studies that showed a reduced reactivity of human peripheral lymphocytes after either in vitro or in vivo exposure to Intralipid or another lipid emulsion composed of long-chain fatty acids (8–10). Thus, we believe that evidence of a role for long-chain fatty acids in the modulation of T cell function is accumulating. Whether this effect and the proposed mechanisms we showed in our study are relevant in pathophysiological states in humans clearly needs more investigation.

Our report did not address the potential role of a selective elevation of plasma linoleate concentrations on the function of circulating monocytes and neutrophils. Neutrophils and monocytes may behave very differently in response to fatty acids than do T lymphocytes. Thus, we agree with Wanten that the effect of long-chain fatty acids shown in one class of white blood cells cannot be extrapolated to other such classes and that more studies are needed to integrate the multiple potential effects of long-chain fatty acids on the immune system in healthy and pathophysiologic states in humans.

The authors had no conflict of interest.

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Effect of nutritional manipulation on brain function: implications for future research

Dear Sir:

I am writing about the recently published review by McCann and Ames (1). This review addresses the behavioral effects of n−3 fatty acids in humans and animals. The authors are to be commended on their thoroughness in researching the extensive literature on this topic and in invoking the necessary methodologic considerations when evaluating the outcomes of studies conducted in both animals and humans. In their discussion of the various behavioral studies included in this review, they raise an important issue—that different neural systems might be affected differently by nutritional manipulations, and, thus, some outcomes might be more sensitive indicators than others with respect to the role of a particular nutrient. From my perspective as a behavioral scientist who works with rodents, I would like to expand on this observation and explore the implications for future research.

Although the terms cognitive and behavioral are often used freely in relation to nutritional interventions, what is meant by these terms is not always defined precisely. Thus, whereas both the human and animal literature encompass a diverse array of behavioral outcomes, there is often little discussion of exactly which specific psychological construct is being measured by each test and how this relates to overall cognitive function. This is despite an accumulation of evidence in both humans and animals during the past 15–20 y that supports the hypothesis that the brain comprises multiple memory systems, each anatomically and biochemically distinct and each processing information in a specialized way (2). On the basis of behavioral dissociations in studies using lesions in rats, 3 independent systems have been identified: 1) flexible use of knowledge involving the hippocampus, 2) habitual responses (reinforced stimulus-response associations) involving the dorsal striatum, and 3) emotional responses (Pavlovian stimulus—affect conditioning) involving the amygdala. In most situations, these systems operate in parallel, and, depending on the circumstances, interact either competitively or cooperatively. For example, depending on the protocol, different types of learning, either cognitive or stimulus-response, can occur in the place version of the Morris water maze. If the start position is varied over trials, the animal is required to use spatial information flexibly, whereas if the start position remains the same, the animal can use the response system, eg, swim 45 degrees left. What is important to note, however, is that when one system is damaged, performance will be impaired on tasks associated with the function of that particular system, but very often enhanced on the tasks associated with the other. For example, animals with hippocampal damage often perform better than do control animals on stimulus-response type learning tasks. Thus, it is entirely possible for an intervention that improves one type of memory to have deleterious effects on another type of memory or to have effects on other measures, such as arousal, that affect task performance.

In summary, the point being made herein is that broad terms such as cognition need to be carefully operationalized and then tested by...
using a comprehensive approach based on a broad battery of valid and reliable neuropsychological tests before conclusions can be drawn as to which of the myriad aspects of brain function are affected by a particular nutritional manipulation. Only then will we be in a position to make fully informed population-based recommendations with respect to dietary interventions.

The author had no conflict of interest in relation to this letter.

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REFERENCES

Reply to P Wainwright

Dear Sir:

We thank Wainwright for her kind words about our review on the n−3 long-chain polyunsaturated fatty acid (LCPUFA) docosahexaenoic acid (DHA) (1). Our review was the first in a series of articles intended for nonspecialists that summarize evidence for causal relations between micronutrient deficiencies during development and brain function. A review on choline will appear in early 2006 (2).

Wainwright raises an important point about the need for scientific precision in assigning results of behavioral tests to specific cognitive functions. We concur with most of her comments and would like to add some additional observations regarding the relevance of results obtained in these tests to public health decision making. Wainwright concludes her letter with the following 2 sentences: “In summary, the point being made herein is that broad terms such as cognition need to be carefully operationalized and then used by employing a comprehensive approach based on a broad battery of valid and reliable neuropsychological tests before conclusions can be drawn as to which of the myriad aspects of brain function are affected by a particular nutritional manipulation. Only then will we be in a position to make fully informed population-based recommendations with respect to dietary interventions.”

Regarding whether the addition of DHA (in combination with AA) to infant formula should be recommended, we believe that the level of precision required is far less than that implied by Wainwright. As many others have noted, and as we summarized in our review (1), several scientific observations regarding DHA and human infants are well established:

1) DHA is present in relatively large amounts in the human brain and retina but not in most other tissues.
2) DHA is naturally present in breast milk, accretes in the brain during perinatal growth, and is maternally supplied.
3) Breastfed infants have significantly higher brain concentrations of DHA than do formula-fed infants.
4) Preterm infants are born with significantly less DHA in their brains than are term infants because significant accretion occurs in the last trimester of pregnancy.

These observations have been clearly established. In addition, DHA-containing formula supplements were granted Generally Recognized As Safe (GRAS) status by the Food and Drug Administration in 2002, are recommended for use by regulatory and advisory bodies in other countries, are widely used in Europe and Asia, and are increasingly present on grocery store shelves in the United States. Despite these facts, organizations such as the American Academy of Pediatrics (AAP), the primary source of pediatric medical practice guidelines and policy in the United States, and UpToDate.com, a widely used medical advice service for doctors, have not supported the addition of LCPUFAs to infant formula (3, 4). The AAP states that they have “no official position” on supplementation, and the most recent advice from UpToDate.com concludes that “additional studies will be needed to prove benefits of LCPUFA as well as provide guidelines for supplementation.”

Our reading of the statements from both of these organizations suggests that a significant reason for their hesitation in recommending the addition of DHA to infant formula is the lack of proof of efficacy as measured by randomized controlled trials (RCTs) that compare performance on standardized tests, such as the Bayley Scales of Infant Development, of LCPUFA-supplemented or -unsupplemented formula-fed children. However, as we point out in our review (1), the mixed, but substantially negative, findings of these RCTs are not particularly surprising. Many studies reproducibly demonstrate poorer performance in cognitive and behavioral tests of rodent and primate offspring whose brains have been depleted of DHA by up to 80% of normal concentrations. However, though clearly significant, performance deficits are modest. In our opinion, these observations strongly suggest that smaller differences in brain concentrations of DHA, such as almost certainly occur between infants fed supplemented and unsupplemented formulas, may result in more subtle but still significant effects on brain function that are difficult to detect with the use of current methods. Therefore, we do not believe that the scientific evidence taken as a whole justifies the need to demonstrate performance differences in RCTs before a judgment can be made about whether to recommend the addition of LCPUFAs to infant formula.

If safety is not an issue, and it seems that there is now considerable evidence that toxicity is not a significant concern (5), why should the addition of LCPUFAs to infant formula not be encouraged? Surely DHA has an important function in the developing brain or there would not be so much of it there. This is common sense. Why should infants be deprived of this substance during a critical period of brain development because of a lack of scientific certainty in establishing a causal link to poor performance on cognitive and behavioral tests in RCTs, which are expected to have limited sensitivity?

Important scientific questions regarding the function of DHA in the brain clearly need to be resolved, and there is a need to develop more sensitive and more precise measures of effects on different neural systems, as Wainwright points out. However, this level of scientific precision may take many years to achieve. On the basis of our review of the literature (1), and as we point out in this letter, the currently available scientific evidence (taken as a whole) strongly...