Continued from page A81

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.

MICHAEL T. OSTERHOLM, Ph.D., M.P.H.
Minnesota Department of Health
Minneapolis, Minnesota 55440
ROBERT W. GIBSON, Ph.D.
University of Minnesota
Duluth, Minnesota 55812
JEFFREY P. DAVIS, M.D.
Wisconsin Division of Health
Madison, Wisconsin 53702
JACK S. MANDEL, Ph.D.
University of Minnesota
Minneapolis, Minnesota 55455

1. Davis JP, Chesney PJ, LaVenture M: Investigations and laboratory team. Toxic-shock syndrome: epidemiologic features, recurrence, risk factors and prevention. N Engl J Med 1980; 303: 1429–1435.
2. Osterholm MT, Davis JP, Gibson RW, et al: Tri-state toxic-shock syndrome study: epidemiologic findings. J Infect Dis 1982; 145: 431–440.
3. Osterholm MT, Gibson RW, Mandel JS, Davis JP: Tri-state toxic-shock syndrome study: methodologic analysis. Ann Intern Med 1982; 96: 899–902.
4. Davis JP, Osterholm MT, Helms CM, et al: Tri-state toxic-shock syndrome study: II. Clinical and laboratory findings. J Infect Dis 1982; 145: 441–448.
5. Feinstein AR: Methodologic problems and standards in case-control research. J Chronic Dis 1979; 32: 35–41.
6. Toxic-shock syndrome—United States. Morbid Mortal Weekly Rep 1980; 29: 229–230.
7. Toxic-shock syndrome—United States. Morbid Mortal Weekly Rep 1980; 29: 297–299.
8. Toxic-shock syndrome—United States, 1970–1982. Morbid Mortal Weekly Rep 1982; 31: 201–204.

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-

Continued on page A97

Continued from page A82

bers of case reports that were submitted to the agencies as instances of toxic shock syndrome, but then rejected from the research. The "statistical significance" found in many of the case-control studies would vanish if only a few of the rejected cases had occurred in non-tampon-users.

4. Had the causal hypothesis about tampons been established before the research was done?

Having failed to take the precautions mandated in scientific research, the investigators now claim that the precautions were unnecessary because the causal hypothesis did not exist before the research began. This claim is contradicted by at least two types of evidence offered by the investigators themselves. The first type of evidence is shown in the content of the questions used for interviews in the very first CDC case-control study [2,3]. As we noted in our previous comments (Am J Med 1984; 76: 351–360), these questions placed a strong emphasis on tampons and even mentioned one brand (Rely) by name, with the interviewed patient being reminded that "you may have received a sample in the mail." The second type of evidence is shown by the gynecologic focus of the questions, as reiterated in the letter from Drs. Reingold and Broome. If an etiologic hypothesis has not yet been formed in a retrospective case-control study, and if the investigators are truly uncertain about what the etiologic agent may be, the questions that are asked will cover a wide range of etiologic suspects. Among such suspects are predisposing diseases, concomitant co-morbidity, previous surgical operations, nutritional status, use of antecedent medications, and many factors other than a predominantly gynecologic focus.

5. Should a suspected risk factor for a disease be used as a criterion for establishing the diagnosis of that disease?

In stating that "it is hardly surprising" for physicians to "take into account previously suspected risk factors" when diagnosing toxic shock syndrome, Drs. Reingold and Broome seem unaware of the scientific difference between a risk factor and a disease. In scientifically proper reasoning, a history of exposure to asbestos or polyvinyl chloride should not affect the histologic interpretation of tissue from the lung or liver; nor should the presence of hypertension, smoking, or hyperlipidemia affect decisions about the diagnosis of coronary artery disease. With an analogous scientific principle, the CDC's diagnostic criteria [2] for toxic shock syndrome quite properly contained no mention of either menstruation or tampons.

When Drs. Reingold and Broome suggest that diagnoses should be made in violation of this scientific principle, the comment reinforces our suspicion that diagnostic bias did indeed occur during the research.

6. Does a 15 percent response rate impair the results of our comparative study?

As we pointed out in our report (Am J Med 1984; 76: 351–360), our study was prompted by the absence of

Continued on page A102

LETTERS TO THE EDITOR

Continued from page A97

suitable scientific attention to the diverse sources of diagnostic bias in the earlier epidemiologic research. Now that diagnostic bias has been shown to occur, the investigators want to argue that it is confined to physicians in the three northeastern states where we conducted our study.

This argument ignores the methodologic difference between a passive descriptive survey and an active comparative study. In a passive descriptive survey, a low response rate is distressing because the responding volunteers may not adequately represent the population being sampled. In an active comparative study, however, the research is concerned with responses to specific interventions. The results depend not on the proportion of solicited persons who volunteered, but on the way those persons responded to the interventions.

In this regard, our study was analogous to a clinical trial. The volunteers received two sets of interventions, consisting of different case vignettes; and the responses were the diagnoses made for those vignettes. Many other comparative clinical trials have reached accurate appraisals of therapy with groups containing much less than 15 percent of the patients who were solicited for admission.

We agree with published comments made by Dr. James Todd, who first described and christened toxic shock syndrome [4]. He denounced the haste with which the tampon research was performed, and urged "caution for the interpretation and hurried public release of results of rapidly performed case-control studies" [5]. State health agencies can play an important role in epidemiologic research; and the CDC, in particular, has earned enormous stature and loyalty as the "West Point" of infectious disease epidemiology. With an increased scope and workload, however, the CDC may not be able to maintain its careful supervision and traditional scientific standards for all of the many projects conducted under its aegis. Respectful of the CDC's importance, dignity, and high reputation, we urge it to sponsor a new, scientifically valid study of the tampon/toxic shock relationship.

MARY R. HARVEY, M.D.
RALPH I. HORWITZ, M.D.
ALVAN R. FEINSTEIN, M.D.
Yale University School of Medicine
New Haven, Connecticut 06510

1. Harvey M, Horwitz RI, Feinstein AR: Toxic shock and tampons: evaluation of the epidemiologic evidence. JAMA 1982; 248: 840–846.
2. Shands KN, Schmid GP, Dan BB, et al: Toxic shock syndrome in menstruating women. N Engl J Med 1980; 303: 1436–1442.
3. Files on toxic shock syndrome investigation, Public Information Officer, Centers for Disease Control, Atlanta, available under Freedom of Information Act.
4. Todd J, Fishaut M, Kapral F, et al: Toxic shock syndrome associated with phage-group-1 staphylococci. Lancet 1978; II: 1116–1122.
5. Todd JK: Toxic shock syndrome—scientific uncertainty and the public media. Pediatrics 1981; 67: 921–923.