DIAGNOSTIC BIAS AND TOXIC SHOCK SYNDROME

To the Editor:

The recent article by Harvey et al (Am J Med 1984; 76: 351–360) purports to show that "a strikingly high amount of diagnostic bias can occur in the toxic shock/tampon relation," and that such bias is of sufficient magnitude "to raise serious doubt about the current epidemiologic evidence of a relationship between tampons and toxic shock syndrome." However, the data presented in the paper neither support this conclusion nor, given the study design, could have been expected to do so.

Although the year in which this study was conducted is not specified in the article, it is clear that the survey took place in 1982 or 1983, because the 1981–82 edition of the *Directory of Medical Specialists* was used. Therefore, physician respondents were well aware of the results of the case-control studies conducted in 1980 and 1981 that demonstrated an increased risk of menstrual toxic shock syndrome among tampon-users. It is hardly surprising that well-informed, conscientious physicians would take into account previously suspected or documented risk factors when considering a differential diagnosis. To argue that because such "diagnostic bias" was present in 1982 or 1983, it must also have been present in 1980, before any studies were conducted or results released, is fallacious. Similar reasoning would suggest that, because clinicians now have an appropriately heightened suspicion of asbestosis or mesothelioma in a retired shipyard worker and of liver cancer in a worker exposed to polyvinyl chloride, the original studies documenting an elevated risk of these diseases among such workers are invalid.

Clearly, the only question that is relevant in evaluating the role of "diagnostic bias" in the "toxic shock/tampon relation" is to what extent such bias was present *at the time of the original case-control studies.* As pointed out by the authors, the first CDC study and the Wisconsin and Utah studies were completed before there were any allegations that tampons were involved in the pathogenesis of menstrual toxic shock syndrome. It was, in fact, the publication of the results of these studies that led to widespread dissemination of this finding. There is no evidence presented in the paper by Harvey et al or, to our knowledge, anywhere else, that such "diagnostic bias" existed in early 1980. Furthermore, there is no evidence that reporting bias (that is, an increased or decreased likelihood that menstruation and/or tampon-associated cases of toxic shock syndrome would be reported) existed then or now.

Harvey et al also discuss at length the possibility that selection bias by earlier investigators led to a greater likelihood that cases of tampon-associated menstrual toxic shock syndrome would be included in the studies. Although the authors claim that "the current research . . . addressed . . . the diagnostic selections performed in a non-blinded review of case reports," no data concerning this type of bias are included in their paper. Instead, the authors infer that such bias must have been present in the original studies because the study questionnaires focused on catamenial product usage and because 98 to 100 percent of the menstrual cases in these studies were associated with tampon use.

The Wisconsin, Utah, and first CDC case-control studies of toxic shock syndrome were designed specifically to examine risk factors for toxic shock syndrome occurring during menstruation. The decision to focus on menstrual toxic shock syndrome followed from the rather remarkable finding that 52 (95 percent) of the first 55 cases were in women and that in 38 (95 percent) of 40 of the cases in which menstrual status was known, the patients had onset during menstruation. It is not true, however, that the questionnaires "concentrated almost exclusively on gynecologic aspects of catamenia." Each of the studies attempted to look at any factors that might have explained the noted association of toxic shock syndrome with menstruation, i.e., catamenial product usage patterns, sexual activity during menstruation, type and frequency of sexual practices, physical activity during menstruation, contraceptive methods employed, history of vaginal infections, etc. Subsequently, frequency of douching, use of feminine deodorant sprays, and other factors also were examined.

The argument that the high prevalence of tampon use among case subjects with toxic shock syndrome enrolled in the studies suggests selection bias on the part of the investigators is circular as well as contrary to the facts. Although menstrual toxic shock syndrome can occur in women who do not use tampons, it is entirely plausible that the elevated risk of toxic shock syndrome among tampon-users is sufficiently great to ensure that the overwhelming majority of cases will be among tampon-users. Furthermore, as we have stated previously, all cases of menstrual toxic shock syndrome submitted that met the rigid case definition were included in the CDC study.

Finally, we do not agree with the authors that the adverse effect of their low response rate (only 15 percent of those physicians who received the questionnaires returned both sets) on the applicability of their results to physicians in general is mitigated by having each participant respond twice. In a recent mail survey of physician practices concerning the diagnosis and treatment of streptococcal pharyngitis, we found that respondents differed markedly from nonrespondents with regard to the country in which they received their medical training, inasmuch as foreign medical graduates were significantly over-represented among the respondents [1]. Whether or not the results of the study of Harvey et al are representative of United States practitioners in general depends entirely on how representative their respondent population is. Unfortunately, no data concerning this point are presented in their paper.

We therefore reject the conclusion of Harvey et al that

Continued on page A81

Continued from page A72

their results "raise serious doubt" about the role of tampons in the pathogenesis of menstrual toxic shock syndrome, although we share their wish that future studies be "objective" and "scientifically valid."

ARTHUR L. REINGOLD, M.D.
CLAIRE V. BROOME, M.D.
Division of Bacterial Diseases
Center for Infectious Diseases
Centers for Disease Control
Atlanta, Georgia 30333

1. Cochi SL, Fraser DW, Hightower AW, Facklam RR, Broome CV: Diagnosis and treatment of streptococcal pharyngitis: survey of US medical practitioners. In: Management of pharyngitis in an era of declining rheumatic fever. Columbus: Ross Laboratories, 1984.

To the Editor:

The study results and interpretation presented by Harvey et al (Am J Med 1984; 76: 351–360) regarding the possible impact of diagnostic bias on the results of case-control studies designed to evaluate risk factors for menses-associated toxic shock syndrome by ourselves [1,2] and others require clarification. They indicate that diagnostic bias was not evaluated in the epidemiologic investigations of toxic shock syndrome and, therefore, they undertook their research to determine whether such bias can occur. A personal communication evaluating the impact of susceptibility, performance, and detection biases on the results of the Tri-State Toxic-Shock Syndrome Study was sent by one of us (M.T.O.) to the authors on February 2, 1982, and acknowledged by the authors on February 22, 1982. In addition, the authors were also informed that we had three articles in press at that time, two on the results of the Tri-State Toxic-Shock Syndrome Study [2,3] and the other that was a methodologic analysis of the study [4]. We are confused as to why the authors continue to maintain that diagnostic bias, a type of detection bias [5], has not been previously evaluated in our study since they know that was done.

Harvey and colleagues suggest that publicity about menses and toxic shock syndrome had an impact on the diagnoses made in patients included in the toxic shock syndrome studies. We have previously presented [2,4] data that refute claims made by the authors regarding this issue. Between January and April 1980, six weeks before the first suggestion of a possible relationship between toxic shock syndrome and menses that appeared in the *Morbidity and Mortality Weekly Report* [6], and 10 weeks before the first association between menses-associated toxic shock syndrome and tampon use was made public [7], 31 of 36 cases of toxic shock syndrome reported to the state health departments in Minnesota and Wisconsin occurred in young menstruating women.

The date of the first national or regional publicity associating the occurrence of toxic shock syndrome with tampon use was June 27, 1980. Case subjects included in the Tri-State Toxic-Shock Syndrome Study who were exclusive tampon brand-users and who were "reported" to the three state health departments before June 27, 1980, and their matched control subjects were compared with those case subjects with exclusive brand use who were reported between June 27, 1980 and September 19, 1980 and their matched control subjects. Twenty-five (42 percent) of 59 case subjects with exclusive tampon use included in the Tri-State Toxic-Shock Syndrome Study were reported before June 27 [2,4]. The distribution of exclusive tampon brand use by brand was similar for case subjects and control subjects during both time periods. Also, for both intervals, there was a statistically increased risk of the development of toxic shock syndrome with tampon use, thus refuting the issue of diagnostic bias as proposed by Harvey et al.

They also indicate that they were impressed with the high prevalence of tampon use among case subjects selected for the epidemiologic case-control studies. Again, they have failed to examine closely the information provided in print regarding cases of toxic shock syndrome included in the Tri-State Toxic-Shock Syndrome Study. Our study intended to focus on menses-associated toxic shock syndrome and was not meant to, nor expected to, comment on risk factors associated with the well-documented nonmenstrual toxic shock syndrome. This meant exclusion of 12 cases of toxic shock syndrome that occurred among men and pre- or post-menopausal women. Subsequently, 80 women identified with toxic shock syndrome were then considered for study. Only 76 of these women had onset during menses and one used napkins only. Thus, only 75 of 92 cases of toxic shock syndrome (80 percent) reported to the state health departments of Minnesota, Wisconsin, and Iowa prior to our study were associated with tampon use. This figure is far less than the 98 to 100 percent tampon use suggested by the authors.

It is with some interest that we find ourselves critical of the potential methodologic bias in the study by Harvey and colleagues. First, an 11 percent response rate without evaluation of the nonresponders is considered a significant flaw in any type of epidemiologic study. We were surprised that the authors even elected to discuss their results in light f the potential significant "response bias" such a study presents. Second, we question the appropriateness of only using physicians from Pennsylvania, New York, and Connecticut, an area where only 5 percent (82 of 1,582) of all cases of toxic shock syndrome had been reported through February 2, 1982 [8]. We believe that the use of states in various geographic regions would be more representative. For example, over 28 percent (449 of 1,582) of all cases of toxic shock syndrome reported through that same date had been diagnosed in the states of Minnesota, Wisconsin, and Iowa, a region with less than 25 percent of the population of the three surveyed states. As with so many other diseases, including Rocky Mountain spotted fever, plague, and histoplasmosis, local interest and the number of medical education opportunities are often ap-

Continued on page A82