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# "Appropriate technology" for vitamin A field research[1,2]

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In the 1980s, the United Nations and nongovernmental agencies initiated a wave of conceptual thinking aimed at advancing the access of low-income populations to certain services and capabilities by using basic, rudimentary, and unsophisticated instrumentation. This so-called "appropriate technology" could reach rugged, remote areas where running water, refrigeration, and electricity were often lacking. The term *low tech* was adopted as a synonym for this effort to reduce the level of technologic complexity to the existing level of poverty, illiteracy, and underschooling of tropical community settings. The syllogism became "complex societies, complex solutions; simple societies, simple solutions." Soon, however, it dawned on many of us in the human biology community that these quick-and-dirty solutions tended more to institutionalize the extant underdevelopment than to advance the societies. Scrimshaw (1) expressed his view on the topic as follows: "Whatever technology is economically, socially and politically feasible as well as effective for relieving malnutrition in developing countries is 'appropriate,' regardless of the degree of sophistication or lack of it."

Isotope-dilution tests are a domain from which research donors often shy away. Such donors need to heed the words of another prophet of our community, the late James Allen Olson (2, 3), who editorialized in these pages the need to move this technology to appropriate venues, including developing countries. This admonition was taken seriously by a consortium of investigators (4), who in this issue of the Journal introduce us to the concept of bioefficacy. This multiinstitutional collaborative team used isotope-dilution tests to examine the thorny problem of the extent of bioconversion of provitamin A carotenoids in Indonesian children.

It seems appropriate that bringing isotope technology to Third World problems for which it is needed should mobilize international collaboration, bridging South and North. In early instances of isotopic studies related to vitamin A status, the University of California joined with the International Diarrhoeal Disease Research Centre–Bangladesh (5), and our 2, respective institutions in Boston and in Guatemala combined their respective comparative advantages (6). van Lieshout et al (4) have extended this collaborative model. The academic home of the present study was Wageningen University, Wageningen, and University Medical Center, Nijmegen, Netherlands. Field operations in a setting conducive to exploring vitamin A nutriture questions were based at the Nutrition Research and Development Centre in the West Javanese city of Bogor, Indonesia. Synthesis of the specific isotope-labeled β-carotene was the contribution of the Leiden Institute of Chemistry (Leiden, Netherlands), and the analysis of the isomerization and the gas chromatography–mass spectrometry were conducted at the College of Pharmacy at the University of Illinois at Chicago.

With the publication of this study, we see the inauguration of a new and useful term: *bioefficacy*. This is defined as the amount of ingested provitamin required to yield 1 μg retinol to the body. This is similar to an expression used by Tang et al (7) in relating the amount of synthetic, octodeuterated β-carotene needed to yield 1 mg retinol in an early, single-dose human experiment. To measure the bioefficacy of β-carotene in Indonesia, van Lieshout et al fed 35 children (aged 8–11 y) 2 capsules daily containing 80 μg [$^{13}C_{10}$]β-carotene in oil and 80 μg [$^{13}C_{10}$]retinyl palmitate in oil for ≤10 wk to reach a plateau in isotope enrichment. Three blood samples were drawn from each child over this period and HPLC coupled to atmospheric pressure chemical ionization liquid chromatography–mass spectrometry was used to measure the isotope enrichment in serum of *1*) [$^{13}C_5$]retinol (derived from the labeled β-carotene), *2*) [$^{13}C_{10}$]retinol (derived from the isotope-labeled retinyl palmitate), and *3*) intact [$^{13}C_{10}$]β-carotene. The amount of β-carotene dissolved in oil required to form 1 μg retinol was found to be 2.4 μg, which is superior to the 1 μg retinol from 3.3 μg β-carotene previously estimated. Note, however, that although the [$^{13}C_{10}$]β-carotene used in this study was synthesized for administration in the *all-trans* configuration, extensive *cis* isomerization of the labeled carotenoid occurred. The β-carotene finally contained in the capsules had a *cis-trans* ratio of 3:1. It is likely that the amount of *all-trans*-β-carotene required to form 1 μg retinol would be <2.4 μg, but it would be important to confirm this because fruit and vegetable β-carotene is in the *all-trans* form. The authors speculate that *cis* isomerization probably occurred during the preparation of the capsules, but we are left with no clue as to when or why such a large amount of isomerization occurred.

The advantage of the plateau method used by the authors is that it requires a limited number of blood samples to derive the conversion factors. Although the chosen approach is useful for the bioefficacy expression, it produces little of the information on the kinetics of β-carotene absorption and conversion that single-dose, multiple-blood-sample, mathematical models would provide. The investigators used $^{13}C$-labeled β-carotene and retinol.

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The liquid chromatography–mass spectrometry method used was recently described by Wang et al (8), of the same collaborative team, who showed that it could be used to quantify β-carotene bioconversion to retinol when given in physiologic doses, ie, doses that would not alter the circulating concentrations of the compounds.

Deuterium-labeled compounds have also been used to study the bioefficacy of β-carotene (7). The present group of investigators questioned whether deuteration of β-carotene might not change the physicochemical properties of the molecule, pointing out that the retention time (80 min) of deuterated β-carotene on a 2-column series HPLC system is different from that of unlabeled β-carotene (9). However, whether such surface affinity differences in a chemical environment have any relevance to in vivo biological properties is not known. They also raise questions as to whether migration of the deuterium within the β-carotene molecule could occur; however, such scrambling (if it exists) would make no difference as long as the mass spectrometer data processing method measured all labeled molecules (that is, if all labeled molecules were subsequently counted and fractionated into the enrichment calculation equations). Such questions about deuterium compared with $^{13}C$ labeling are important in studies of the bioefficacy of intrinsically labeled carotenes in a plant matrix because cost becomes a factor favoring deuterium labeling (plants labeled via deuterated water) over carbon labeling, which would have to be done in a closed chamber with $^{13}CO_2$.

The efforts of van Lieshout et al serve us beyond being a model of appropriate development and technology and of creative collaboration. They reach to the core of a thorny scientific and policy problem: namely, what is an appropriate conversion factor to apply to provitamin A compounds in predicting the formation of active vitamin A in humans? With regard to the ethical advocacy of one or another intervention program for alleviating hypovitaminosis A in a population in which it is endemic, it is important not to overestimate the expected effect or to rely on means that will fail to deliver the needed results (10). Some observers are optimistic that current evidence supports a high potential for plant-based vitamin A sources to correct vitamin A deficiency (11), whereas others looking at the same literature are much more skeptical (10). Approaches such as used in the Bogor-based study promise substantial advances in this domain. First, the authors illustrate a wide variation in the bioconversion of β-carotene in oil from individual to individual; this almost certainly occurs with plant matrices as well. Then, they leave us with a rational approach that could eventually apply the bioefficacy principle to studies of provitamin A in actual fruit and vegetables. With such studies, we should be able to get solid answers regarding the true bioefficacy of the most widely relied on plant sources, such as carrots and dark-green leafy vegetables. In another policy area, however, these studies seem to support the promise (12) that high doses of β-carotene in oil could aptly substitute for the present schedules of preformed vitamin A (retinyl palmitate) in capsules for prophylactic supplementation (13) with little risk of adverse consequences or toxicity for infants, pregnant women, or lactating mothers (and no risk of accidental intoxication).

It is a welcome and refreshing development that the wisdom to separate the level of technical sophistication from the definition of what is an appropriate technology for use in developing societies continues apace. The problems afflicting populations of low-income countries merit solutions. It does us well to remember the words of Olson (2): "Further uses of labeled tracers both in determining endogenous reserves of nutrients as well as in quantitating rate processes in human[s] are clearly a wave of the future in human nutrition." van Lieshout et al have produced a model of how North-South collaborations on the use of stable isotopes can address vital, contemporary problems of public health. Olson's predicted future has become our working present, and the results from Indonesia have taken us a league down the road of promise for field application of isotope dilution in human vitamin A research.

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