Letters to the Editor

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Letters should be submitted in duplicate in double-spaced typing on plain white paper with name and address of sender(s) on the letter. Send them to Jerold F. Lucey, MD, Editor, Pediatrics Editorial Office, Fletcher Allen Health Care, Burlington, VT 05401.

Mantoux Test in Kawasaki Disease

To the Editor.—

Localized erythema at the site of a previous bacillus Calmette-Guérin (BCG) inoculation is a relatively specific and early manifestation of Kawasaki disease (KD),[1] and redness and crusting are characteristic features at the site of BCG immunization during the acute phase of the illness.[2] With these findings in mind, we evaluated the tuberculin skin test reactivity of children with KD, as determined by a commercially available (Sclavo, Siena, Italy) and intradermally injected (5 TU) purified protein derivative (PPD). Eight children, 5 female and 3 male, between 1 and 3 years of age who met the diagnostic criteria for KD established by the Japanese Kawasaki Disease Research Committee were examined. These children had not been vaccinated with BCG, nor did they have a history of exposure to tuberculosis. The Mantoux test was performed during the acute phase of the disease, after intravenous gamma globulin administration, and then 1 and 2 months later. None of the patients developed coronary arteritis in the follow-up study. Redness, induration, and crusting at the site of PPD inoculation were a common feature in all children tested. In contrast, a positive tuberculin reaction was never observed in pediatric patients with Epstein-Barr virus-induced infectious mononucleosis (n = 8), scarlet fever (n = 6), exanthem subitum (n = 8), measles (n = 3), viral syndromes associated with fever and rash (n = 14), or erythema multiforme minor (n = 3). Three KD children were still weakly tuberculin-positive when sampled during convalescence, 1 month after onset of symptoms. However, the cutaneous sensitivity to intermediate strength PPD inoculation had completely disappeared by the 2-month control. In accordance with these findings, the in vitro proliferative response of circulating KD T lymphocytes to PPD stimulation (0.5 TU/mL) was significantly higher in the acute than in convalescent patients (37.300 ± 1.700 vs 3.400 ± 650; values expressed as mean ± SD of net cpm ^{3}H-thymidine uptake after 3 days of culture; $P < .001$ by one-way Kruskall-Wallis analysis of variance).

It is generally recognized that activated immune system cells play a pivotal role in determining the multisystem vasculitis subjects with KD. Although KD occurs worldwide in children of all racial groups, with a clear prevalence in those of Japanese ancestry, its etiology remains unknown. It has been postulated that superantigens are implicated in the disease process,[3-5] but not all experimental data supports this proposal.[6-8] There is also mounting laboratory evidence that autoimmune responses directed against self-epitopes shared by mycobacterial heat shock protein (HSP) 65 and its human homolog HSP63 protein may be the most potent factor predisposing to KD.[1] The detection of a strong antibody and cellular reactivity against mycobacterial HSP65 and its human P1 cognate antigen in the blood of KD children[9] agrees well with this hypothesis. Sensitivity to tuberculin in KD could, perhaps, be viewed against the background of these related findings and PPD skin testing could prove a valid diagnostic aid for identifying so-called atypical KD[10-12] in children who have not received BCG vaccination.

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Treatment of Lead-exposed Children

To the Editor.—

I am writing in response to the recommendations in the statement "Treatment Guidelines for Lead Exposure in Children," by the Committee on Drugs, reported in the July 1995 issue of *Pediatrics.* The Committee did an admirable job in reviewing the various aspects of treating lead poisoning; however, there are several points that were made that need to be clarified.

Although no one would argue that treatment is indicated for lead encephalopathy, there have been no studies, to my knowledge, of a double-blind, controlled nature, showing that treatment

of lead poisoning, in the absence of clinical symptoms, is of any use in either reversing any neurologic or developmental abnormalities or, in fact, in prevention of such. To recommend that patients with blood levels between 24 μg/dL to 45 μg/dL should not "routinely receive chelation therapy because no evidence exists that chelation avoids or reverses neurotoxicity" ignores the fact that the same can be said for children with lead levels of 45 μg/dL to 70 μg/dL, in which the Committee is suggesting therapy. I know of no other condition in which the Food and Drug Administration (FDA) has licensed a treatment based *solely* on a cutoff point in a laboratory test. Thus, lead seems to stand out as one peculiar disease with one peculiar therapy for no logical reason. It is interesting to note that, in the discussion of penicillamine, the Committee states "when children were removed from further exposure and treated with penicillamine, the decline in blood lead levels and the reversal of hematologic toxicity were more rapid than the decline in toxicity resulting solely from eliminating the source of lead exposure." This suggests the fact that chelation therapy results in a lower blood lead burden than simply removing the child from the lead exposure.

In basic toxicology we teach that it is not necessarily the peak concentration of an intoxicant that causes problems but it is the time course, or the area under the curve, of the intoxicant that determines toxicity or long-term effects. In the case of lead poisoning, it is assumed that the longer a lead level stays elevated, the longer the lead has the opportunity to reach the sites of toxicity, primarily the brain. Thus, it makes intuitive sense that the more rapidly a lead level drops, the more likely the child is to escape unharmed. Because research has not indicated a level of lead at which there is no form of toxicity in some experimental model, our goal should be to effectively lower lead as rapidly as possible through both aggressive environmental intervention and chelation.

The decision whether to use a chelator or not should depend on the likelihood of compliance with the treatment management and the likelihood that the chelation will cause a rapid drop in total body lead burden without significant side effects experienced by the patient. Of the drugs currently used in chelation, clearly succimer has the safest spectrum of side effects, safe enough to be used in levels below 45 μg/dL despite the FDA's license of treatment in children with lead levels above 45 μg/dL. There have been studies to show that succimer does chelate well at levels below 45 μg/dL, as well as levels above 70 μg/dL, the window that the FDA chose for succimer's use. Thus, it makes little sense to me that we should stand by the lack of double-blind, controlled studies to prove effectiveness. Thus, I do agree with the Committee's statement that if blood lead levels persist in the range of 25 μg/dL to 45 μg/dL despite repeated environmental study and abatement, "some patients may benefit from oral chelation therapy by enhancing lead excretion." It seems to me that this last statement should be bolded, underlined, and scored.

It has never been shown if the decrease in lead over time, when chelation is not used, is attributable to the excretion of lead or the deposition of lead in depots. If one believes the multicompartment model of lead distribution, and one believes that the equilibrium favors the long-term deposition of lead in bone, then one has to assume that most of the drop in blood lead occurs with a coincidental rise in boney lead. This produces an older individual with an elevated "carcass" lead. Bone fractures and immobilization have been reported associated with the apparent liberation of bone lead producing enough elevation in blood lead to require chelation. Animal studies show that pregnancy and lactation release carcass lead and a coincidental elevation in both maternal blood and fetal lead levels. Loss of bone mass with age is also thought to produce a resultant elevation in blood lead levels. Thus, failure to clear lead through enhancement of lead excretion may produce an adult possessing an internal "time bomb."

It amazes me that with lead poisoning we look for "strong evidence" that chelation avoids or reverses neurotoxicity. In very few other conditions do we ask for such rigorous proof before adopting therapy. For over 30 years, antibiotics have been used to treat otitis media with little hard scientific efficacy data. There is currently a debate on whether or not this is correct because there has been no committee report stating that we should withhold such antibiotic therapy. Most pharmaceutical research on drugs is performed to prove efficacy, not to disprove efficacy, and the sole test of the dark side of drugs is looking for acute and chronic toxicology.

Before we withhold therapy with a drug that will clearly rapidly lower circulating blood lead levels, we should ponder for a moment the Tuskegee study, in which therapy that was thought to be effective at that time was purposely withheld from a group of patients simply to prove "scientifically" that therapy will prevent neurotoxicity. It may seem that this is a little strong. However, if you let your mind "blur" for a minute and imagine what it must have been like at the beginning of the Tuskegee study, I'm sure that you could well imagine the similarity between that study and attempting to withhold therapy from children with elevated lead levels.

The FDA approved succimer for treating lead levels of over 45 μg/dL because that was the indication that McNeil asked for. The application was based on succimer as an orphan drug to treat lead poisoning, not on any efficacy data.

It seems to me we are giving very mixed messages regarding lead poisoning. If we really believe that it is the elevated blood lead level that is responsible for neurodevelopmental danger and that chelation lowers this lead, we should not caution against the use of such agents.

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To the Editor.—

We read with interest the carefully updated "Treatment Guidelines for Lead Exposure in Children" issued by the AAP Committee on Drugs.[1] The Committee identifies the major remaining question regarding the role of succimer as the indications for its use in patients with blood lead levels in the range of 25 μg/dL to 44 μg/dL. The Committee also mentions that the National Institute of Environmental Health Sciences is supporting a study on the long-term outcome after treatment with succimer, and strongly endorses participation in current research protocols. The Treatment of Lead-exposed Children (TLC) Trial is supported by the National Institute of Environmental Health Sciences in cooperation with the Office of Research on Minority Health, National Institutes of Health. It is a randomized, placebo-controlled, double-blind trial of succimer chelation in children 12 to 32 months old. All children get residential clean-up and vitamin and mineral supplementation. TLC has four clinical sites in Baltimore, Cincinnati, Newark, and Philadelphia, and plans to randomize more than 1000 children. The outcomes include scores on developmental tests, behavior, and growth 3 years after randomization. We at TLC appreciate the AAP endorsement of participation; we point out that the range of blood lead treated by TLC is 20 μg/dL to 44 μg/dL, rather than 25 μg/dL to 44 μg/dL as mentioned by the Committee. This broader range is consistent with Centers for Disease Control and Prevention guidelines,[2] which call for children to be referred for medical evaluation at 20 μg/dL or higher. In 1989, there were about three times as many 1- to 2-year-old children in the United States with blood leads above 20 μg/dL as there were with blood leads above 25 μg/dL, and twice as many 3- to 5-year-olds.[3] The evidence supports no threshold for the effects of lead on IQ; in fact, lead-induced developmental delay is probably detectable down to blood leads around 10 μg/dL.[4,5]

We also wish to make a technical comment. As we constructed the TLC treatment protocol and estimated the amount of drug we would need, we noted that the Chemet (succimer, McNeil) label gives dose calculations both by body weight and body surface area, but gives a table only for weight. The weight table, however, appeared to be most appropriate for a child about 5 years old. The young children in TLC needed much more drug (in some cases, twice as much) when their doses were calculated on a body-surface-area basis. The evidence for efficacy of the drug was derived from studies that dosed by body surface area, and decrease in blood lead concentration is dose-dependent.[6] We think that the Committee on Drugs should recommend body surface area calculations for this drug.

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In Reply.—

We appreciate the information from Rhoads and Rogan regarding the treatment of lead-exposed children (TLC) trial that will include children down to a blood lead of 20 μg/dL. The issue of thresholds for detectable effects of lead remains controversial and is less relevant in the face of the purpose of this trial: ie, will the benefits of treatment outweigh the risks associated with chelation therapy? This large-scale trial using body surface area will be useful to demonstrate any benefit of that approach over weight-based calculations. The Committee on Drugs felt that difficulty with accuracy in body-surface-area calculations in clinical practice and the potential for mathematical error supported the use of weight-based calculations until new data were derived. We await the findings of this study to give us guidance, both on the issues of effectiveness of treatment and the most appropriate dosing to achieve those results.

Dr Marcus revisits a number of previously discussed issues regarding lead toxicity. We believe the reasons for these "mixed messages" between screening and abatement recommendations and treatment are partly based on the disagreement within the pediatric community over the validity and clinical impact of the much-discussed and seemingly heavily politicized lead research studies. The recommendation of the Committee on Drugs tried to carefully consider the aspects of the controversy surrounding these issues and to offer some concrete suggestions for the clinician. In doing so it was inevitable that some practitioners with strong positions would not completely agree with all the recommendations. Some aspects of these treatment guidelines may not in all respects be scientifically founded and the Committee recognizes this. Clinicians still must use the available data to reach a balanced assessment of risks and benefits. This was the approach of the Committee on Drugs in writing this document.

The Food and Drug Administration's licensure of this compound with an indication based on a single laboratory test is not considered appropriate by many, including Dr Marcus. This point has been made in a previous editorial and was not the basis for the recommendations[1] regarding treatment.

If one ignores the significant methodologic problems of the epidemiologic studies of lead and intelligence, they still show only small effects of lead at these lower blood lead concentrations. It was the opinion of the Committee that the pediatric community has not yet widely accepted these studies as sufficient evidence to divert limited resources into widespread screening programs, abatement, and chelation therapy targeted to this lower exposure range. Given this uncertainty and hesitancy it would not be appropriate for the Committee to suggest treatment of children in these lower concentration ranges without some support from the scientific data other than theoretical issues. Thus, as with anything that is as uncertain and controversial as the blood lead issue has become, it was necessary for the Committee on Drugs to make some decision as to when to treat. The TLC trial supported by the National Institute of Environmental Health Sciences (NIEHS) may provide data to definitively answer this question.

The suggestion, based on the penicillamine data, that "chelation therapy results in a lower blood lead burden than simply removing the child from the lead exposure" misstates the findings of the study that merely addressed rate of decline. An important factor neglected in this discourse regarding chelation therapy is the apparent inability of many public health jurisdictions to effectively deal with terminating the environmental exposure to lead because of scarce fiscal resources. Children are then being treated with chelators while in a contaminated environment. This issue has only been addressed in animal studies.[2]

The Committee on Drugs believes the TLC trial of the NIEHS has a sound ethical basis with an emphasis on environmental and nutritional improvement for both study groups. Clinicians, while awaiting more definitive data on side effects and cost of the use of chelators, can still encourage removal of sources of exposure and improved nutrition, which are the keystones of treatment in any case. Hopefully the study undertaken by NIEHS will give us some guidance on at least one part of the puzzle. We hope that decisions concerning the treatment of lead poisoning will be made on the basis of scientific data.

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"Back to Sleep" Program

To the Editor.—

Both retrospective and risk factor studies[1–5] have shown that infants who sleep in the prone position increase their risk of sudden infant death syndrome (SIDS). These data compelled the American Academy of Pediatrics in 1992 to recommend that parents avoid letting infants sleep in the prone position.[6] Subsequent research demonstrated a drop in both prone sleeping and SIDS.[7–9] These outcomes resulted in a renewal of the recommendation in 1994.[10,11] Recent survey data indicate that pediatricians and family physicians are less likely to recommend the prone position[9–14] and that prone sleeping has decreased from 74% to 58% for infants over 1 month of age.[8–11]

Currently, we are conducting a telephone survey of parents of infants and following the infants until they are 12 months old. The survey concerns feedings, naps, and night wakings, similar to a study carried out with older infants.[15] Data collected thus far on 2- and 4-month-old infants on sleep position seem relevant now.

We recruited subjects from birth announcements in two Michigan counties. Eighty-two percent of this sample had either parents or grandparents listed in telephone directories. Letters were mailed to parents (or grandparents) and the phone survey began at 2 months. Only 9% refused participation, the majority of whom never returned calls left on answering machines after multiple requests. Another 6% of families had moved, did not speak English, or never answered their telephones. This sampling yielded a total of 201 families who agreed to participate (85%).

We asked, "Do you typically put ____ on (his/her) back, side, or stomach when you place (him/her) in (his/her) crib?"