

## Wound Botulism Associated With Black Tar Heroin

*To the Editor.*—Dr Passaro and colleagues<sup>1</sup> may have incorrectly identified the source of *Clostridium botulinum* spores when searching for an explanation of an outbreak of wound botulism (WB) among injecting drug users (IDUs). The authors postulate that the source of the botulism spores is contaminated “black tar” heroin (BTH) injected subcutaneously (“skin-popping”). However, it is possible that the spores come from the soiled skin of IDUs and subsequently get inoculated subcutaneously or intramuscularly during the injecting process.

The number of subcutaneous injections and the amount of BTH injected monthly correlated with the increase of WB cases raises the possibility that the increased number of subcutaneous injections rather than the dose of BTH accounts for the increase in the rate of WB in skin-popping heroin users. However, the authors indicate that there was no significant difference between the rate of adequate skin cleansing in cases compared with controls. It is unlikely that skin preparation will inactivate *C botulinum* spores. In addition, the infrequency of WB among cocaine or amphetamine injectors is not surprising. When injected subcutaneously or intramuscularly, these drugs have significantly reduced psychoactive effects, cause significant pain, and must be injected intravenously to produce the desired effect. On the other hand, heroin produces a significant although attenuated effect when injected intramuscularly. Most long-term heroin users eventually will “skin-pop” or “muscle” as the preferred intravenous route becomes unavailable because of sclerosed veins.

The authors also failed to detect *C botulinum* spores in BTH and state that they were “unable to procure BTH samples large enough to adequately test for *C botulinum*.” This is surprising given the extraordinary amount of heroin available at any given time of day or night in many California cities. Without more direct evidence of the presence of *C botulinum* spores in BTH, their causal interpretation of their data is suspect.

Although the authors correctly address WB as one of the many medical complications of IDUs, they too readily conclude with an implication of the drug itself. We think it is important to look to the role of the underlying living conditions that many drug users endure because of the limited availability of effective drug treatment programs or programs that assist users to inject safely.

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1. Passaro DJ, Werner SB, McGee J, Mac Kenzie WR, Vugia DJ. Wound botulism associated with black tar heroin among injecting drug users. *JAMA*. 1998;279:859-863.

*To the Editor.*—The 1994-1996 outbreak of WB in California has been linked to skin-popping BTH.<sup>1</sup> We consulted with 7 of these patients, 4 of whom had presentations with unilateral cranial nerve findings, considered atypical of classic WB.

**Report of Cases.**—*Case 1.*—A 34-year-old man presented after choking while trying to take his crushed methadone in apple sauce and realizing he could no longer swallow pills. He had 3 days of weakness of his right eye, blurred vision, and

difficulty speaking and swallowing. On examination, he had bilateral eyelid ptosis, with lateral rectus muscle weakness of his left eye greater than his right and decreased strength in his right arm.

*Case 2.*—A 35-year-old woman presented complaining of the inability to purse her lips to smoke cigarettes. This followed 3 days of diplopia and difficulty speaking and swallowing. On examination, she had weakness of the lateral rectus muscle of her left eye, a decreased gag reflex, and trouble lifting her arms.

*Case 3.*—A 49-year-old man presented with respiratory arrest. He could not lift his head or arms but was able to open his eyes. He had dysphagia, dysarthria, and diplopia.

*Case 4.*—A 47-year-old woman (the girlfriend of case 3) presented with dyspnea and respiratory arrest. She was treated with bronchodilators and sent home. The next day she was brought back to the emergency department of a second hospital in respiratory arrest.

*Case 5.*—A 44-year-old man presented with several days of weakness, dyspnea, difficulty speaking and swallowing, and diplopia. On examination, he was unable to abduct his right eye, had difficulty opening his left eye, and had a left facial droop.

*Case 6.*—A 44-year-old man awoke with cross-eye and blurred vision. His speech became slurred and he had difficulty swallowing. He developed progressive descending weakness and increasing respiratory hypoventilation and was intubated on the second hospital day.

*Case 7.*—A 43-year-old man complained of diplopia and dizziness for 3 days. He developed difficulty speaking and was drooling when he talked. He made choking sounds when he tried to swallow. On examination, he had right-sided ptosis and inability to abduct his right eye.

**Comment.**—The common features of these cases is their atypical signs and symptoms of WB. First, many patients had asymmetric findings of unilateral cranial nerve weakness and peripheral motor weakness. Second, not all wounds appeared clinically infected. The 2 patients (cases 5 and 7) with wounds that appeared infected were given antibiotic therapy, but their neurologic symptoms progressed. Third, treatment with botulism antitoxin was delayed (60 days) in all these cases, while other diagnoses were considered. A false-positive edrophonium challenge test result led to the diagnosis of myasthenia gravis and Eaton-Lambert syndrome in 2 patients. These misdiagnoses have occurred in previous cases.<sup>2-5</sup> Fourth, of the 6 patients who developed respiratory insufficiency, all had pro-

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Edited by Margaret A. Winker, MD, Senior Editor, and Phil B. Fontanarosa, MD, Senior Editor.

longed ventilator dependent courses (ranging from 32-90 days), despite receiving antitoxin. Finally, all patients were continuing to use tar heroin, despite being in methadone programs, and were suspected of malingering or having drug-seeking behavior. Only after it became apparent that a local cluster of cases of WB was occurring did physicians' sensitivity to the possible diagnosis become heightened.

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1. Passaro DJ, Werner SB, McGee J, MacKenzie WR, Vugia DJ. Wound botulism associated with black tar heroin among injecting drug users. *JAMA*. 1998;279:859-863.
2. Centers for Disease Control and Prevention. Wound botulism—California, 1995. *MMWR Morb Mortal Wkly Rep*. 1995;44:889-892.
3. Swedberg J, Wendel TH, Deiss F. Wound botulism. *West J Med*. 1987;147:335-338.
4. Rapoport S, Watkins PB. Descending paralysis resulting from occult wound botulism. *Ann Neurol*. 1984;16:359-361.
5. Mac Donald KL, Rutherford GW, Frelman SM, et al. Botulism and botulism-like illness in chronic drug abusers. *Ann Intern Med*. 1985;102:616-618.

*In Reply.*—We used several lines of reasoning to conclude that contamination by *C botulinum* spores occurs when heroin is “cut” during distribution within California. First, proper skin cleansing should reduce the number of *C botulinum* spores on the skin, and our finding that skin cleansing did not prevent WB is evidence that skin is not the source of spores. Dr Bamberger and Mr Terplan imply that the primary reason skin cleansing is performed before drugs are injected is to inactivate microorganisms. However, unless prolonged skin preparation is undertaken, the primary aim of skin cleansing is to mechanically remove bacteria. Brief contact with soap or alcohol is helpful because it promotes solubilization of skin oils and the removal of contaminants.<sup>1</sup>

Second, we know of no evidence from our study or from the literature that suggests skin hygiene of IDUs has worsened in the acquired immunodeficiency syndrome era; it seems unlikely that the increase in WB is because of a decline in hygiene during the same period. In addition, nearly every case of WB has occurred in California. Postulating a decrease in skin cleansing only among California IDUs—and not among IDUs in other western states where BTH is being distributed—strains credulity.

Third, although we have not cultured *C botulinum* from the few samples of heroin tested to date, we have cultured the organism from the inside of a syringe used by a WB patient who skin-popped. As Bamberger and Terplan suggest, there is no shortage of heroin available for illegal use. However, no California health agency—state or local—has a legal basis for working with Schedule I narcotics unless arrangements have been made with the California Department of Justice. Our botulism laboratory has sought, but has not yet received, seized heroin from the Department of Justice so that we may attempt to extract *C botulinum* spores from large heroin samples.

Dr Horowitz and colleagues identify critical stumbling blocks to timely treatment of WB in IDUs. The authors point out that 4 of their 7 WB cases presented with cranial nerve findings that were not entirely symmetric. We do not know what proportion of drug injection-associated WB presents with asymmetric weakness, but the illness may present as symmetric paralysis (botulism) superimposed on cerebral anoxia or infarction, presumably resulting from years of illicit drug injection.

We also wish to amplify the assertion by Horowitz and colleagues that treatment was unnecessarily delayed. These delays were seldom the result of subtle variations in clinical pre-

sentation. Delays occurred more commonly because clinicians did not initially consider the diagnosis of WB, especially when patients “were suspected of malingering or having drug-seeking behavior.” In these cases, seeking a detailed drug use history (including route of administration) and knowing the medical complications of drug injection could have saved lives or averted months of ventilatory support.

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1. Butz AM, Laughom BE, Gullette DL, Larson EL. Alcohol-impregnated wipes as an alternative in hand hygiene. *Am J Infect Control*. 1990;18:70-76.

## Recruiting Volunteers for a Typhoid Vaccine

*To the Editor.*—The Medical News & Perspectives<sup>1</sup> article regarding the use of volunteers in a typhoid infection study was both fascinating and distressing.

The Food and Drug Administration committee members, the Center for Vaccine Development at the University of Maryland School of Medicine, the National Institute of Allergy and Infectious Diseases, and the World Health Organization have a laudable intent. However, in the tradition of their predecessors such as Hunter (syphilis), Walter Reed (yellow fever), Courmand (cardiac catheterization), and, more recently, Harrington et al<sup>2</sup> and Herbert,<sup>3</sup> they should be willing to consider exposing themselves to the potential “minimal” risk of the study. Did the knowledgeable and informed members of these various institutions consider this option? If only 24 volunteers are needed, that likely is fewer than the potential number of authors of the article(s) describing the outcome.

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1. Marwick C. Volunteers in typhoid infection study will aid future vaccine development. *JAMA*. 1998;279:1423-1424.
2. Harrington WJ, Minnick V, Hollingsworth JW, Moore CV. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. *J Lab Clin Med*. 1951;38:1-10.
3. Herbert V. Experimental nutritional folate deficiency in man. *Trans Assoc Am Phys*. 1962;75:307-320.

*In Reply.*—Dr Matz raises the question of investigators serving as subjects in their own clinical trials. The path to licensure of vaccines is long (an average of 12 years), highly selective, and expensive. A vaccine candidate must be evaluated in clinical trials that progress from phase 1 (safety and immunogenicity dose response in small numbers of subjects) to phase 2 (safety and immunogenicity in larger numbers, additional age groups, and special-risk populations) and, finally, to large-scale phase 3 efficacy trials.

Volunteer models of experimental challenge can assess efficacy for certain vaccines. In modern vaccinology, challenge studies supported by US governmental (Food and Drug Administration, National Institutes of Health, Department of Defense, Environmental Protection Agency) and international (World Health Organization) agencies have accelerated the evaluation of vaccines against influenza, cholera, *Plasmodium falciparum* malaria, *Shigella* dysentery, enterotoxigenic *Escherichia coli* diarrhea, and *Neisseria gonorrhoeae* urethritis.<sup>1-4</sup> The volunteers are healthy community adults who are informed of the purpose of the study and its risks and procedures; efforts are taken to ensure that neither coercion nor inducement influences the decision to participate. Over the years, vaccine safety and challenge studies at the Center for Vaccine Development have included investigators and their family members, although the overwhelming majority of

participants from the Baltimore community have no connection to the University of Maryland. This issue is complex. Some argue that investigators should not enroll in their own trials because of potential for bias. Similarly, recruitment of staff and students working in the departments of investigators potentially could be coercive. Moreover, many US investigators who work on orphan vaccines to prevent diseases such as typhoid or shigellosis are ineligible for participation in vaccine or challenge studies. The ineligibility stems from their having previously received a licensed or experimental vaccine or having experienced the wild-type infection consequent to carrying out field studies in endemic areas in less developed countries. Under any circumstances, the number of subjects required for the clinical trials involved in evaluating a vaccine candidate far exceeds the number of investigators who could participate. Thus, the need for informed, motivated community participants is pressing.

The healthy adult volunteers who will participate in a typhoid challenge will have a high probability of developing clinical illness, although the rapid intervention (within a few hours) with highly effective ciprofloxacin should result in a mild, uncomplicated clinical course. Their altruistic participation will hasten the development of a new generation of typhoid vaccines that in the future may help control the emergence of antibiotic-resistant *Salmonella typhi*.<sup>5</sup> Regrettably, there is little recognition of the indispensable role played by such volunteers, without whose participation practical advances in vaccine development would virtually grind to a halt.

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1. Clements ML, Betts RF, Tierney EL, Murphy BR. Resistance of adults to challenge with influenza A wild-type virus after receiving live or inactivated virus vaccine. *J Clin Microbiol.* 1986;23:73-76.
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3. Coster TS, Killeen KP, Waldor MK, et al. Safety, immunogenicity, and efficacy of live attenuated *Vibrio cholerae* O139 vaccine prototype. *Lancet.* 1995;345:949-952.
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5. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant *Salmonella typhi*: a worldwide epidemic. *Clin Infect Dis.* 1997;24(suppl 1):S106-S109.

### Simian Virus 40—Contaminated Polio Vaccine and Cancer Rates

*To the Editor.*—In their report on contamination of poliovirus vaccine with simian virus 40 (SV40), Dr Strickler and colleagues<sup>1</sup> mistakenly claim that “earlier studies of cancer risk following exposure to SV40-contaminated vaccine were generally limited by small sample size or short follow-up.” I refute this suggestion and contend that my report,<sup>2</sup> which they include in this group, neither was of limited sample size nor was it a short follow-up as arguably the others they refer to were.

The sample totaled 810 children with malignant disease observed during 10 years in 2 major Australian hospitals and was not construed as limited in size or follow-up by either the reviewers or Editor of *Nature*. To include this report with the others Strickler et al consider limited and small is merely their perception, which conflicts with reality. The survey showed a significant association between the immunization with Salk vaccine and childhood malignancy in the 1- to 14-year-old age group ( $\chi^2$ , 12.182;  $P < .005$ ). To misrepresent my findings is

unconscionable. In the interests of scientific integrity, Strickler et al are obliged to state precisely what makes a sample size not limited, what constitutes an adequate follow-up, and how the report they dismiss conflicts with the criteria they espouse.

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1. Strickler HD, Rosenberg PS, Devesa SS, Hertel J, Fraumeni JF, Goedert JJ. Contamination of poliovirus vaccines with simian virus 40 (1955-1963) and subsequent cancer rates. *JAMA.* 1998;279:292-295.
2. Innis MD. Oncogenesis and poliomyelitis vaccine. *Nature.* 1968;219:973-975.

*In Reply.*—Dr Innis does not question the methods or findings of our study or its conclusion that birth cohorts immunized with SV40-contaminated poliovirus vaccine during infancy or childhood have not experienced an increased risk of cancer. Instead, his letter concerns a statement in our introduction. He feels his 1968 letter to *Nature*,<sup>1</sup> 1 of 7 references given to make this point, should not be considered small or as having short follow-up.

We have elsewhere reviewed the decades of epidemiologic studies that have evaluated the relation of SV40-contaminated vaccines to cancer risk.<sup>2</sup> In his study, Innis observed a higher frequency of past immunization with inactivated poliovirus vaccine among 706 childhood cancer cases older than 1 year (88%) than among individually matched noncancer controls (81%), a statistically significant effect of small magnitude.

Innis' comments regarding follow-up time are confusing since his study was a case-control investigation. Although enrollment of cases and controls took place during a 10-year period, no cohorts of exposed and unexposed individuals were ever followed. In addition, his comments regarding sample size are difficult to assess since the number of cases with specific forms of cancer were not reported, obscuring the specificity of association. More important, it is impossible to assess the correct number of cases and controls likely exposed to SV40 because the year of vaccination was not examined in relation to the period of SV40 contamination. The small effect observed in the Innis study leaves open the possibility that confounding or small biases in the selection of cases and controls could also explain the findings.

None of the recent large population-based birth cohort investigations in Germany,<sup>3</sup> Sweden,<sup>4</sup> or our study in the United States, involving millions of person-years of observation for more than 30 years, have found any association between poliovirus vaccine history and development of cancer. Only 1 case-control investigation besides the study by Innis has been reported. In 1965, Stewart and Hewitt<sup>5</sup> in the United Kingdom compared 999 childhood leukemia cases and 1108 cases of other childhood malignancies to individually matched controls, and found no relationship with vaccine history. Although the epidemiologic record is not entirely consistent, the preponderance of evidence to date argues against any relation between exposure to SV40-contaminated poliovirus vaccine during infancy or childhood and subsequent risk of cancer.<sup>2</sup> Because many exposed individuals are still younger than 40 years, however, continued monitoring of these birth cohorts remains warranted. It is also an open question whether SV40 may be an infectious cause of human disease in other settings.

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### Sex at Risk: Politically or Factually Correct?

*To the Editor*.—One of the secondary themes of my book,<sup>1</sup> reviewed by Dr Post in *JAMA*,<sup>2</sup> is that political correctness largely precludes factual correctness. The review by Post was another example of this.

For example, she substitutes “paradoxically” for “phasi-cally” in a quoted passage that should read “intercourse but not masturbation phasically increased men’s testosterone lev-els.”<sup>1(p99)</sup> She also states that I claim to be “nonpartisan,” although in my preface I explicitly note, “The review of the low risk of HIV [human immunodeficiency virus] transmission during vaginal intercourse is more partisan than the other two reviews, because of the common assumption of such a risk in both lay and professional circles.”<sup>1(pviii)</sup>

Post opines that because I prefer the neutral term *homo-sexual* to *gay*, I am “culturally nonrepresentational” and there-fore “nonscientific.” It is debatable whether failure to use the faddish term *gay* is nonrepresentational (sampling bias is among the issues covered in my book), but the leap from there to being nonscientific is a non sequitur. It appears that part of the doctrine of political correctness is if you don’t have some-thing deconstructive to say, don’t say anything at all.

Nevertheless, I not only appreciate her positive comments (and her acknowledgment of my scientific conclusions) but also agree with the gist of her statement that my book not be “unquestioningly subsumed into any curriculum or general body of knowledge.” But then I believe that applies to all discourse.

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1. Brody S. *Sex at Risk: Lifetime Number of Partners, Frequency of Intercourse, and the Low AIDS Risk of Vaginal Intercourse*. New Brunswick, NJ: Transaction Pub-lishers; 1997.

2. Post LL, reviewer. *JAMA*. 1998;279:963. Review of: Brody S. *Sex at Risk: Lifetime Number of Partners, Frequency of Intercourse, and the Low AIDS Risk of Vaginal Intercourse*.

*In Reply*.—Since receiving the critique from Dr Brody, I have reread his book, reviewed the notes that I made prior to com-mitting my thoughts about his book to paper, and discussed his book with several colleagues. My first comment is that Brody is absolutely correct that I misquoted him on one occa-sion, substituting the word “paradoxically” for “phasically.” This was an error of my spellchecker since my original draft had reported the word correctly. However, since the respon-sibility for the review is mine, I sincerely and shamefacedly apologize.

My second comment is that, in Brody’s deconstruction of my words, he misconstrues my intention in naming him nonpar-tisan. Of course, any research or writing is bound by the per-spective, culture, and conscious leanings of the author. None-theless, I stand by my assertions that Brody is:

1. using partisan terms (*homosexual* rather than *gay*—I know since I am a member of the lesbian community);
2. using partisan assumptions (ie, considering penile-vagi-nal intercourse as “normal” and ignoring other penetrative sexual practices of lesbians, gay men, and heterosexuals);
3. forcing the reader to draw on previous and profound

knowledge of statistics, epidemiology, evolutionary biology, and sexology and;

4. generally using language that is highly abstruse, multi-syllabic, and polydisciplinary, which renders his conclusions inaccessible, difficult to interpret, and nearly impossible to apply pragmatically.

Ironically, Brody’s letter to *JAMA* expressing his point of view in disagreement with my own is broad in its praise of my having correctly synopsisized the conclusions that he was at-tempting to promulgate. Equally ironically, the language and assumptions of Brody’s letter validate the principal focus of my review: that his book is overly complex and esoteric and, possibly, prejudiced.

I encourage readers to read *Sex at Risk* for themselves and draw their own conclusions. In that way, the purpose and in-tent of the review will have been fulfilled.

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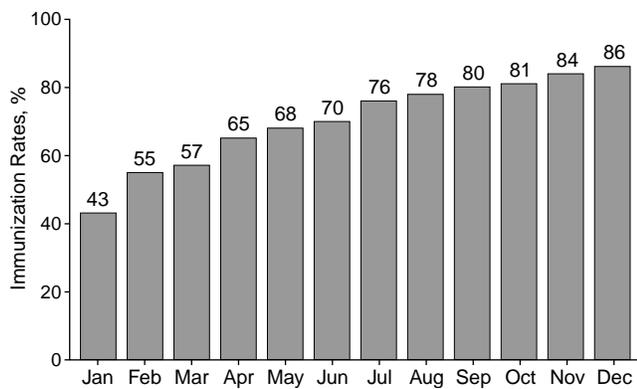
### Improving Vaccination Coverage Through Accelerated Measurement and Feedback

*To the Editor*.—A previous study documented success in im-proving immunization rates of 136 000 children served by 200 public health clinics in Georgia through the application of a 7-year program of “measurement and feedback.”<sup>1</sup> This mea-surement and feedback program consisted of annual sampling of charts to determine the proportion of 2-year-olds up-to-date on their immunizations at each clinic, communication of clinic-specific rates, including their rank order, and awards for best performers.<sup>2</sup> From 1988 to 1994, up-to-date rates in-creased from 53% to 89%.

Such an impressive improvement in rates was especially welcome news in the aftermath of the nationwide measles epidemic that occurred between 1989 and 1991, which left ex-posed the dismal state of vaccine coverage among preschool-aged children in the United States.<sup>3</sup> However, Georgia’s effort was an uncontrolled, long-term, “natural” experiment termed “real-time science as seen in the plan-do-study-act cycle of quality improvement,”<sup>4</sup> which was potentially affected by any number of outside factors not associated with the measure-ment and feedback intervention. We present another example of real-time science that we believe adds to the evidence that measurement feedback is effective.

In recent years, Utah has had the distinction of having the lowest immunization rates in the United States: only 64% of 2-year-olds were up-to-date with immunizations in 1996.<sup>5</sup> In 1997, the Salt Lake City-County Health Department (SLC-CHD) applied the measurement and feedback approach to approximately 5000 8- to 27-month-old children who received their immunizations at 5 SLCCHD clinics. Computerized pa-tient records, using a system designed and managed by Cust-om Data Processing, Chicago, Ill, gave us an ongoing 100% sample of all records for data purposes, a reminder system for children who were behind on their immunizations, and real-time access to immunization records of children presenting for service.

We encouraged our clinics to solve problems in their own ways. Common interventions included retrieving missing im-munization data from parents, increasing attention to missed opportunities, creating reminder systems, instituting aggres-sive outreach including after-hours telephoning, performing home visits, and tracking down children who had moved. Us-ing the Centers for Disease Control and Prevention’s Clinic Assessment Software Application as a measuring tool, rates and rankings of each clinic were documented monthly. Incen-tives for clinics and individuals also were built into the process.



Immunization coverage in 1997 (4 diphtheria-tetanus-pertussis, 3 polio, and 1 measles-mumps-rubella vaccinations by 2 years of age) for 5259 children aged 8 to 27 months.

During the 12-month period from January through December 1997, up-to-date immunization rates of children served by the SLCCHD increased from 43% to 86% (Figure). This improvement is similar to other recent natural experiments in immunization delivery.<sup>6</sup> While Georgia pioneered the method, the SLCCHD's accelerated use of measurement and feedback demonstrates that change can take place much more rapidly. Also, rapid improvement in immunization rates following the application of measurement and feedback supports a causal relationship between the program and outcome observed.

Additional costs incurred by the accelerated measurement and feedback program were limited to minor modifications in computer system programming and the need for a part-time data analyst. Reliable, accessible, and comparative immunization data increased the efficiency and effectiveness of clinical and support staff and, by their own report, made their jobs more enjoyable.

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3. Schlenker TL, Bain C, Baughman AL, Hadler SC. Measles herd immunity—the association of attack rates with immunization rates in preschool children. *JAMA*. 1992;267:823-826.
4. Thompson RS. Systems approaches and the delivery of health services. *JAMA*. 1997;277:670-671.
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### Drug Overdoses With Antimalarial Agents: Prescribing and Dispensing Errors

*To the Editor.*—We describe 3 previously undocumented episodes of severe overdosing with antimalaria drugs reported to the Centers for Disease Control and Prevention.

**Report of Cases.**—*Case 1.*—A 45-year-old woman was admitted to a California hospital on September 15, 1997, with *Plasmodium vivax* malaria, acquired in Honduras. She was treated with 1250 mg of mefloquine hydrochloride on admission, followed by 1260 mg of primaquine (84 tablets) the next day. In addition, primaquine, 15 mg daily, was given for the

next 5 days. On September 16, the patient developed abdominal cramps, nausea, hallucinations, black urine, and jaundice. Liver function tests showed markedly elevated findings (total bilirubin, 127  $\mu\text{mol/L}$  [7.4 mg/dL]; aspartate aminotransferase, 3309 U/L; alanine aminotransferase, 2654 U/L) on September 18. Liver transplantation was considered, but the results of liver function tests had returned to normal by October 15. Overdose of primaquine was not considered to be a cause of her acute liver failure until 6 months later.

**Comment.**—Vivax malaria is treated with 1500 mg of chloroquine over 3 days and 15 mg of primaquine daily for 14 days.<sup>1</sup> The probable oral lethal dose of primaquine is 5 to 50 mg/kg (350-3500 mg for this patient).<sup>2</sup> The dose-dependent toxic effects of primaquine (abdominal cramps, intravascular hemolysis) and the small margin between therapeutic and toxic doses limit the daily adult dosage to 15 or 30 mg. High doses of primaquine in rhesus monkeys have resulted in acute fatal hepatotoxic effects.<sup>3</sup> This episode reinforces the need for expertise in malaria treatment as well as vigilance by nursing and pharmacy personnel.

**Case 2.**—An 82-year-old woman with onychomycosis was prescribed terbinafine (Lamasil), 250 mg daily. A dispensing error resulted in the patient's being given mefloquine hydrochloride (Lariam) instead. Following 10 days of daily mefloquine, she complained of confusion, agitation, ataxia, dizziness, and speech difficulties and had high-frequency hearing loss. When the medication error was detected 2 months later, the patient had taken 250 mg of mefloquine hydrochloride daily for 61 days (total dose, 15 250 mg). With the exception of mild residual hearing loss, symptoms had resolved 1 year later.

**Case 3.**—A 53-year-old man with onychomycosis was prescribed terbinafine (Lamasil) but was given mefloquine hydrochloride (Lariam) on 2 occasions. Between March 12 and September 25, 1997, the patient took 250 mg of mefloquine hydrochloride daily for 3 weeks. After onset of nausea and fatigue, he changed his dosing from daily to 2 to 3 times per week for the following 23 weeks (total dose, 16 250 mg over approximately 6 months). By mid June, after 3 months of mefloquine overdosage, he noted weakness, depression, disorientation, and paresthesia. Symptoms reportedly persisted 1 year following onset of illness.

**Comment.**—In the United States mefloquine hydrochloride at a dosage of 250 mg once weekly is the drug of choice for chemoprophylaxis of chloroquine-resistant *Plasmodium falciparum* malaria.<sup>4</sup> Although terbinafine has been available topically since 1993 under the trade name Lamasil, the 250-mg oral dosage form has been marketed in the United States only since May 1996. Along with demonstrating the wide therapeutic margin of mefloquine, these cases illustrate the potential for medication error with these 2 similarly named 250-mg tablets.

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## Incorporating Human Factors Into the Design of Medical Devices

*To the Editor.*—The recent report of a patient death due to an inadvertent morphine overdose due to misprogramming of a patient-controlled analgesic pump<sup>1</sup> highlights the importance of incorporating human factors into the design of medical devices.<sup>2,3</sup> *Human factors* is the study of the interrelationships between humans, the tools they use, and the environments in which they live and work. The error in question apparently resulted from the user's inadvertent entry of an inappropriately low morphine concentration setting. The interface of this patient-controlled analgesic pump offers the minimum drug concentration as the initial choice. Paradoxically, if the user inadvertently selects an initial morphine concentration of 0.1 mg/mL when, in fact, it is 1 mg/mL, a 10-fold higher dose will be administered. This occurs because the device divides the desired unit dose (eg, 2 mg per activation) by the concentration (eg, 1 mg/mL) to calculate the drug volume administered with each pump activation (eg, 2 mL). Neither display of the programmed settings nor the operator manual's admonition to verify settings prior to use were sufficient to prevent a fatal error.

While it is often difficult to ascertain the degree to which a device's interface design contributes to human error, independent analyses of this and similar devices suggest ample opportunity for user interface design improvements. In general, the proper application of a structured human factors program throughout a device's design and development may be the most reliable way to identify and correct user interface attributes that could promote user error. User testing is usually an important component of an effective human factors program.<sup>3,4</sup>

Poorly designed medical devices, whether disposable syringes or complex imaging systems, can promote user error and lead to adverse patient outcomes. Typically, the clinician shoulders the bulk of the blame, yet neither censure nor additional training is likely to completely mitigate poor design. Patient safety will be enhanced if the medical community demands better designed medical devices (through standards, regulations, and market forces). The Food and Drug Administration recently introduced new regulations<sup>5</sup> that require manufacturers to establish and follow organized design processes that include a focus on the evaluation of user needs and requirements.<sup>6</sup>

At the request of the Food and Drug Administration and in collaboration with relevant international committees (eg, International Electrotechnical Commission Technical Commercial-62 [IEC TC 62]), the Human Engineering Committee of the Association for the Advancement of Medical Instrumen-

tation (AAMI), under the auspices of the American National Standards Institute, is currently drafting a standard for the human factors design process for medical devices. Once developed and approved, this document will be put forth as an international standard and is expected to be used as guidance by the Food and Drug Administration to ensure that manufacturers pay proper attention to human factors as they design and validate new medical devices. Greater input from health care professionals is critical to the success of this process. We are particularly in need of interested clinicians who have expertise in primary care and home health care. (For more information, please contact Nick Tongson at AAMI, [nick\\_tongson@aami.org](mailto:nick_tongson@aami.org) or [703] 525-4890.)

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The views expressed herein are those of the authors and do not necessarily reflect the official position of any of the organizations for which they work.

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## CORRECTION

**Incorrect Wording.**—In the Original Contribution entitled “Effect of Excessive Weight Gain With Intensive Therapy of Type 1 Diabetes on Lipid Levels and Blood Pressure” published in the July 7, 1998, issue of THE JOURNAL (1998;280:140-146), there was incorrect wording in 2 tables. On pages 143 and 144, in Tables 2 and 4, the entries that read “Insulin dose,  $\mu$ /kg per day” should have read “Insulin dose, U/kg per day.”

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