

DOHaD: from ‘hypothesis’ to practice

I’ve known David Barker from when this field was still a ‘hypothesis’ – and I envied him mightily. We physicians are fortunate if our clinical description or invention is honored with an appellation, usually attached to a disease or surgical instrument. To have a ‘hypothesis’ named for you is a rare distinction indeed!

The field has of course matured, from ‘hypothesis’ to near ‘orthodoxy.’ I’ve met young students who talk passionately about DOHaD, but have never heard of David Barker. ‘*Sic transit Gloria mundi.*’ In retrospect of course, it now seems obvious that the many chemicals and nutrients to which the fetus is exposed must, through epigenetic and other programming mechanisms, affect health and disease in later life. As Thomas Huxley reportedly exclaimed upon reading Darwin’s *Origin of Species*: ‘How extremely stupid not to have thought of that.’ Great insights remain hidden in plain sight – until they don’t.

Since the first international meeting in Bombay, scientific acceptance of the developmental origins of disease has grown exponentially. The 2011 DOHaD meeting in Portland had to be capped at 700 participants. I can safely predict a continuing increase in scientific investigations and investigators addressing the many and complex issues undoubtedly involved.

Although scientific ‘hypotheses’ can leap to ‘orthodoxy,’ changes in clinical practice and policy generally follow a much slower, gradual ascent. For example, between the time our first observational study strongly suggested that vitamin A deficiency in young children dramatically increased their risk of dying¹ and global policies were formulated to tackle the problem, it took eight enormous randomized community-based trials in six countries,² a force-fed intensive consultation among leaders in the field,³ and multiple ‘high-level’ WHO and UNICEF conferences, culminating in a joint meeting co-hosted by the Director of UNICEF and the Director General of WHO. However, in the end, movement began.^{4,5} Over half a billion high-dose vitamin A capsules are now distributed every year (as well as other methods for improving young children’s vitamin A status), over 50 countries report reaching at least 80 percent of their target audience at least once a year, and an estimated near-half million children’s lives are saved each year.^{4,6} Vitamin A coverage has become a standard metric published in UNICEF’s annual report, ‘State of the World’s Children’.⁶ Changing policy and practice only became possible once (most) scientists agreed that the data proved the hypothesis, and a relatively simple, cost-effective intervention was shown to make a profound difference.

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Blindness prevention activities have progressed mightily over the past three decades, because of organized efforts to identify priority issues, and the sometimes lucky discoveries that fostered their solution. Three such discoveries provided the basis for three major policy and programmatic initiatives. Semi-annual large-dose vitamin A supplements for xerophthalmia, a major cause of childhood blindness (as well as excess systemic infectious morbidity and mortality); annual ivermectin dosing of all individuals in poor, rural areas of sub-Saharan Africa afflicted by ‘river blindness’ (onchocerciasis) has virtually stopped the disease in its tracks, whereas face-washing and periodic administration of the antibiotic azithromycin (as part of the ‘SAFE’ strategy: surgery of distorted eye lids; azithromycin dosing once or twice a year; face washing; and environmental hygiene) have effectively blocked transmission and repeated re-infection with *Chlamydia trachomatis*, virtually eliminating the blinding consequences of trachoma. Adoption of vitamin A prophylaxis (and its use to treat measles) was largely driven by ‘child survival’ advocates, the other two interventions by a broad-based coalition of individuals, NGOs, and international and bi-national agencies deeply committed to the prevention of avoidable blindness in low- and middle-income countries.

A uniquely cost-effective, proven intervention – an ‘actionable item’ (e.g. vitamin A supplements or ivermectin) – is a game-changer; however, even game-changers require widespread, well organized, persistent advocates. Those who were interested in blindness prevention, led by Sir John Wilson, began organizing coordinated efforts in the 1970s. Their organization, the International Agency for the Prevention of Blindness (IAPB), developed a consensus about effective policies and programs, primarily aimed at garnering attention at the national and international levels, and spurring the World Health Organization’s interest. Each newly validated cost-effective intervention strengthened IAPB’s argument and hand.

By the late 1990s, IAPB and WHO formed a joint initiative, ‘Vision 2020,’ a highly orchestrated, global advocacy effort that attracted increasing numbers of partners formulating and pursuing locally appropriate strategies in the pursuit of explicit goals. These initiatives have already resulted in measurable, if not necessarily uniform gains. For example, the single most important cause of avoidable blindness in low- and middle-income countries, un-operated cataract, has seen great progress in India, where the cataract surgical rate (CSR) has risen tenfold over the last three decades (from 500 to 5000 operations per million population), whereas there has been very little change elsewhere (Indonesia, China and sub-Saharan Africa still have CSRs below 500).⁷

DOHaD, a relatively recent, but exciting and clearly important area of scientific inquiry, will no doubt one day follow a trajectory similar to that of blindness prevention. However, it has a harder row to hoe. The outcomes DOHaD seeks to impact are distant, perhaps multi-generational. This will frustrate documenting the safety and efficacy of any 'actionable item' (whether like vitamin A for blindness, or folic acid supplementation for neural tube defects), unless innovative approaches, such as early biomarkers, are developed and shown to be valid predictors of future benefits. Nevertheless, we anxiously look forward to the opportunity to translate DOHaD concepts from hypothesis to practice, or better yet, from science to policy.

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