the general public; therefore, scientists are quite often regarded as presumptuous and arrogant.

In contrast, "quacks" are well accepted by the media because they respond better to the media's needs and easily adjust to the public's taste and expectations.

Physicians in particular usually hesitate to publicly criticize information offered by quacks for fear of libel suits; thus, they inadvertently increase the credibility of the quacks.

On a different level, patients often feel helpless and hopeless in the course of their disease. Therefore, they tend to repudiate scientific facts and to resent experts who represent the establishment, while seeing promoters of quackery as persons with the insight to penetrate the establishment's "fakery."

Prospect

The media can readily promote modern quack medicine. Attempts to fight quackery by law enforcement may be ineffective because laws are amenable to changes, and legislators usually yield to media pressures. On the other hand, scientific rejection may be insufficient in view of the increasing popularity of unconventional medicine. Therefore, quack medicine should be fought on its own grounds—namely, in the media—and the fight should involve media experts.

The issue is still wide open. In the words of the already cited New York Times editorial:

> Because of the continuing intractability of cancer, Laetrile will doubtlessly be resurrected in a new form. Physicians should not again wait for 27 State Legislators to tell them of the crisis of confidence in scientific medicine. The next time around they should start sooner to reason with the desperate.

The story of Joseph M. is but one example.

Toxic Shock Syndrome: Chronology of State and Federal Epidemiologic Studies and Regulatory Decision-Making

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SEVEN CASES OF AN UNUSUAL NEW ILLNESS were reported in the November 25, 1978, issue of Lancet by James Todd, MD, a pediatric infectious disease specialist at the University of Colorado School of Medicine (*1*). The illness was characterized by high fever, low blood pressure, a diffuse erythematous rash with subsequent skin peeling, vomiting, diarrhea, and multiple abnormalities in laboratory findings. These cases had occurred in four girls and three boys between the ages of 8 and 17 years. All five patients studied prospectively had *Staphylococcus aureus* isolated from at least one body site, although not, interestingly, the blood. Todd named this illness toxic shock syndrome (TSS) and suggested that it might be caused by a toxin elaborated by *S. aureus*. Despite this report, there was only infrequent recognition of TSS by the medical community until early 1980.

State Health Agencies

In Late January 1980, the Minnesota Department of Health (MDH) and the Wisconsin Division of Health and Social Services (WDH) officials reported to the Centers for Disease Control (CDC) nine cases of illness compatible with TSS that had occurred in the two States in the preceding 3 months. Unlike the cases reported by Todd, these cases had occurred not in children, but in adult women. In addition, most of the women had become ill during their menstrual period.

Also in January 1980, coincidentally with the first case reports by the two State health agencies, the MDH began an actively defined epidemiologic surveillance system for TSS (*2*). Intensity of surveillance was constant from the beginning through June 1981. Active

components of the system included a monthly survey for TSS cases among the patients of infectious disease specialists at regional medical centers and a similar monthly review with greater than 80 percent of the hospital infection control practitioners (nurse epidemiologists) in the State. The passive components of the system included an average of one lecture per week regarding TSS by health department personnel to various health professional groups throughout the State; quarterly update articles regarding the epidemiologic, clinical, and microbiologic aspects of TSS in the MDH Disease Control Newsletter, a publication received by more than 6,000 State health professionals; update articles and interviews in various news media; and reviews of all *S. aureus* isolates submitted to the health department or to Patrick Schlievert, PhD, a TSS toxin researcher at the University of Minnesota, Minneapolis, for pyrogenic exotoxin testing.

Menstrual status was never considered by the State health officials as a possible criterion for the TSS case definition. In fact, based on Todd's experience, State health officials anticipated that most cases would occur in children and be associated with *S. aureus* focal infections. Between January and April 1980, 31 of 36 TSS cases reported to the State health departments in Minnesota and Wisconsin occurred in young women who were menstruating. For this reason, consideration was given to menstrual risk factors, including the possible role of menstrual fluid and vaginal growth of *S. aureus* and catamenial product use.

By late May 1980, an epidemiologic case-control study was completed in the State of Wisconsin; it included 35 patients with menstruation-related TSS and 105 age-matched controls (*3*). Statistically significant findings included increased use of tampons by TSS patients as compared with controls and fewer patients than controls using any methods of birth control. Other health and hygiene variables were examined, and none were found to be significantly different between cases and controls.

In Minnesota, catamenial product use was examined for 29 cases reported between 1979 and early 1980 and 58 noncase women (*4*). While this early study indicated that the use of tampons was significantly greater among TSS case women than among noncase women, there were potentially serious epidemiologic problems inherent in its "quick and dirty" retrospective design. However, conclusions and experiences gained in this initial case-control study served as an important beginning for more complete epidemiologic investigations.

Tri-State Toxic-Shock Syndrome Study. During the summer of 1980, following the two reports (*5,6*) regarding TSS in the Morbidity and Mortality Weekly Report (MMWR) and various news media reports of the disease, consideration was given to conducting an extensive and further refined case-control study. By August 1980, the Minnesota Department of Health began development of a protocol to evaluate potential menses-associated TSS risk factors and to evaluate clinical laboratory findings associated with TSS. It was anticipated in the early planning for the study that all cases that occurred since November 1979 would be admitted to the study and then, as cases occurred, they would be prospectively enrolled. By late August 1980, discussions regarding the study had taken place between officials of the Minnesota, Wisconsin, and Iowa State health departments. All three States agreed to participate in the study, and at that time it was labeled the "Tri-State Toxic-Shock Syndrome Study" (TSTSSS) (*7*).

'By March 6, 1981, 7,321 individual reports or summaries of individual reports from the complaint files of manufacturers had been reviewed to identify those that were related to TSS or TSS-like illnesses. Unfortunately, none of the firms' records contained sufficient information to use CDC's case definition criteria to confirm TSS.'

Meetings were held with representatives of three different tampon manufacturers during the summer of 1980 in an attempt to learn more about catamenial product use among American women and, more specifically, about the construction and composition of tampons. Based on this information and discussions with various clinicians and epidemiologists around the country, an extensive 27-page questionnaire was developed. It was decided that all cases of TSS would be admitted to the study except those in men and those that ended in death. Two women, matched by age, would be chosen as neighborhood controls for each patient. Additional factors concerning the method of selection of controls are detailed elsewhere (*7*).

Because of the significant publicity in the news media on September 19, 1980, associated with the findings of the Centers for Disease Control TSS Study No. 2 (*8*), it was decided to close case admissions to the TSTSSS at that time to minimize selective reporting bias. Therefore, the cases in the study were to be those reported to the State health departments in Minnesota, Wisconsin, and Iowa between October 1, 1979, and September 19, 1980.

Eighty women with an onset of TSS during that period and 160 neighborhood controls participated in the study. Of the 80 women, 76 had onset of illness during their

Menstrual status was never considered by the State health officials as a possible criterion for the toxic shock syndrome case definition. In fact, State health officials anticipated that most cases would occur in children and be associated with Staphylococcus aureus *focal infections.*

menstrual periods. The odds ratio for developing menses-associated TSS with any use of tampons compared with no use of tampons was 18.01 ($P < 0.001$). The odds ratio ranged from 5.29 to 27.5 for individual brand use compared with no use. When exclusive brand use of a particular tampon brand was compared with the exclusive use of all other brands, Rely was the only brand associated with a significantly increased odds ratio (2.49, $P = 0.005$). However, multiple logistic regression analysis showed that the risk of TSS was more closely associated with the tampon's fluid capacity (absorbency) than with the use of all tampon brands. The results of the Tri-State study confirmed previous findings regarding the increased risk of developing menses-associated TSS with tampon use when compared with no use of tampons, and the study provided the first evidence that women who use any brand of tampons have a greater risk of contracting TSS than women who do not use tampons.

Results from the three-State study were shared with representatives from the CDC and the Food and Drug Administration (FDA) on January 11, 1981, and with tampon manufacturers on January 12. On January 13, results of the study were made available to the general public.

State health agency surveillance. The incidence of TSS in Minnesota, as reported through the MDH surveillance system, remained relatively constant between January 1980 and June of 1981 (*2*). As of June 30, 1981, 197 confirmed cases (15 percent of all nationally reported cases) had been documented in Minnesota residents. Sixty-one cases with onset of TSS prior to 1980 were retrospectively recognized and reported to the MDH after the initiation of the State's surveillance. In addition, 15 probable cases were reported: 2 with onset before 1980, 10 with onset in 1980, and 3 with onset during the first 6 months of 1981.

The case fatality rate was 6.6 percent (13 of 197). One hundred ninety-three (98 percent) of the patients were white, three were black, and one was Japanese-American.

The mean age of women with menses-associated cases was 23.3 years; for the nonmenses-associated cases, it was 25.7 years. The age ranges were also similar: 14 to 47 years for the menses-associated cases and 11 to 45 years for the nonmenses-associated cases. The incidence rate of TSS among menstruating women was 8.9 per 100,000 women years. However, the age-specific incidence rates per 100,000 menstruating women-years were 2.3 for women under 15 years, 13.7 for women 15 to 24 years old, and 6.6 for women 25 years and older.

The onset of 136 cases was between January 1980 and June 1981, the 18 months of active surveillance in Minnesota. One hundred fourteen cases, or 83.8 percent, were tampon-associated. The total number of TSS cases per calendar quarter ranged from 20 to 24 cases and the number of tampon-associated cases ranged from 15 to 21. There was no significant difference ($P < 0.20$) in the quarterly distribution of all cases or of only tampon-associated TSS cases during the 18 months. In 55 tampon-associated cases, the onset of illness was during the 9 months of surveillance in which Rely brand tampons were on the market, and in 59 tampon-associated cases, the onset of illness was during the 9 months following the voluntary removal of Rely from the market. However, there were significant differences in the frequency of use for specific brands of tampons between the 9 months that Rely tampons were being marketed and the 9 months following their voluntary removal from the market. For example, while exclusive use of Rely accounted for 25 of the 55 cases (45.5 percent) reported during the first 9 months of surveillance, it accounted for only 1 of the 59 cases reported between October 1980 and June 1981. Whereas Tampax tampons accounted for only 7 of 55 cases (12.7 percent) during the first 9 months of surveillance, they accounted for 27 of 59 cases (45.7 percent) during the second 9 months of surveillance.

This constant rate of tampon-associated cases and the change in brand association could be explained by comparing the exclusive tampon brand style used by women with tampon-associated cases with onset between October 1980 and June 1981 and the average market share or percentage of all tampons sold in the State by specific fluid capacity during that same time. Of the 49 women with TSS who used one tampon brand style exclusively, 53 percent used a brand style in the highest fluid capacity category, whereas the respective average market share in Minnesota during that time for tampons in the highest absorbency category was 28 percent and for the lowest absorbency category, it was 58 percent ($P < 0.001$).

Although national surveillance data during the summer of 1981 indicated that there was a significant decrease in the number of cases of TSS reported for the nation, this was in contrast to the experience in Minnesota, where the incidence of TSS remained relatively constant. Work

done by the WDH also helps to interpret national surveillance data during that time. A review of cases of TSS received by the WDH through January 30, 1981, with onset of illness before January 1, 1981, showed that media publicity significantly influenced surveillance in Wisconsin. (*9*). Data gathered in Wisconsin by the surveillance system for TSS were very similar to the CDC surveillance data with regard to the epidemiologic curve, the percentage of cases that occurred in male patients, percentage of cases with initial illness before 1980, and the quarterly distribution of cases that occurred in 1980. The WDH officials found that self-reported illness after publicity on TSS was in part responsible for the peak of reported cases with onset of illness in August and September of 1980 in their State. These results suggest that trends seen in the national surveillance data may be artifacts of the predominantly passive surveillance system established for TSS.

Centers for Disease Control

After the initial notification of the nine cases by the Minnesota and Wisconsin State health agencies in January 1980, informal surveillance for TSS was begun at the Centers for Disease Control by Kathryn Shands, MD. A particular problem with the surveillance of this possibly new disease was the lack of diagnostic criteria and, although Todd had hypothesized that *S. aureus* was involved in the pathogenesis of the disease, this hypothesis remained unproven. On February 21, 1980, Shands met with Todd and Neal Halsey, MD, an associate of Todd, to unify the clinical criteria into a standardized case definition. In a review of the cases which Todd had reported and those reported by the staffs of the Minnesota and Wisconsin health departments, consistent features were noted. By combining these features the investigators, including the CDC and State epidemiologists, worked out a case definition that forms the basis for the case definition used by CDC today (*10*).

By May 23, 1980, 55 cases of TSS had been reported by individual physicians or State health departments in 13 States. These reports were summarized in the MMWR for that date (*5*). There was no geographic clustering of cases, although Minnesota and Wisconsin, where surveillance for the disease had been most intense, reported more cases than other individual States. The mean age of persons with TSS was 24.8 years, with a range of 13–52 years. In 7 of the 55 cases, or 13 percent, the patients had died. All but three of the cases were in women.

The association of the onset of illness with the menstrual period was striking. Of 40 patients from whom a menstrual history had been obtained, 38 (95 percent) had had onset of illness within 5 days of the start of their menstrual period. Further, 13 patients had had a recurrence of symptoms during a subsequent menstrual period. In 33 of 45 patients (73 percent), *S. aureus* had been recovered by culturing a specimen from the throat, cervix, vagina, or rectum.

CDC Study No. 1. Because of the striking potential relationship of the onset of TSS to the menstrual period, a national case-control study was designed on June 11 to search for potential risk factors for the development of TSS. It concentrated on menstrual characteristics and sexual practices. One of the hypotheses to be tested, which was already being investigated by Dr. Jeffrey Davis of the Wisconsin Division of Health, was the possibility that tampons might be important in the pathogenesis of the disease. Information about basic demographic data, frequency of sexual intercourse, contraceptive methods used, characteristics of the menstrual period, and catamenial product usage was also sought. In the period June 13–19, 52 women who had had TSS, comprising all women of menstrual age who had been reported to CDC, and 52 women controls, who were matched for age and geographic location and had been selected by the women with cases from among their friends, were interviewed by telephone by CDC staff. On June 19, the results of this study, subsequently called CDC Study No. 1, were hand tabulated to look for important variables. The results indicated that TSS was associated with the use of tampons.

In all 52 cases, the women had used tampons. In 44 pairs, both the case and the control women had used tampons. In eight other pairs, however, the case woman had used tampons but the control had not ($P < 0.02$). There was no significant difference between case and control women in the mean number of tampons used per day nor when tampon use by brand was analyzed. Seventeen women with TSS had had a vaginal culture performed when they were ill and before they had received antibiotics; 16 of these (94 percent) yielded *S. aureus*.

By June 23, computer analysis of data from CDC Study No. 1 confirmed the hand-tabulated results. In addition, data from separate studies being conducted by Davis (*3*), as well as the Utah Department of Health (*11*), also supported a relationship between the use of tampons and TSS. On June 27, the MMWR reported that tampon use was associated with the development of TSS in women (*6*).

Intense activity followed the publication of the report in the June 27 MMWR. Many questions remained unanswered. Many epidemiologic and laboratory efforts to answer these questions were considered, and appropriate protocols were developed by CDC staff. Although *S. aureus* had been found in the vagina of almost all women with TSS who had been appropriately studied, the car-

Although S. aureus had been found in the vagina of almost all women with TSS who had been appropriately studied, the carriage rate of this organism in the vagina of healthy women during menstruation was not known. . . . Why were cases being recognized in menstruating women now and not a year ago or 10 years ago? Was there something in tampons now that was not present earlier?

riage rate of this organism in the vagina of healthy women during menstruation was not known, although the carriage rate in other phases of the menstrual cycle was about 10 percent. Why were cases being recognized in menstruating women now and not a year ago or 10 years ago? Was there something in tampons now that was not present earlier? Could tampons be contaminated with *S. aureus*? Why did *S. aureus* appear to be causing TSS? Was there an interaction between *S. aureus* and tampons that led to disease? How was the disease caused, since bacteremia in these patients was rare, yet the disease was so severe? How common was TSS? Was TSS common and severe enough to require immediate regulatory action by the Food and Drug Administration to remove tampons from the market place?

Within 2 weeks of the June 27 issue of MMWR, possible answers to some questions were available. The prevalence of *S. aureus* in the vagina of healthy menstruating women was determined by culturing specimens from 65 healthy women attending family planning centers in several locations in the United States; only six (9 percent) had *S. aureus* isolated from the vagina. On July 3, Schlievert, then at the University of California at Los Angeles, notified CDC that he had found a toxin, elaborated by strains of *S. aureus* from TSS patients, that he believed was responsible for the development of TSS (*12*). Shortly afterward, Merlin Bergdoll, PhD, University of Wisconsin, reported that he had found a toxin that he believed might be responsible for the development of TSS (*13*); these two toxins now appear to be the same material (*14*). On July 10, Mitchell Cohen, MD, a CDC officer in Seattle, reported that plasmids were not found in strains of *S. aureus* from women with TSS, implying that toxin production was not plasmid mediated. Tampons purchased at retail outlets and unused tampons sent in by women with TSS from boxes that they were using at the time of their illness were cultured by CDC and FDA; none were found to be contaminated by *S. aureus*. Meanwhile, the number of reported cases of TSS continued to rise; by July 11, 1980, 131 cases of TSS had been reported.

CDC Study No. 2. After the findings of CDC Study No. 1 were announced, surveillance results and data collected by the Utah Department of Health suggested that a particular tampon brand, Rely, had been used by many women with TSS. As a consequence, a second case-control study, later called CDC Study No. 2, was devised on September 2, 1980, to examine specifically tampon brand use by case and control women. In CDC Study No. 1 the researchers had been unable to examine adequately the use of individual tampon brands as risk factors because of potential differences in the accuracy of recall of tampon brands used by cases and controls, as well as differences in the availability of tampons over time.

During the period September 5–8, 50 women with cases and 150 controls matched by age and geographic area were interviewed by telephone. Unlike CDC Study No. 1, which included women with illness onset as early as 1977, all 50 women with cases had had onset of illness during July or August 1980, and their tampon use habits reflected usage patterns of currently available products. All women with cases reported to CDC who had had onset of illness during July or August were included in the study.

The results confirmed the association of tampons with TSS (*8,15*). In all 50 cases the women had used tampons compared with only 125 controls (83.3 percent, $P < 0.01$). In 42 cases, the women had used only one brand of tampon during the period in which they became ill, as had 113 of their matched controls. When the case-control sets of exclusive brand users were analyzed, a significant difference was observed in the use of Rely tampons for cases and controls. In 71 percent of the cases, the women had used Rely brand tampons compared with only 26 percent of the control women ($P < 0.0001$). The odds ratio was 7.7 for Rely usage compared with use of all other brands of tampons. When all 50 cases were analyzed for either predominant use or even use of a single tampon of a particular brand, the findings were similar.

On September 19, the results of CDC Study No. 2 were announced in the MMWR (*6*). By this date, 299 cases of TSS had been reported and, in 25 cases, (8.4 percent) the patients had died. On September 22, the manufacturer of Rely announced the voluntary withdrawal of its product from the market.

Epidemiologic followup since September 1980. At CDC, the period since the announcement of the results of CDC Study No. 2 has been used to consolidate sur-

veillance efforts, further describe the clinical spectrum of TSS, and further investigate its pathogenesis. Through April 16, 1984, a total of 2,509 cases of TSS have been reported to CDC, with the earliest case occurring in 1960, although in retrospect, cases clinically consistent with TSS have been reported in the medical literature as far back as 1927 (*16*). A retrospective examination of the temporal occurrence of reported TSS cases showed an increase in cases in the last quarter of 1979, compared with earlier periods, with a distinct peak in cases in August 1980 (132 cases) followed by a slight decline in September. Then there was a sharp drop in reported cases occurring in October to about one-half the cases that had occurred monthly in August and September, followed by a gradual decline to the 30 to 40 cases per month now recorded.

The increase in TSS cases reported in 1979–80 has been attributed to increased recognition and reporting of cases, as well as to real increase in the number of cases occurring. Similarly, a number of reasons for this decline have been put forth (*2,9,10*). These include the decrease in the number of women using tampons, hypothesized changes in the prevalence of strains of *S. aureus* capable of causing TSS, the withdrawal of Rely brand tampons from the market, the variable effects of publicity (both in the lay press as well as in the medical literature) on the reporting of cases, the effect of possible litigation on reporting of cases, changes in the manner in which cases are reported to the national surveillance system, and possible earlier recognition of cases, leading to earlier and more appropriate treatment, so that cases no longer meet the strict CDC case definition. It is likely that some, and possibly all, of these factors have played some role in the decline of reported cases since August 1980. CDC staff believe, however, that the decline in the number of cases reported reflects, in part, a true decrease in the incidence of TSS.

As knowledge of the disease has increased, a wide range of clinical settings where TSS may occur has been recognized. The vast majority of cases have occurred in females, and 99 percent of the cases that occurred during menstruation were associated with tampon use. About 15 percent of cases, however, did not occur during menstruation (*17*) but in association with focal staphylococcal infections. These observations underline the diverse conditions in which TSS may occur and the fact that the pathogenesis of TSS may be different in varying circumstances.

Despite the considerable accumulation of information in the 4 years since TSS was first recognized in menstruating women, important questions remain to be answered. In particular, definition of the interaction between tampons and *S. aureus* in the vaginal environment will be of paramount importance in the final understanding of much of the epidemiologic and laboratory evidence accumulated.

Food and Drug Administration

On June 13, 1980, CDC staff telephoned FDA's Executive Director of Regional Operations, Emergency and Epidemiologic Operations Branch (EEOB), to report a possible association of menstrual tampon use with the development of TSS. Although CDC had first published information on TSS in the May 23, 1980, MMWR (*9*), the association of the disease with tampon use had not been made in that article. Because menstrual tampons are medical devices under the authority of the Federal Food, Drug, and Cosmetic Act, EEOB immediately relayed CDC's information to FDA's Bureau of Medical Devices (BMD).

On June 24 and 25, FDA representatives, who had traveled to CDC, Atlanta, Ga., reviewed epidemiologic studies conducted by CDC and the Utah and Wisconsin State health departments. The results of these studies were to be reported in the upcoming June 27 MMWR, and the article would publicly announce an association between tampons and TSS. On the basis of the data presented at the meetings, FDA staff expressed the view that further studies were necessary to support that association more firmly. CDC staff, however, felt that the existing data were sufficient, and the article was published (*6*). FDA published an advisory on TSS in its July Drug Bulletin that described TSS symptoms, recommended treatment, and the results of the CDC, Wisconsin, and Utah studies (*18*).

An FDA June 27 telegraphic message to its regional offices and consumer affairs officers stated the agency's position on the issue of TSS—it had no basis for initiating regulatory action at that time. Also, the message stated that FDA intended to continue working with CDC staff to evaluate data on TSS. Persons who contacted FDA and said that they felt they might have TSS—or might have had it in the past—were advised to contact their physicians. Those who requested further information about TSS were referred to the June 27 MMWR or to CDC.

On July 16, former FDA Commissioner Dr. Jere Goyan identified an FDA task force that would work closely with CDC to review TSS data and planned epidemiologic studies. The task force consisted of epidemiologists, scientists, and physicians from selected offices throughout FDA and a BMD contact person. The task force reviewed the manuscripts of the CDC and the Wisconsin epidemiologic studies that were subsequently published (*3,6,19*). In addition, CDC continued to inform FDA of its surveillance activities and laboratory studies.

Over the next several months, the results of those activities led FDA to take several actions to deal with this public health issue. Investigators in the agency's field offices collected information relating to reported cases of tampon-related TSS; FDA headquarters staff met with tampon manufacturers to discuss new CDC and State epidemiologic findings and the necessary steps to protect the public; the Federal rule-making process was employed to assure adequate information about TSS on tampon package labels; and an educational program was initiated to inform tampon users about TSS.

Tampon inspections and investigations. Early in September 1980, two reported deaths from TSS within 1 week indicated a need for a more comprehensive investigation by FDA to determine whether tampons could, in fact, be shown to be a causal factor in TSS. On September 10, 1980, BMD issued a top priority assignment to all FDA field districts requesting followup investigations of all complaints of injury or death associated with the use of tampons. Staff of district offices were also requested to inspect all known tampon manufacturers' plants to obtain information on complaint file reports, materials used in the tampon and in the manufacturing process, a history of sterilization, and data on the testing of materials and labeling. To avoid duplication of efforts, FDA field inspectors were instructed on October 29 by the Emergency and Epidemiologic Operations Branch to follow up on complaints only, to collect information on the products, and to arrange for State agencies to follow up for medical information.

The tampon-associated complaints received by FDA and tampon manufacturers were reviewed by BMD staff. Of the 362 complaints received by FDA as of January 19, 1981, 128 fit the CDC case definition for TSS (*8*); they included 14 deaths. Other complaints included vaginal ulcerations, lacerations, and vaginitis. Brand information was included in some reports but absorbency information was often missing. No firm conclusions could be drawn from these data because of the inability to verify or clarify the information in many reports. By March 6, 1981, 7,321 individual reports or summaries of individual reports from the complaint files of manufacturers had been reviewed to identify those that were related to TSS or TSS-like illnesses. Unfortunately, none of the firms' records contained sufficient information to use CDC's case definition criteria to confirm TSS, although TSS was used to describe some reported illnesses. Also, because of the variations in the form, content, and methods used to collect the reports, BMD found it impossible to arrive at definitive conclusions regarding the etiology of TSS.

Because *S. aureus* had been identified as a possible causative factor in TSS, CDC and FDA investigated the possibility of tampon contamination. CDC cultured 504 tampons purchased between June 1980 and January 1981 and FDA cultured tampon samples from 40 tampon boxes from each of the five U.S. manufacturing plants in April 1981. *S. aureus* was not detected, although it was recognized that a much larger number of tampons would have to be cultured to rule out contamination. However, data from CDC studies and the literature indicated that the vaginal prevalence of *S. aureus* among menstruating females ranged from 0 to about 17 percent, decreasing the likelihood that tampon contamination is needed to introduce vaginal *S. aureus*.

Voluntary withdrawal of Rely tampons. On September 12, 1980, FDA representatives attended a meeting at CDC to review the findings of a second CDC epidemiologic study on TSS cases occurring in July and August 1980. Although the study indicated all brands of tampons were associated with TSS, Rely tampons were associated with a risk of developing TSS significantly greater than that with the other brands.

On September 16, FDA representatives met with CDC and Procter & Gamble (P&G), the manufacturer of Rely, to discuss the available data on TSS compiled by both the company and CDC. P&G representatives vigorously questioned the validity of the CDC study and attributed the conclusions concerning Rely tampons to the biasing effect of media publicity that specifically mentioned Rely in connection with TSS at the time that the CDC study was conducted. FDA officials requested that P&G further review the CDC data and then discuss with FDA whether the product should be removed from the marketplace, that is, a manufacturer-initiated recall.

Following the P&G meeting, FDA met with representatives of all major U.S. tampon manufacturers to discuss the latest CDC findings and to inform them that a press release concerning TSS was planned for the end of that week. On September 17, FDA and CDC issued the joint press release announcing that use of Rely tampons was associated with an increased risk of developing TSS. The conclusions of the second CDC study were published in the September 19 MMWR (*8*).

In a meeting at the FDA on September 22, results of the earlier Utah study (*11*) and a new study conducted by the Minnesota Department of Health were announced. The Utah data supported the findings of the second CDC study and indicated that Rely was associated with TSS more frequently than were other brands of tampons. Preliminary results of the Minnesota data indicated an association between TSS and all tampon brands.

On September 22, P&G voluntarily suspended the sale of Rely tampons and issued a press release announcing its action. Retailers were requested to remove Rely from their shelves and consumers were offered a refund on

unused products. The news accounts reported that P&G estimated its loss at $75 million. The details of the company's voluntary withdrawal of Rely from the marketplace, the reimbursement program, and a national media campaign to inform consumers of the company's actions were formalized in a consent agreement signed by FDA and P&G on September 26, 1980.

Tampon labeling. To facilitate coordination of FDA's consumer, scientific, and compliance activities concerning tampons and TSS, Commissioner Goyan requested on October 1, 1980, that the Bureau of Medical Devices establish a TSS Working Group. The group was formed and produced weekly status reports from October 31, 1980, to June 19, 1981, when it was disbanded after completing its work.

Between October 3 and 8, 1980, the Bureau's Associate Director for Compliance chaired meetings between FDA and tampon manufacturers to determine what actions the firms planned to take concerning TSS and to encourage them to include TSS information on or in each tampon package. Subsequently, all U.S. tampon manufacturers voluntarily included some type of TSS information with their product.

While the firms were moving toward developing voluntary package information on TSS, FDA saw the need for uniformity in the presentation of that information. On October 21, FDA published a proposed regulation in the Federal Register (45 FR 69840) requiring a warning statement concerning TSS on tampon packages. Interested persons were given until November 20, 1980, to comment on the proposed regulation. In response to two requests and because new information had become available, FDA published a notice in the Federal Register on April 28, 1981 (46 FR 23766), reopening the comment period until June 29, 1981. The new information that had become available consisted primarily of the results of the Tri-State Toxic-Shock Syndrome Study conducted by the Minnesota, Wisconsin, and Iowa State health departments. On June 11, 1981, Dr. Michael Osterholm of the Minnesota Department of Health and Davis met with FDA to present the results of the study, which concluded that the risk of TSS increased as tampon absorbency increased.

During the comment periods, more than 300 comments on the regulations were submitted to FDA from consumers, manufacturers, State and Federal health agencies, consumer organizations, and industry. Almost all comments favored some form of labeling concerning TSS. The final FDA regulation requiring that TSS information appear on tampon packages was published in the June 22, 1982, Federal Register (47 FR 26982). As a result of the Tri-State Study data on tampon absorbency, the final regulation required that tampon labeling advise women to use tampons with the minimum absorbency needed to control menstrual flow.

Toxic-shock syndrome education. In addition to promulgating the tampon labeling regulation, FDA provided considerable information to health professionals and consumers about the danger of TSS and its association with tampons. For example, information directed to health professionals on TSS diagnosis and recommended treatment was published in three FDA Drug Bulletins (*18,20,21*).

In another communications effort, a periodically updated FDA consumer brochure on TSS (*22*) has been distributed throughout the United States to FDA consumer affairs officers to be included in local consumer workshops and information-exchange meetings.

Conclusion

The manner in which decisions were made at the Food and Drug Administration from 1980 to the present regarding toxic-shock syndrome and its association with menstrual tampons is a classic example of how epidemiologic studies can directly influence U.S. health policy decisions. An FDA final regulation required TSS information on tampon packages marketed in the United States.

Information on toxic shock syndrome has been widely disseminated to the U.S. public through a number of channels.

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The Role of Epidemiology in the Regulation of Oral Contraceptives

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Synopsis

The U.S. Food and Drug Administration (FDA) has relied to a great degree on epidemiologic studies in the regulation of oral contraceptives (OC). These epidemiologic studies range from individual case reports of adverse reactions to case-control studies and cohort studies.

Important findings about adverse reactions to OCs have been communicated through "labeling," which includes information leaflets provided as package inserts for physicians and patients. Also, the FDA communicates its position through publications in medical journals, the FDA Drug Bulletin, public advisory committee meetings, workshops, and symposia. The agency responds to new epidemiologic information; labeling guidelines are under continuing review and revision.

Patterns of oral contraceptive use have been affected by the dissemination of this information. There has been a decline in the use of OCs, a shift to formulations with lesser steroidal content, and a greater emphasis on OC use in optimal groups, such as young, nonsmoking women.

Considered for future epidemiologic studies that may have an impact on regulatory action are a clarification of the role of various progestins in regard to blood lipid alteration and atherogenesis, a delineation of the possible persistence of cardiovascular risk after termination of OC use, and further clarification in regard to neoplasia, particularly breast and cervical carcinoma.

THE FOOD AND DRUG ADMINISTRATION (FDA) has relied extensively on epidemiologic findings in its regulatory approach to oral contraceptives (OC). It is fair to say that no other class of drugs has been subjected to as exhaustive epidemiologic study as have OCs. The circumstances have been favorable from an epidemiologic point of view. A potent physiologic agent had been given to large numbers of healthy women. By 1980, it was