used in doses ≤ 150 mg/d. Reports of studies on photosensitive patients list yellowing of the skin and transient gastrointestinal symptoms as the most-common side effects of carotenoid treatment. As Herbert stated, there have been several reports of retinopathy from canthaxanthin ingestion, but this problem seems to be reversible with time if canthaxanthin intake is stopped (3, 4). Retinopathy does not seem to occur in patients taking β-carotene alone (5). There have also been isolated reports of other side effects. However, in these reports it has not been definitely established whether the side effects were due to the carotenoid ingested or to a component of the vehicle used in the carotenoid preparations. In fact, in the case of aplastic anemia associated with canthaxanthin suntan-pill mentioned by Herbert (6), which appeared the same week as did my article with which he takes issue (7), the authors are careful to point out that definite evidence is lacking for the role of canthaxanthin as a cause of the patient’s aplastic anemia: this caution is well taken, because the composition of the pills as to vehicle or even dose of canthaxanthin was not known. Unfortunately, in this particular case, the patient refused transfusions, so we will never really know whether she could have survived her illness. I think it is not imprudent to say that the safety record of β-carotene, and even of canthaxanthin, in the treatment of photosensitivity diseases has been quite good.

However, despite the above data, it must be emphasized that those who wish to sell carotenoids for a new use have an obligation to perform the studies required by the FDA to demonstrate safety and efficacy. I strongly urge the FDA to vigorously enforce their ban on the sale of suntan pills until the involved sellers of these products have completed the required studies: I also reiterate my statement to Fenner (1): “I would warn people not to take tanning pills until appropriate well-controlled studies are done on canthaxanthin, until we are sure there is no long-term toxicity.”

Micheline M Mathews-Roth

Channing Laboratory
180 Longwood Avenue
Boston, MA 02115

References

Human requirements for riboflavin

Dear Sir:

The recent article by Campbell et al (1) has provided some impressive and useful new data, documenting the wide range of regional riboflavin intakes and status values in different parts of China and demonstrating the robustness of the glutathione-reductase index. We are somewhat less happy, however, with their conclusion that “riboflavin allowances are set too high, both in China and in Western countries,” for the following reasons:

It is not clear to what extent clinical signs of deficiency have been sought by Campbell’s group, and been shown to be absent, in those parts of China where they found riboflavin intakes to be very low. At the start of some nutrition-intervention studies in Henan Province, China, we likewise observed very few oral signs of riboflavin deficiency in the adults (2) but unpublished observations in a class of 6–12-y school children, at that time and in the same community, showed half to have angular stomatitis. Likewise in Thailand, where we monitored riboflavin status in preschool children in two villages over 2 y, the appearance of angular stomatitis was correlated to some extent with inadequate dietary riboflavin, but the children with clinical signs were only 5% of those with biochemical deficiency; we rarely saw evidence of lesions in the adults (3). Clinical signs that responded to riboflavin supplements have been regularly seen in The Gambia in subjects whose intakes were near the lower end of the range reported in Campbell et al’s study (4, 5). They were, however, very variable with season and between different population groups within the same community, which was not the case for riboflavin intakes nor for the glutathione-reductase test values. We believe that because clinical signs are somewhat nonspecific and are influenced by local infection, they need to be verified by a specific response to prolonged riboflavin supplementation. The clinical signs that are classically associated with riboflavin status are lesions of the perioral cavity: typically, angular stomatitis and cheilosis. Like dental caries, these signs may reflect the particular environment within the mouth of the growing child, who is developing and expanding an immune defense system with each exposure to a new infection. Riboflavin is important for the regeneration of reduced glutathione, an important component of both the preventive and radical-quenching antioxidant defense systems of the tissues and the immune system (6). This defense may be more vulnerable in the riboflavin-deficient, growing child than in the adult.

Because the procedure for estimation of mean per caput intakes in Campbell et al’s study included children aged as young as 2 y, it is not clear from their paper how many adult subjects in China obtain as little as the lowest mean daily intakes shown in Table 2. It is also not clear whether the authors accounted for riboflavin losses that occur when food is preserved for winter consumption. Vegetables, an important source of riboflavin, are commonly preserved by drying in the sun, and this practice may
account for the seasonal variation in riboflavin status that we observed in China (7). Our main worry is whether the absence of overt clinical-deficiency signs equates with adequate status. It seems unlikely that clinical deficiency is the most sensitive index of impaired function. There are indications that functional abnormalities may occur in human subjects with reduced riboflavin stores but without any clinical deficiency signs. Thus, impaired function was reported by Sterner and Price (8) during an experimental depletion study in which no clinical abnormality could be detected (9), and a recent study from Hyderabad described an extensive functional improvement (in hand steadiness) after riboflavin supplementation in a population whose clinical deficiency signs were comparatively infrequent and whose clinical response to the supplement was relatively unimpressive (10). Gambian subjects given riboflavin supplements showed improvement in iron utilization in the absence of clinical-deficiency signs (5). Although these examples do not provide absolute proof, they do suggest that functional abnormalities may occur in the absence of clinical signs and that allowances need to be set sufficiently high to correct them.

CJ Bates
DI Thurnham

Medical Research Council
Dunn Nutritional Laboratory
Milton Road
Cambridge CB4 1XJ
United Kingdom

Reply to CJ Bates and DI Thurnham

Dear Sir:

We are less sanguine than Bates and Thurnham on their ready acceptance of the evidence in support of the recommended dietary allowance (RDA) for riboflavin. We have attempted to review virtually all of their previous work but will limit our comments to the citations in their communication.

In an earlier study of two villages in Thailand (1), Bates and Thurnham claim that “the appearance of angular stomatitis was correlated to some extent with inadequate dietary riboflavin” ; however we found no evidence for this observation in the original report. Mean riboflavin consumption in the village with the twofold greater prevalence of stomatitis in children was 0.22 ± 0.11 mg/1000 kcal whereas mean consumption in the second village was 0.20 ± 0.10 mg/1000 kcal. Rather surprisingly, mean erythrocyte glutathione reductase activity coefficient (EGRACs) over a 14-m period ranged from 1.05 to 1.25, indicating riboflavin adequacy, not deficiency; also, a “poor correlation . . . was found to exist between angular stomatitis and biochemical ariboflavinosis.”

Bates and Thurnham state that clinical signs “that responded to riboflavin supplements have been regularly seen in The Gambia,” but we are not so convinced of the specificity of this association, at least in the cited reports (2, 3). Furthermore the data are much too limited for estimation of an RDA for riboflavin. The subjects investigated (2) were pregnant and lactating women who likely have higher requirements; in addition, supplemenation comprised a locally baked biscuit (~430 kcal/d) and a tea drink that raised the intake not only of riboflavin but also of most other nutrients near to the recommended amounts (4). Thus this investigation neither tested uncomplicated riboflavin depletion-repletion effects nor included nonpregnant, nonlactating subjects. It also should be noted that in the original publication (2) it was stated that “no clear-cut association between clinical signs and the highest (EGRAC) values could be detected.” The authors also were puzzled by the paradox that the routine deterioration of riboflavin status (ie, higher EGRAC values) during pregnancy subsequently recovered during lactation—without riboflavin supplementation. The second reference on the Gambian studies cited by Bates and Thurnham was a commentary (3) that contained no original data; the papers cited therein do not include evidence showing that riboflavin-deficiency symptoms were specifically reversible by graded doses of riboflavin intake.

We share the concern of Bates and Thurnham that the RDA for riboflavin should include an allowance for putative physiological dysfunctions, which may occur at intakes higher than those required for clinical deficiency symptoms, but we are not convinced that the data of Sterner and Price (5) demonstrated this point as Bates and Thurnham assert. Although Bates and Thurnham suggested that “no clinical abnormality could be detected” in the study by Sterner and Price (5), it should be noted that none was sought. Although Sterner and Price reported significant alterations of five personality traits in six adult males during severe riboflavin deficiency, these

References