

What might be the benefits to the population as a whole of delaying infection and disease? Some experts have predicted that the effect of the introduction of a partly protective vaccine will be reduction in morbidity and mortality in the first years of life, with negligible effect on transmission.¹⁰ Data from phase III trials, scheduled to begin in multiple African sites in 2008, will be crucial for determination of the public-health usefulness of the vaccine. Pending licensure, decisions will need to be made about whether or not this vaccine should be used widely and, if so, how best to incorporate it with existing control measures, such as insecticide-treated bednets and early diagnosis and treatment of malaria.

Finally, what do these results mean to the mother who brings her young child to a clinic in sub-Saharan Africa, or to the policymaker who is deciding what malaria controls to use when funds are limited? We can tell them that we are indeed closer to having a vaccine for malaria which might reduce morbidity and mortality. Nevertheless, the malaria-vaccine community must continue efforts to develop an even more efficacious candidate vaccine; ideally, a vaccine that can one day prevent every child from ever having or dying from this disease. Dedicated investigators worldwide are pursuing numerous approaches, including prime-boost and adenovirus-vectored vaccines. A radiation-attenuated sporozoite vaccine is expected to undergo initial testing in human beings in 2008.¹¹ The next 5–10 years will probably be the most exciting in the long journey to bring a malaria vaccine to the developing world.

Judith E Epstein

US Military Malaria Vaccine Program, Naval Medical Research Center, Silver Spring, MD 20910, USA
judith.epstein@med.navy.mil

I thank Peter G Smith, London School of Hygiene and Tropical Medicine, London, UK, for helpful discussions and comments. I am in military service and prepared this Comment as part of my duties. The views in this Comment are mine and do not necessarily reflect the official policy or position of the US Department of the Navy, Department of Defense, or Government.

- 1 Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. *Lancet* 2007; **370**: 1543–51.
- 2 Gordon DM, McGovern TW, Krzych U, et al. Safety, immunogenicity, and efficacy of a recombinantly produced *Plasmodium falciparum* circumsporozoite protein-hepatitis B surface antigen subunit vaccine. *J Infect Dis* 1995; **171**: 1576–85.
- 3 Stoute JA, Slaoui M, Heppner DG, for the RTS,S Malaria Vaccine Evaluation Group. A preliminary evaluation of a recombinant circumsporozoite protein vaccine against *Plasmodium falciparum* malaria. *N Engl J Med* 1997; **336**: 86–91.
- 4 Kester KE, McKinney DA, Tornieporth N, et al. Efficacy of recombinant circumsporozoite protein vaccine regimens against experimental *Plasmodium falciparum* malaria. *J Infect Dis* 2001; **183**: 640–47.
- 5 Bojang KA, Milligan PJ, Pinder M, et al. Efficacy of RTS,S/AS02A malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial. *Lancet* 2001; **358**: 1927–34.
- 6 Alonso PL, Sacarlal J, Aponte JJ, et al. Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial. *Lancet* 2004; **364**: 1411–20.
- 7 Alonso PL, Sacarlal J, Aponte JJ, et al. Duration of protection with RTS,S/AS02A malaria vaccine in prevention of *Plasmodium falciparum* disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. *Lancet* 2005; **366**: 2012–18.
- 8 Young JF, Hockmeyer WT, Gross M, et al. Expression of *Plasmodium falciparum* circumsporozoite proteins in *Escherichia coli* for potential use in a human malaria vaccine. *Science* 1985; **228**: 958–62.
- 9 Ballou WR, Hoffman SL, Sherwood JA, et al. Safety and efficacy of a recombinant DNA *Plasmodium falciparum* sporozoite vaccine. *Lancet* 1987; **1**: 1277–81.
- 10 Maire N, Tediosi F, Ross A, et al. Predictions of the epidemiologic impact of introducing a pre-erythrocytic vaccine into the expanded program on immunization in sub-Saharan Africa. *Am J Trop Med Hyg* 2006; **75**: 111–18.
- 11 Luke TC, Hoffman SL. Rationale and plans for developing a non-replicating, metabolically active, radiation-attenuated *Plasmodium falciparum* sporozoite vaccine. *J Exp Biol* 2003; **206**: 3803–08.

Food colourings, preservatives, and hyperactivity

See [Articles](#) page 1560

Quod ali cibis est aliis fuit acre venenum (What is food to one, is bitter poison to others) is attributed to Lucretius (99–55 BC), and the sentiment could well express serious manifestations of hypersensitivity to food. In ancient times, when eating was a major challenge for survival, the perception of adverse reactions to nutrients was probably very different from nowadays. Today, in affluent parts of the world, adverse reactions to food can be divided into two categories: one being what is perceived as related to food but is only disrupting daily life; the other potentially leading to severe illness, such as IgE-mediated food allergy.

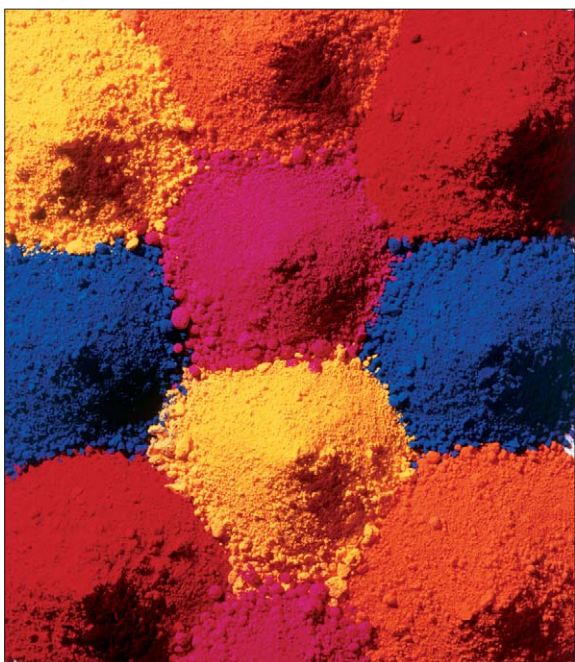
Feingold's report on hyperkinesis and learning disabilities associated with artificial food flavours and colours, published in the 1970s,¹ fuelled a large debate and can be attributed to the first category of adverse reactions to food mentioned above. The few prospective studies published afterwards have been summarised in a meta-analysis.² The study in 2004 by Bateman and colleagues³ generated several comments, including one in *The Lancet*.⁴ Bateman recruited a sample of 3-year-old children from the general population. A subgroup completed an investigation that included skin-prick tests for allergy and double-blind placebo-controlled

food challenges, as well as an assessment for hyperactive behaviour. This study revealed a discrepancy between objective behavioural testing by health professionals, which showed no influence of food colouring and additives, and subjective observations of hyperactivity by parents in the group of children getting food colouring and additives. But several questions remained open after careful analysis, because the study emphasised the subjective impression of food-related hyperkinesia but did not provide clear evidence to the professional that foods need to be considered in the assessment of the possible causes of hyperkinesia.

The same group of investigators started a new study, which is published by Donna McCann and colleagues in today's *Lancet*.⁵ In addition to 3-year-old children, a second group of 8–9-year-old children from a general population were studied. Children with hyperactivity were identified and tested with a mixture of food colourings and additives that corresponded to an average daily intake during 1-week crossover challenge periods. Various measures of behaviour by health professionals, parents, or teachers were the primary outcome measures. The study showed statistically significant differences in hyperactivity scores when the children were on or off food colourings and additives, as shown by increased hyperactivity scores in both age groups. Interestingly, the authors reported "substantial individual differences in the response of children to the additives". This observation corresponds to the clinical observation of high sensitivity to food colouring and additives in some hyperactive children, and unresponsiveness in others. The researchers are currently characterising these subgroups.

McCann and colleagues did not address intra-individual differences over time, but one might speculate that some children have periods of hyperexcitability that correlate with increased sensitivity to food colouring and additives. This idea raises the question of the amount of food containing colourings and additives that can reasonably be eaten by children.

Overall, McCann and colleagues have shown that 3-year-old and 8–9-year-old children might have signs of hyperactivity when on a diet containing usual amounts of colouring and additives. What practical implications does this have for the community? Physicians taking care of children with hyperactivity could advise parents who wish to do so to start an elimination trial of artificial colourings and additives. Complete restriction is not



Science Photo Library

warranted according to McCann's results. Only some hyperactive children will respond favourably to such a trial, and further research might highlight subgroups of individuals particularly susceptible to colouring and additives. Elimination measures should then focus on these children.

Artificial colourings and additives represent only one aspect of hyperactivity in children. Efforts from health professionals and parents should also focus on adequate drug treatment and psychological measures, and relevant guidelines remain valid.⁶

*Philippe A Eigenmann, Charles A Haenggeli

Children's University Hospital, 1211 Geneva, Switzerland

Philippe.Eigenmann@hcuge.ch

We declare that we have no conflict of interest.

- 1 Feingold BF. Hyperkinesia and learning disabilities linked to artificial food flavors and colors. *Am J Nurs* 1975; **75**: 797–803.
- 2 Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr* 2004; **25**: 423–34.
- 3 Bateman B, Warner JO, Hutchinson E, et al. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Arch Dis Child* 2004; **89**: 506–11.
- 4 Eigenmann PA, Haenggeli CA. Food colourings and preservatives—allergy and hyperactivity. *Lancet* 2004; **364**: 823–24.
- 5 McCann D, Barrett A, Cooper A, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007; **370**: 1560–67.
- 6 Brown RT, Amler RW, Freeman WS, et al. Treatment of attention-deficit/hyperactivity disorder: overview of the evidence. *Pediatrics* 2005; **115**: e749–57.