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HIDDEN HUNGER: THE ROLE OF NUTRITION, FORTIFICATION, AND BIOFORTIFICATION

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Good afternoon. I'm delighted to be here and given the opportunity to address this august audience. I'm going to talk a little bit differently than most of the other people have, from a clinical and a health perspective.

So we've heard something about the role of the Rockefeller Foundation in moving forward an important agricultural agenda over the recent past. There's also been reference made that the traditional area of interest of the Rockefeller Foundation had been in public health. And indeed the institution where I am Dean, Johns Hopkins School of Public Health, was the first school of public health founded in this country, and it was founded with support of the Rockefeller Foundation.

One of the first faculty members recruited to the school was this gentleman, E.V. McCullen, who we stole away from Wisconsin where he did work on an agricultural research station. He became the first professor and chair of biochemistry at the Hopkins School of Public Health. And as many of you probably know, he is the person who first described vitamin A. This is their paper from 1913. So what goes around comes around. E.V. McCullen's portrait hangs in our board room.

Now, one of the most important early observations of the classical deficiency, the one in which most public health and clinical research is focused, up until about two decades ago, was on the very striking ocular manifestations of the deficiency. Let me just run through those briefly for you, because those are what gave us the clue that something else was going on.

So the earliest ocular manifestation of vitamin A deficiency is night blindness. Children traditionally huddle in the corner of their hut, they can't see their food after dusk or dark, they don't walk around the village because vitamin A, as you probably all know, is an important component of rhodopsin, the pigment in the eye that allow us to see under low levels of illumination. With more severe deficiency, these develop keratinized metaplacia of the conjunctiva, so epithelial, mucus epithelium starts to become stratified squamous epithelium, and these are known as Bitot spots. With the most severe deficiency, you actually get ulceration, rapid melting of the cornea, at which point this eye is lost.

Children who go on to develop this melting of the eye, so-called keratomalacia, are usually very, very sick and malnourished. This is a child that I saw in Indonesia, where I spent a number of years living and working and studying this problem. This child has keratomalacia in that eye, and that eye is blind. As you notice, this child is severely malnourished with protein energy malnutrition, swollen legs, pneumonia, diarrhea. A child with advanced vitamin A deficiency is not a child who has a high likelihood of living, unless treated promptly and vigorously in the hospital. So the fact that keratomalacia would be associated with a high rate of mortality was no surprise.

The story that I'm going to tell you today was stimulated by this type of child. This type of child actually came to the clinic because he was night blind. Otherwise, the child looks quite healthy, well-nourished, no diarrhea, no pneumonia. There's no particular reason why this child should have a higher likelihood of dying than children living in the same village.

We were following 4,000 children, examining them every three months over the course of year and a half, to learn more about the determinants of vitamin A deficiency, because we wanted to identify ways in which we could prevent deficiency and therefore prevent these eye signs and complications. What we discovered quite accidentally, and much to our surprise, was that the vitamin A status of a child, when controlling for all other factors – protein energy, malnutrition, respiratory disease, diarrhea – the vitamin A status of a child was directly related to that child's risk of dying.

So what you see here is that children who had normal eyes at a previous example – and that doesn't mean that their vitamin A status was normal, and in fact we know from biochemical studies that their vitamin A status was quite deficient, but not so deficient that they had abnormal eyes. If you looked at their mortality rate and compared that with children that had night blindness three months previously, you will find that the children with night blindness died at three times the rate of the children who had normal-looking eyes. Children with Bitot spots, more severe deficiency, died at six times the rate, and children with night blindness and Bitot spots died at almost nine times the rate of children who had vitamin A deficiency but not sufficient to cause ocular signs.

Well, we didn't know for certain whether the vitamin A status caused this dramatic increase in mortality or whether the vitamin A deficiency was simply tracking along with other conditions which we did not know how to measure and therefore did not record. The only way you can in fact determine whether there is a causal relationship, although this is pretty suggestive evidence that there is, is dose response relationship – the one where you can prove causal relationship is to simply change one variable, and that variable being vitamin A status. Which you change that by randomizing children to a large dose of vitamin A every six months or not.

So the next study we carried out was exactly that. It was a large population. This is not the population being studied; these are our field workers. There are 565 field workers. The population studied was nearly 15,000. And these are the results:

Children were dosed at baseline, again at six months, or not, randomized by village. This is the cumulative mortality over that time period. What you can see, I think quite strikingly, is that the blue line, which are children living in the 250 villages in which they were dosed with

vitamin A once every six months, the mortality rate was about only two-thirds the mortality rate of children who were living in the controlled villages. So that from this data, it dramatically appeared that one dose of vitamin A, a large dose, one dose of vitamin A every six months, reduced childhood mortality by at least a third.

We and then others have followed up with additional studies of similar design but slight variation. This is a study we carried out in Nepal subsequently, and this is each of the four-month intervals into the study. The blue bars are the mortality rates for the children receiving placebo. The yellow bars are the mortality rates for children who were receiving the vitamin A. At every interval until we finally topped the study, the children receiving vitamin A again had roughly a one-third reduction in their mortality.

Then just to prove the point, when we decided to stop the study at this point because the results were both clinically and statistically significant, we continued it for eight more months but gave the children who were originally assigned to the placebo group, vitamin A. You can see at the end the mortality in both the original placebo group and the vitamin A group, now both being vitamin A groups, are identical. So we brought that mortality rate down.

By 1992, there were six studies that were carried out in Asia, all of relatively similar design, testing this hypothesis – two in Indonesia, two in India, two in Nepal. One of the studies in India did not show much of an impact, but there were a lot of complications in that study. More striking to me, and somewhat surprising, was how similar the results were in all these studies. This is a 34% reduction – that was our first study. Another one done in Indonesia was nearly a 50%. One done in southern India was again about a 50% reduction. And then two that were done in Nepal were 24 to 30% reductions. Considering the wide variation in culture, diets, infectious disease load, and what-have-you, between these three different countries, I was quite surprised at how common and similar the results of these studies were.

So the question then comes up, is – Why are children who are vitamin A deficient dying at increased rates? Or to flip that on its side, is – Why giving vitamin A reduced childhood mortality? This is the relative risk of dying of measles. This means that in Nepal, the children given vitamin A only had one-quarter the risk of dying of measles. In southern India, they had half the risk of dying of measles. The same of diarrhea for both Nepal and India and in other countries in which we studied this. What this is basically telling us is that the vitamin A did not, deficiency did not increase your risk of getting an infection – what it did was increase the severity of that infection. In other words, it reduced your ability to ward off or fight severe infection.

We move very quickly into India when somebody contacted me not about the mortality issue but was concerned about the very large proportion of African children with measles who were going blind from measles, and they wondered why the children were going blind from measles. So I visited there, and we worked up a number of studies. What struck me was that looking at children with measles-related blindness, usually coming on within a month or two within the onset of the measles, looked strikingly like vitamin A deficiency. There is nothing really quite so depressing as seeing children who are blind – these are children in a school for the sighted and nonsighted working together. Their cause of blindness had been related to a previous about of measles. You can see these were corneal ulcers that had scarred and caused white

opacity. This was their teacher who in fact had himself gone blind at the age of five, following measles. But he was partially sighted and therefore was able to relate to the children's status.

So we carried out a study in a small mission hospital in Vumi, Tanzania, which demonstrated rather unequivocally that at least half of the corneal opacification following and associated with measles was in fact due to vitamin A deficiency, and that when it came to bilateral blindness almost 80% of the measles associated with blindness was in fact due to vitamin A deficiency – and measles had simply exacerbated this.

So we then asked the question whether the very high case fatality rates seen in hospitals with children with severe measles in Africa might not also be related to vitamin A deficiency, mimicking what we were seeing in the field in Asia. What we carried out here in this same hospital was a classic, randomized trial. Look at the larger numbers down here, 0 to 6 years of age, so it's a larger group of children (Please refer to power point). Children who were admitted to hospitals with severe measles were all treated identically, except half were randomized to routine therapy, and half were given, in addition to that, vitamin A on two successive days. The children who received the vitamin A died at only half the rate of those who received routine therapy.

These are children who were destined within about four or five days, so whatever the vitamin A was doing in the field to prevent death, here it was in fact preventing it within a very short time period after administration. I was only within about four months of publishing that paper that both the World Health Organization and UNICEF offered a joint statement recommending that vitamin A given in the routine treatment of all measles. In fact that's a recommendation that's even made here now in the United States for special populations by the American Academy of Pediatrics.

So what's going on here? What seems to be happening is that, as your vitamin A status declines – and this is obviously schematic – the first thing that happens before there are any ocular manifestations at all, is that the systemic consequences of that deficiency begin to occur. You have an increased risk of severe infections, an increased risk of mortality, reduction in growth, and increased risk of anemia. It's only with more severe deficiency that you begin to see the ocular complications of night blindness, the xerophthalmia, the melting of the cornea.

If we look around the world and carry out epidemiologic surveys as we have, you'll find that almost throughout the entire developing world, most children are vitamin A deficient. In addition – and it's not a story I'm going to tell today – the same is true of most pregnant women.

So in summary, if we look at vitamin A deficiency disorders on a global basis, there are roughly 155 to 200 million children who suffer from this condition every year, roughly 3 million children and 3 million pregnant women develop the eye conditions of vitamin A deficiency every year, roughly half a million children go blind from vitamin A deficiency every year, and, in the absence of vitamin A intervention programs, somewhere between 1 and 2½ million children would die every year.

By 1992 there had been a common interest to do something about this problem. World Health Assembly passed a resolution, the UNICEF Executive Board, and Ending Hidden Hunger

– all of these around eliminating vitamin A deficiency by the year 2000. Well, the year 2000 has come and gone, and we obviously have not eliminated vitamin A deficiency, but we have begun to make a significant impact.

First of all was the need – obviously when one wants to move from science to policies, you have to get the attention of the policymakers, which usually means getting the attention of the public as well. So it was not bad to get some publicity about these issues. During the Clinton Administration thee was a major push through USAID and other agencies. Jim Grant was someone who famously went around the world with oral rehydration packets in one pocket and vitamin A capsules in the other pocket. My Christmas present in 1997, December 25th editorial in *New York Times*, "Malnutrition's 20-cent Treatment." I don't know who wrote this. I don't know why they wrote it. I don't know where they got the 20 cents from. But nonetheless, it's all about vitamin A reducing childhood mortality and blindness.

So one approach – and it's the approach we use in studies because it's the easiest one to control, but it has turned out to be the one that has been most widely used as the national intervention programs, has been used of these large-dose supplements. The size of the supplements is graded with age, but roughly six months to a year of age, a child is given 100,000 international units, above one year of age, 200,000 international units once every six months. This is the standard UNICEF capsule. In India they either use the capsules, but traditionally and originally for cost savings they use the syrup itself given just by a spoon.

It does work. Bangladesh has had a very successful capsule distribution program for many years. You can see these are the prevalence rates, the proportion of children under six years of age who have these signs of xerophthalmia simply as a marker for how extensive the deficiency is in the population. Then 3½% of the children were night blind. Following the institution of the distribution program, less than 1%. The WHO cutoff is a 1% level. Bitot spots – in '82 there was almost 1%; in 1987, 0.2%, and so forth and so on. So it really can make a difference.

In Nepal where they also have a distribution program where children 6 and 60 months are given it twice a year, the annual cost is estimated for the entire program – now, this is a program where they mobilize 45,000 women volunteers, and they call a halt to other activities in the country two days a year, and you'll see families carrying their children to a central place where someone gives them a vitamin A capsule – the annual cost for that program, because they're using village volunteers is $1.7 million. The annual savings is $1.5 million. The cost per child is roughly a dollar and a quarter. The capsule only costs 4 cents, and sometimes less than that. But having to distribute it is actually what adds to the cost, and the cost per death averted is about $300.

The second approach, of course, is to use some other mechanism for delivering the vitamin A, rather than actually having to mobilize people – and that's your standard fortification. This is a program that we experimented with in the Philippines. It's called "Star margarine." It's heavily hydrogenated. It's used by the poor people because it doesn't need refrigeration. While it might clog up all of your and my coronary arteries, the average Filipino gets very little in the way of lipids, so in fact for them it's in fact a beneficial substance. We convinced the makers of Star margarine – in fact which is originally Proctor & Gamble before they sold it to the local

beer company – to fortify it on an experimental basis with vitamin A. And they did so, and then in fact not only did it work but it became very popular. They got the government, for the first time that the Philippine government ever did this, they actually put a label on, saying that this was a particularly healthy product because it's fortified with vitamin A. Every other province then in the Philippines decided to add vitamin A – so they could get the seal – and we started to get very concerned that people would get an overabundance of vitamin A.

We had earlier worked with, as they had in the Philippines, fortifying MSG, monosodium glutamate with vitamin A. This did not work. It worked physiologically. The problem, however, is that MSG is marketed, in Indonesian which means, "the whiter it is, the better it is," and vitamin A, of course, turns it yellow. So we told the company, just advertise, "the yellower it is, the better it is." They didn't go along with this, and we never really worked out a way to keep it white and have it filled up with vitamin A.

The problem with regular fortification, however – and we've encountered this everywhere around the world we've gone – is that the people who most suffer from vitamin A deficiency are the poorest segments of society, and it's very rare that there is some centrally processed food to which you could conveniently add vitamin A that these people could afford to buy.

It does work, however. This is a study we carried out in Indonesia, which shows that villages in which the local markets were given the fortified MSG versus those were not given the fortified MSG. If you looked at, again, cumulative the MSG nonfortified villages had almost twice the childhood mortality rate than those that were consuming by simply buying it at the local market the MSG that was fortified with vitamin A.

How did we get into this problem? Why is there so much vitamin A deficiency in the world? Well, we don't suffer from vitamin A deficiency in part, but only in part, because we consume quite a lot of the active vitamin A, retinal – that's the active molecule. How do we get that active molecule? We get it either through our regular dietary food items, which are always animal products – egg, cheese, milk, liver, liver being a huge source because liver is where vitamin A is stored – in addition to which, of course, almost everything that we consume, from Kelloggs to milk, has been fortified with vitamin A. And by the way, young children and pregnant women, lactating women, take multivitamins which contain vitamin A.

But what about people in the developing world? Well, people in the developing world do not consume animal products. They consume, as you heard earlier, rice or corn, what-have-you. Rice, of course has, in the traditional sense, no vitamin A whatsoever. So where they have to seek their vitamin A is through beta-carotene molecule that actually looks like two vitamin A molecules bound together, so in theory at least, if you split it, you should get two vitamin A's for one beta-carotene – but it doesn't work that way. One of the reasons it doesn't work that way is because the beta-carotene is assiduously held by the cellular matrices of the green leafy vegetables in which it occurs. So in fact you don't get even one or even close to one vitamin A for each beta-carotene that's consumed.

Nonetheless, diet is an important component and source of vitamin A, and this is one of the many brochures that are put out, encourage breastfeeding. And in fact, breastfeeding is the

most significant source of vitamin A to a young infant during the first six months of life. But if the mother is severely vitamin A deficient, as is common in the developing world, while her quantity of breastmilk will be identical to that of someone here in the United States, the quantity of vitamin A, the concentration of vitamin A in that breastmilk will be much lower and the child will be vitamin A deficient. And of course, promoting green leafy vegetables, yellow fruits and so forth that are good sources of beta-carotene.

The thing that concerned me all along is that most nutritionists and dietitians felt that the answer – as if there were one answer to the vitamin A deficiency issue – was getting people to grow and consume more green leafy vegetables. It was our contention that it did not appear to be a solution, or if it was, it was only a partial solution – because if that were the case, you simply would not see as much vitamin A deficiency as we did. These are the typical kinds of posters, the kinds of things to eat – carrots, of course, papaya, mango, what-have-you.

A colleague of mine in Indonesia, back in 1972, carried out a very important, simple clinical trial which nobody paid any attention to. That was one in which he fed Indonesian women large doses of green leafy vegetables, cooked green leafy vegetables, which is what you have to do if you're going to liberate the beta-carotene from them and break down the cellulose, or not. And then looked at what happened to their serum vitamin A levels – and not anything happened to their serum vitamin A levels. So people didn't like that, so they ignored that study, which is often what happens in science when someone comes up with a new and unpleasant piece of data.

Fortunately, by the 1990s, Clive West and his colleague had begun a series of these studies, following up on the earlier evidence. So this is what happens to the serum retinal levels of children who are given either a retinal-rich supplement, a large amount of fruit, vegetables, or placebo. So placebo, nothing happens to the serum retinal. If they give them a retinal-rich food item, as you can see, the serum retinal goes up considerably, given fruit, it doesn't go up nearly as much; and given green leafy vegetables, it hardly goes up at all.

The traditional, and as Cathy Woteki told you about, that earlier Institute of Medicine Food Nutrition Board conversion ratio said that you needed six molecules of beta-carotene to get one molecule of vitamin A. Given this mounting evidence, when the Food and Nutrition Board calculated their latest data, again that Cathy referred to, they decided that that really was too generous, and in fact you needed 12 molecules for beta-carotene for 1 molecule of vitamin A. So that just reduced the amount of vitamin A in the vegetable diet by half.

If you look at the actual studies that are carried out in developing countries, the children who live in developing countries – not an estimate for healthy children in the United States, the results are even far less supportive. The green leafy vegetable rate looks like maybe you need about 26 molecules of beta-carotene to get 1 molecule of vitamin A.

Olaf, who was studying this problem back in 1924, said there are indications that human beings, in contrast to herbivorous animals, may not assimilate much fat-soluble A derived from plants. He had the answer back in 1924.

So this is what the world's vitamin A dietary availability looks like when you use these three different estimates (Please refer to power point). The orange bar is the original FAO/WHO 6 to 1 ratio. As you can see, Europe, Africa, almost South America and Asia, have an adequate per capita amount of vitamin A in their food supply. As soon as you apply the IOM's latest recommendation of 12 to 1, which are these greenish/bluish bars – Europe, the U.S., Japan, what-have-you – adequate amount per capita. Africa now is a little bit below. South America is further down, and Asia is way down. There is not enough per capita on average, as if everybody got their per capita average allowance in any case. And if you look Clive West's data, which are probably the most relevant to the developing world, it's the yellow bar. And the West for the most part doesn't have an abundance of vitamin A. Africa, South America and Asia have very, very low availability levels.

So on average the per capita amount of vitamin A in the food supply of every region but Europe and the U.S., is only half what the average person needs. So of course, vitamin A deficiency is going to be extraordinarily widespread.

Now, there are several ways of approaching this problem, even from a dietary perspective. One of them, of course, is to use traditional breeding practices, and these are bananas that are being bred out for high beta-carotene content. This is a gentleman who is here in the audience who waved some golden rice at you at lunchtime. But now you know, not only was it nice to see his picture on the cover of *Time* Magazine, but now you know where this rice could save a million kids a year comes from – it's the story you've just heard.

There was a nice editorial, "The Green Revolution Strikes Gold," and these are the early pictures that they published with those articles, showing the biofortified, genetically modified rice, to versions of the rice that they genetically modified to make beta-carotene.

That, of course, led to an enormous controversy which continues to this day. In that *Time* Magazine article, the first compelling example of a genetically engineered crop that may benefit not just the farmers who grow it but also the consumers who eat it.

Of course, there is a whole string of issues that remain to be determined before golden rice finds its appropriate niche within the panoply of solutions that we need for this problem. We have to know what the bioavailability, what the organoleptic acceptability, whether the people will like the taste and the appearance and the smell, what the agricultural yields will be, because farmers aren't going to grow it unless they can make as much money from it as they did previously, what the regulatory hurdles are, and then, of course, issues on increasing the concentration, for which he has some very exciting new data, and the adaptation to local strains, which they are in the process of carrying out even as we speak.

One of the most important and difficult issues they initially faced was the fact that there were somewhere on the order of 70 patents that were surrounding their original technology, which when you actually looked at it from the perspective of the later techniques and what you could do in developing countries, this reduced to 12, and they have some good news about what they've been able to do about those 12 as well.

One of the main issues, now that they've perhaps tackled successfully, is increasing the concentration by the new approaches that they've taken to this. But this was something that they had worked out. The original material contained 1.6 micrograms per kilograms, the RDA per child. You could then figure out how many grams a child would have to eat to meet a hundred percent of their dietary requirements, a child would have to eat 1.8 kilograms of rice a day. That's not likely to happen, but, of course, there's no reason why the rice has to provide all of their vitamin A requirements, as long as they're getting some green leafy vegetables, as long as they're getting some milk, as long as they're getting other things. Then you could look at if they need 30%, you could estimate even at this concentration, 600 grams of rice. If it provides only half the intake, 300. And if you can get the beta-carotene three times higher – which they seem to in fact have accomplished – then you'd only perhaps need a hundred grams of rice, which is roughly what a preschooler in the Philippines consumes a day. So we're getting into a range of real possibilities, but the field trials remain to be carried out.

Of course, this brought forth a lot of positive and negative advertising, so in a series of full-page advertisements, I remember seeing most graphically in the *New York Times* Sunday Magazine section on a weekly basis, biotechnology research is golden rice, with a color for the opportunity, and they talk about vitamin A deficiency in a child that's suffering. And that was followed with an article in that same magazine, "The Great Yellow Hype." None of this has added very much to our understanding, simply two op ed pieces. "Food for the future – Someday rice will have built-in vitamin A, unless the Ludites win." That was an op ed piece in the *New York Times*.

So where are we now? In summary, there are roughly a million children blinded or who die unnecessarily every year. The importance of vitamin A deficiency and its control has been well recognized and accepted. Its one of the Millennium Development Goals. It has been in the Declaration of the Rights of Children. There are now 400 million vitamin A capsules that are distributed by UNICEF alone every year in agreement with local governments. There are national programs in over 70 countries. Three years ago, the last time we looked, 40 countries reported having reached over 80% of the population that was targeted to receive vitamin A supplements. And according to the World Bank, this is the single-most, cost-effective health intervention available today at less than $1 per day. The discoveries and recognition of the extent of the so-called sub-clinical vitamin A deficiency – but it's not sub-clinical; it's just nonocular. It's not sub-clinical because it kills people.

The recognition of the extent and the importance of this in childhood and perhaps the maternal mortality as well, has, of course, spurred agricultural and biotechnology developments and increased the search for approaches to dealing with this very important problem.

Thank you very much.