutrient malnutrition, taught by a high-profile, international faculty.

## Thanks

Many people were involved in my medical and scientific training at the Universities of Vanderbilt and California at Berkeley, as well as at the ETH in Zürich. The late Philip Felts, my mentor at Vanderbilt, assured me that as valedictorian of my class I was not obliged to be a surgeon, and encouraged me to go into endocrinology. At Berkeley, Janet King taught me respect for nutritional science, and Norman Kretchmer introduced me to international nutrition on an unforgettable trip to study diabetes in aboriginal children in the Australian outback.

In Zürich, I have had the extreme good fortune to have worked alongside Richard Hurrell for the past 10 years. His scholarship and integrity have made a deep impression. Working with Emorn Wasantwisut in Bangkok, Pieter Jooste in Cape Town and Sumithra Muthayya in Bangalore has been an enormous pleasure. I have also had a steady stream of unusually talented and amiable PhD students working in developing countries. With respect to my Professorship at Wageningen, I would like to express my appreciation to Unilever for their generosity in initiating this Chair, in particular, to Jan Weststrate and Marti van Liere. For allowing me to take up this position in Wageningen, I would like to thank the Council of Wageningen University and Research Center represented by the Rector of the University (Prof. Martin Kropff) and the Chair of the Division of Human Nutrition (Frans Kok). I look forward to working with Inge Brouwer, Alida Melse and Saskia Osendarp, and am entirely counting on their hardworking day-to-day leadership, considering I will only be at Wageningen the equivalent of one day a week! I would also like to thank Gea Brussen and Lous Duym, in the Division of Human Nutrition, for arranging this event today.

Finally, I would like to thank my family for bringing me so far. My young children, Henry and Sophie, are very proud of their father and would have been more than happy to have skipped two days of Swiss school to be here. And Tanja, for your sense of humor, for your ability to somehow balance running both a company and a family, and for always putting things back into the right perspective.

### Conclusions

In conclusion, malnutrition remains the world's most serious health problem and the single biggest contributor to child mortality. With more than a third of the developing world's population suffering from micronutrient deficiencies, unless policies change, these deficiencies may prevent many countries from achieving the Millennium Development Goals —in Sub-Saharan Africa, where malnutrition is increasing, and in South Asia, where it is improving only slowly. The 2004 Copenhagen Consensus of eminent economists (including several Nobel laureates) concluded that the returns of investing in micronutrient programs are second only to fighting HIV/AIDS among a long list of ways to meet the world's development challenges. The Consensus concluded, "...no other technology offers as large an opportunity to improve lives at such low cost and in such a short time."

Divided, micronutrient deficiencies may stand, but united, integrated strategies targeting multiple deficiencies driven by public-private partnerships will, in the end, cause them to finally fall. We need to seize this opportunity to ensure that, worldwide, the next generation of children grow up and develop to their full mental and physical potential.

Thank you.