

Discovery Science for Global Health

A bright new dawn – or a case of the Emperor’s New Clothes?

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This is an unusual issue of *Sight and Life*, and some readers might be surprised by the complexity and detail of the content that Klaus Kraemer and his editorial team present here.

We can read about the wonders of the microbiome – the myriad organisms that travel through life with us and affect our health and well-being. We can read of genetics and epigenetics and metastable epialleles, of genomics and epigenomics, and of nutri-genetics and nutri-genomics; and why not nutri-epigenetics? We can read of the proteome and the deep proteome, the metabolome and every other type of –ome, even including the nutriome (a new one for me, I confess). We can read of systems nutrition and flexible phenotypes and metabolic-inflammatory health, some of which can be analyzed by a next-generation “*sequential windowed data independent acquisition of the total high resolution mass spectra (SWATH-MS) on triple time-of-flight mass spectrometer*” (page 72). Who would have thought we would read about such wonders in the pages of *Sight and Life*?

Some of you will be quite reasonably challenging the presence of such basic science in a journal known for its core mission of eradicating malnutrition worldwide. Others will be daunted by the complexity of the topics addressed. Please bear with us, nevertheless, because the manner in which we navigate these scientific swamps and harness these new technologies has very important implications for future global health, and it lies squarely within *Sight and Life*’s vision of “*a world free from malnutrition*”.

And for those of you who do wish to challenge the relevance of basic research, this is precisely what I propose to do on your behalf in this contribution. I myself strongly believe that discov-

ery science in nutrition will paradoxically lead us more quickly to effective interventions than continuing to feel our way in the dark with trial after trial that yield results that disappoint and perplex us. This conviction needs to be stress-tested, however, if we are not to promise a false dawn.

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Trials and tribulations: Interpreting unexpected outcomes from micronutrient interventions

Some years ago, I used this title for my EV McCollum lectures and made the argument that nutritional science lacked both the discipline and the method to make the quantum leaps in progress that are required to eliminate malnutrition. We are seduced by the possibility of a silver bullet that will provide a quick fix.

This tendency has been encouraged by the fact that decades – or even centuries – ago, single-nutrient interventions enjoyed some remarkable results. Lemons cured scurvy in seafarers, beriberi is a thing of the past, iodine fortification has saved countless children from cretinism, folic acid has prevented neural tube defects, and mass administration of vitamin A has saved lives. But these were the low-hanging fruit, and a greater number of attempted interventions have either failed or else have caused adverse outcomes, iron supplementation being the most prominent example of late. When our favorite supplement doesn’t work, we argue that we should have given more of it



Andrew Prentice with co-pilot in his microlight

(or perhaps less), or that we should have given it to a different age group, or in a different population, or in combination with something else; for surely it must work!

We can use the example of iron to illustrate how basic science has transformed our understanding of this micronutrient's biology and how this might lead to fresh intervention approaches within the near future. Our former view was that humans were very poorly designed to absorb dietary iron and therefore needed all the help they can get. We worried about phytates blocking absorption, and gave mothers and children large non-physiological bolus doses of readily absorbable iron taken without food to avoid the phytates. With the discovery of hepcidin (the hormone that acts as the master regulator of iron) and the mapping of the molecular pathways involved in iron absorption and distribution, we now know that our former views, and the attempted therapeutic interventions that arose from them, were shamefully misguided.

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The new biology informs us that children in infectious environments are working hard to keep iron out of their systems because it will feed the pathogens that threaten them. With the benefit of hindsight, we can see that we were mistaken in our ignorant attempts to batter down the gut epithelial barrier and swamp the chaperone systems (transferrin) that nature has taken eons to evolve. The hepcidin blockade explains why supplemental iron has limited efficacy in poor populations and why, when properly studied, supplementation has been shown to do harm.

But how can we use this new knowledge to eliminate iron deficiency? There are at least three clear messages:

- > First, elimination of infections and inflammation will be the most powerful route to eliminating iron deficiency. Instead of battering down the exquisitely evolved hepcidin blockade, we must find the right key, politely open the door, and pass the iron respectfully to the waiting chaperones.
- > Second, because hepcidin cleverly integrates information about iron need and threat of infection, it has exciting potential to be developed into a point-of-care diagnostic that may inform health workers that a person is “safe

and ready to receive iron,” thus allowing targeted approaches that should be both safer and more effective. In conjunction with the National Nutrition Agency (NaNA) of The Gambia, and supported by the Bill & Melinda Gates Foundation through our HIGH Consortium (Hepcidin & Iron in Global Health), we are currently trialing this concept in young children and pregnant mothers.

- > Third, we now know that unabsorbed iron from our previously used mega doses alters the gut microbiota, favoring enteric pathogens. Therefore we need to develop new formulations where any unabsorbed iron will not be accessible to those pathogens. Novel nano-particulate formulations are showing great promise in this regard.

These are examples of how basic molecular sciences can point to a pathway to impact and can completely reroute the direction of endeavor.

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Facing up to our disappointments and starting out on a new path

Let's consider now the issue of how nutrition interventions could improve reproductive outcomes. Naturally we are all believers in the concept that optimizing a mother's diet must be good for her baby, but we are faced by multiple frustrations. There are numerous meta-analyses of the effects of multiple micronutrient (MMN) supplementation on birth outcomes, and we can interpret the results with either a “glass-half-full” or a “glass-half-empty” mindset. The optimist in us all points out that there is unequivocal evidence for benefit, and we cling to such hopes because our entire field, and many whole organizations within it, are dependent upon such success, and – *inter alia* – we have spent tens of millions of research dollars studying over 74,000 pregnancies to reach these conclusions.

But let's put ourselves in the shoes of the brutally incisive health minister of Ugangambwe to whom we are pitching for the funds to implement a country-wide MMN intervention in pregnant women. He could rightfully point out that the 43 g increase in birth weight is less than one tenth of a standard deviation, and that gestation has been lengthened by just 18 hours (and with confidence intervals including zero). The 12% reduction in low birth weight equates to a number needed to treat (NNT) of around 30 in SE Asia and around 100 in Africa, and, statistically speaking, most of this effect will occur by moving babies who were a few grams under the cut-off to a

few grams over the cut-off. The same is true for pre term birth, except that the NNT will be close to 100 in most populations and the majority of the effect will be achieved by shifting a few babies a day beyond the 37 weeks threshold used to define preterm. And the minister will go on to point out that we have had no effect on stillbirths or neonatal deaths. At this stage, we make a rapid retreat from the minister's office with our nutritional tails between our legs.

Such nihilism can be crushing, and it risks diverting funding away from nutrition – but such a trend is already evident, and we need to reverse it by providing some shining examples of success. To counteract the nihilism, we can point out that the effects of MMNs might be additive to those of iron and folate, which is almost always used as the control group. This might well be true, but the meta-analyzed effects of iron are also disappointing. This in turn might be because we generally exclude iron-deficient and anemic women from such trials at recruitment, thus diminishing our ability to show benefit. The bottom line is that we can use our rose-tinted glasses to speculate and can hope that the benefits of MMNs are better than they appear, but after all this investment, we still do not know whether or not that is true. There are trial designs and settings where a placebo can be legitimately used (especially in view of concerns about the safety of iron) and where exclusions can be minimized. I am aware of one such trial that will shortly report interesting and encouraging results.

Where do we go from here? Do we admit defeat? Do we carry on regardless with more of the same? Or do we regroup and design a fresh approach? Surely it must be the latter.

To those of you who are still unconvinced that we need discovery science, let me set you a quiz:

1. What is the cause of pregnancy-induced hypertension and pre-eclampsia?
2. What causes fetal growth retardation in poor mothers?
3. What causes stillbirths and fetal malformations?
4. Why are babies so vulnerable to neonatal sepsis?
5. What causes stunting?

I could go on, but I think you will have got the point by now. Anybody who can answer anything other than “We don't really know” can come and have my job as a professor.

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**“We must believe, together
with Bill Gates, that the intelligent
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Against this background, we can share Bill Gates's frustration that the diet-related health deficits in poor populations are proving so intractable, but we must also share his vision that the intelligent application of innovation will get us out of the swamps.

Discovery research: Science fact or science fiction?

So how do we distinguish science fact from science fiction? How do we cut through the hype and focus on the most promising avenues to pursue? This is a significant issue for scientists and funders alike, and it is becoming ever more challenging as the plethora of methodologies expands.

One can't help but recall Hans Christian Andersen's tale of *The Emperor's New Clothes*. Most readers will know the plot, but for those who don't, a vain and wealthy emperor is promised a new suit of clothes by two swindling tailors. He is told that the cloth will be so fine that it is invisible to anyone unfit for their position or hopelessly stupid. The tailors pretend to dress him, and he walks among his subjects, who applaud the fine new robes for fear of being thought unfit or stupid, until a child – too young to follow the pompous deceit – cries out that the king is naked. Are we discovery scientists pulling off a pompous deceit? Are we persuading our funding bodies to fund an illusion?

My answer is a firm “no”, yet I believe that if we want to get a proportion of funding redirected from “suck it and see” empirical trials towards high-class science that will re-write the therapeutic manual in global health, we have an obligation to show some clear examples of success. To use a very useful phrase coined, I believe, by Chris Wilson at the Gates Foundation, we must show that we can move “from nice-to-know to need-to-know.”

The development of powered flight:

An analogy for our endeavor

On the windowsill of my office is a picture of Dr Dave Hilmers – a collaborator from Houston who helped us with our stable-isotope iron absorption studies. He is smiling out from beneath a flying helmet at the controls of my microlight in The Gambia (an ultralight to US readers).

His picture brings to mind a powerful analogy for our current endeavors in discovery science for global health nutrition: the invention of heavier-than-air flight. This is credited to the Wright brothers in 1903. They were not alone in their endeavors – in fact, it was a highly competitive field. Most proponents were taking the empirical approach, jumping from mountainsides with flimsy and uncontrollable wings strapped to their backs. There were many failures, and many people died trying. Despite their lack of formal education, the Wright brothers applied a much more back-to-basics, analytical approach founded on hypothesis, experimentation and progressive refinement. They made a small, home-made wind-tunnel and thereby devised

completely new methods for pilot control. Success did not come overnight, but once they had achieved the key breakthrough (three-axis-controls), their progress was astonishing and led to the most versatile and reliable means of human transport invented to date.

But let's return to Dave Hilmers to extend the analogy with reference to global health. Before training as a pediatrician and scientist, Dave was a Shuttle astronaut, and flew four extra-terrestrial missions. He had therefore flown in the most advanced aircraft ever invented. My microlight is the antithesis of the Shuttle: basic in the extreme, it has been simplified so that – without aileron, elevator or rudder – it can be flown with precision. In other words, a stroke of innovative genius of the type that Bill Gates seeks (involving in this case the design of flexible wings) allowed a great invention capable of space flight to be reverse-engineered so as to give a very low-cost basic equivalent.

A suggested road map for discovery science in global health

Although I have been (self-) challenging in this article, I remain totally convinced that intelligently applied discovery science will provide us with the next-generation interventions that we so urgently need. I would suggest the following as some of the components of a roadmap to success:

1. We need to attract the very best brains to nutritional science and to collaborate with the world's brightest minds in diverse related fields in order to achieve quantum progress in the new world of "big science". Many of these minds will need to be mathematicians in order to be able to cope with the complex challenges laid out elsewhere in this issue.
2. We must educate funding bodies to the fact that there are no quick fixes, and we must assist them to make complex decisions as to which domains of discovery science are likely to yield most benefit. Metaphorically speaking, we must help the Emperor (funding bodies) to detect the scoundrels, and we must educate his courtiers to tell him the truth. Sometimes these decisions are surprisingly simple – for example, the human genome is (largely) immutable, whereas the epigenome is modifiable by diet (see article on pages 35–38), therefore investments in epigenetics are likely to be more fruitful than investments in genetics.
3. We must be more critical of methods applied in empirical research; and at the same time, we must advocate for clearly thought out, cleverly designed, well implemented and robust trials containing sufficient measures of intermediate markers to allow insights into why the trial has failed if it does.
4. Blue-sky investigators should be forced to apply the "pathway to impact" test. Even if the impact may be quite far

over the horizon, they should at least be able to articulate a cogent plan for their pathway to impact.

5. As the visionaries in our field push the boundaries of potential medical interventions (such as bacteriophage manipulation of the microbiota to eliminate enteric dysfunction in low-income settings, or CRISPR-Cas9 editing of CCR5 to eliminate HIV), we will need to greatly enhance our systems for safety testing and high-level ethics oversight.

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As a scientist working at the coalface, you would expect me to argue that we also need more funding. We do, but perhaps a greater challenge is to invest the research dollars that are available more wisely than we have done in the past. The millions of dollars that have been spent on some large empirical trials predicated upon a poor initial reasoning and producing zero results would keep whole institutes in Africa going for many years. Such precious research dollars could perhaps be spent more wisely. And if we are to advocate greater investment in discovery science, we need to strengthen institutions in low-income settings so that they can participate as respected partners in the methodological renaissance.

The future *will* be bright – for mothers and children worldwide – if we can wisely harness the spectacular power of these new technologies in discovery science.

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I am most grateful to the following colleagues for their very helpful feedback: Amat Bah, Carla Cerami, Hal Drakesmith, Phil James, Sophie Moore, Martin Mwangi, Sant-Rayn Pasricha, Dan Raiten, Matt Silver and Rita Wegmuller.

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