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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."

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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-

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proximated by the actual number of cases of the disease occurring in this specific area. The authors may find a very different result if the same questionnaire is distributed to physicians in other regions.

Last, the point must be made that the review of the cases in this study has taken place following considerable research and publicity about toxic shock syndrome, particularly the association with tampons. It is difficult to extrapolate this situation to 1980.

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The Reply:

The many protests of the investigators who did the research can be answered with replies to six main questions:

1. Was the "decision to focus on menstrual toxic shock syndrome" made before or after "the rather remarkable finding" that so many cases were menstrually associated?

In our previous publication [1], we presented a chronology of events indicating that this decision was made after only a few cases had been reported spontaneously, long before the actual research began. The subsequent publicity from state health departments and from other media then encouraged physicians (and patients) to submit reports of cases that seemed menstrually related. Consequently, a high association would inevitably be found in the reports collected at the health agencies and at the CDC.

2. What are the several sources and effects of diagnostic bias in the toxic shock syndrome/tampon relationship?

As we have previously pointed out [1], diagnostic bias can arise and can affect the results in three different ways. First, when a patient is actually under clinical care, a physician influenced by publicity about menstruation, tampons, and toxic shock syndrome may decide to call the ailment toxic shock syndrome, rather than something else. Second, a physician affected by requests from health agencies may decide to submit a report of a case of toxic shock syndrome if it was associated with tampons, but not to report cases in which tampon usage did not occur. Third, a knowledge of the use of tampons may have affected the investigators when they reviewed the submitted material and decided which reports to retain as "proved" cases of toxic shock syndrome.

The investigators devote their "rebuttal" to the first and second sources of bias, but the third source, which they ignore, may have been the most cogent problem.

3. Was bias created when the investigators failed to use objective methods in reviewing the submitted material to decide which patients had toxic shock syndrome?

Since readers of a published research report cannot be present when the research is done, the customary standards of science call for investigators to provide assurance that the data were acquired by objective, unbiased methods. For example, when a cause-effect relationship is suspected between therapeutic agents and their outcomes, scientific proof usually requires the use of randomization to assign the treatments, and double-blind procedures to observe the outcomes. This requirement is intended to keep the investigators' preconceptions about a hypothesis from affecting the objectivity with which evidence is collected and interpreted.

In the case-control studies under discussion, these scientific precautions would require that the investigators be "blinded" to the catamenial status of the patients when deciding whether a submitted case vignette met the criteria for toxic shock syndrome. Since these elementary scientific safeguards were not used in the tampon/toxic shock syndrome studies, no assurance can be given that bias was absent.

Another potential safeguard against bias was also omitted in the research. The investigators did not maintain (or have not reported maintenance of) a "screening log" to keep track of the numbers and characteristics of all persons considered for admission to the research studies. The virtue of such a "log" is that it can be used, if questions of biased admission later arise, for analytic enumerations to compare the persons who were included or excluded. The toxic shock syndrome investigators state that all of the included patients fulfilled the subjectively appraised diagnostic criteria for toxic shock syndrome, but no quantified data have been presented for the num-

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