The Neurosurgeon in Sport: Awareness of the Risks of Heatstroke and Dietary Supplements

To the Editor:

After seeing numerous media reports such as "Football Deaths May Be Linked to Supplements" (Reuters, July 29, 2002), we read with interest the recent editorial in *Neurosurgery* by Bailes et al. (4), who contended that the recent increased incidence of heat-related deaths among American football players may be related to the use of nutritional supplements such as ephedra and creatine. Although we share their concern that athletes, coaches, trainers, and physicians need to be educated properly regarding ways to prevent heat-related exercise problems among athletes, we are concerned that this editorial and the resultant media attention that it garnered have served to mislead the scientific community and the public about the possible causes of heat-related deaths among athletes and the safety of nutritional supplements. Because some of our work was cited supposedly in support of the authors' position, we felt compelled to respond to this editorial.

The authors began their editorial by citing statistics from the National Center for Catastrophic Sports Injury Research indicating that the number of heat-related fatalities in American football decreased from 4.4/yr in the 1965 to 1974 period to 1.6/yr in the 1975 to 1985 period and 0.6/yr in the 1985 to 1994 period. They suggested that the decreased incidence of heat-related fatalities was a result of increased efforts to educate trainers, coaches, and athletes about proper hydration. They also suggested, however, that from 1995 to 2001, a reversal of this downward trend was observed, with a total of 20 deaths occurring during this period, including 4 deaths in 1995, 1998, and 2000 and 3 deaths in 2001. *Figure 1* in the original article was presented to illustrate the supposed upward trend in heat-related fatalities among American football players, from a high of 14/yr (an aggregate of several years in the early 1960s) to a low of approximately 2/yr in 1988 to a new high of 4/yr in 2000. The graphed points in the figure actually continue to increase past the last data point in 2000 to suggest a continued upward trend to approximately six hypothetical deaths in subsequent years. This upward trend was assumed despite the fact that three heat-related deaths of football athletes were actually recorded in 2001. The authors contend, "Recent trends in football heatstroke fatalities toward significant increases may, in part, be attributable to or aggravated by the use of dietary supplements. Credible scientific evidence has been found that amphetamine derivatives and the ergonomic aid creatine may contribute to subclinical dehydration and heatstroke in selected individuals" (4, p 283).

We have several concerns about the presentation of these data and the opinion that dietary supplementation may be related to these heat-related fatalities. First, no statistical analysis was presented in the editorial to support the authors' contention that a "significant" upward trend in the incidence of heat-related fatalities among American football players has actually occurred in recent years. Although any potentially preventable heat-related fatality is one too many, the data curve in *Figure 1* of the original article shows an overall decrease in the incidence of heat-related fatalities since the 1960s. In addition, the incidences of heat-related death of 4/yr and 3/yr in 2000 and 2001 are consistent with the incidences in many of the years from the mid-1970s to 1994 that the authors suggested were low-incidence years. Second, the authors did not discuss the number of heat-related fatalities in American football during the past few years in the context of the overall risk of playing football. For example, according to an annual study recently released by the University of North Carolina at Chapel Hill (64), 23 football players died in 2001. Of these, 8 athletes died as a result of injuries sustained on the field (primarily head and neck injuries), 12 died as a result of natural causes precipitated by vigorous workouts, and 3 died as a result of heatstroke. That analysis makes it clear that the risk of sustaining fatal head and neck injuries and/or dying as a result of natural causes during vigorous training are greater than the risk of heat-related death. Third, little attention was paid to the fact that today many American football players in some positions are 50 to 100 pounds heavier than the players in the same positions 10 to 20 years ago (47). From the 1960s through the mid-1980s, it was rare to find a 300-pound lineman. In recent years, it has not been unusual to find high school teams with 280- to 350-pound linemen, and many Division I-A college football teams boast front lines whose average weight per player is 315 to 330 pounds (47, 58). According to the National Center for Catastrophic Sport Injury Research statistics (47), most heat-related deaths in recent years have occurred in individuals who weighed more than 250 pounds, with many athletes weighing more than 300 pounds (47, 58). Other factors that may have contributed to the fatalities, such as the impact of recent heat waves during fall football camp (9, 11, 12, 18, 47), possible hyponatremia as a result of excess water intake after practice (11), inadequate recognition and treatment of athletes with heat illness and excessive fatigue (9, 12, 17, 18, 47), and/or inadequate medical supervision of athletes engaged in intense training in hot and humid environments, were not addressed in detail (9, 12, 17, 18, 47). All of these factors were reported in the media, in autopsy reports, and/or in the 2001 National Center for Catastrophic Sport Injury Research annual report on football injuries as actual contributing factors to the deaths of football players in recent years.

Finally, despite these apparent contributory factors, the authors speculated that the increased incidence of heat-related fatalities in recent years could be attributed only to the increased use of dietary supplements (specifically ephedra and creatine) that has presumably occurred as a result of the passage of the Dietary Supplements Health and Education Act in 1994. Yet, the authors presented no data correlating heat-related fatalities to supplement use, other than to reference survey research reporting that athletes take nutritional supplements and isolated case reports suggesting that ephedra supplementation has been re-

lated to a number of unsubstantiated adverse events. Moreover, the authors presented no data to indicate that any of the athletes who recently died as a result of heatstroke were even taking ephedra or creatine at the time that they died. We think that these authors' position misrepresents the literature regarding the safety of ephedra and creatine dietary supplements. For example, although we do not endorse athletes' taking ephedra alkaloids (substances that are banned by the U.S. Olympic Committee, the International Olympic Committee, the National Collegiate Athletic Association, and the National Football League), the authors failed to inform readers that a number of clinical trials have indicated that synthetic ephedrine and herbal ephedra alkaloids can safely promote weight loss in obese and trained populations when used in appropriate doses by healthy individuals (2, 3, 7, 8, 10, 13, 14, 19, 33, 46, 61). We think that the authors' failure to cite these studies and others in discussing the safety of a supplement that they contended has increased the incidence of heat-related fatalities is misleading and inappropriate.

The authors also contended that there is "credible scientific evidence" that creatine supplementation causes intramuscular fluid shifts that alter plasma volume, promotes dehydration and muscular cramps, causes diarrhea, and is associated with heat intolerance. To support their contention that creatine is associated with these problems, the authors primarily cited survey and review articles that actually discuss the lack of scientific evidence that creatine causes these anecdotally reported side effects. The authors failed to inform readers that the vast majority of scientists who have conducted research on creatine think that it has no influence in or relationship to these problems. This opinion is based not on speculation but rather on the facts that no clinical trial has reported such side effects and that numerous studies that have recently attempted to examine the validity of these anecdotal reports have found that creatine supplementation has no effect on thermal stress and/or dehydration (34, 45, 49, 56, 62, 63), muscle cramping (20–28, 30–32, 36, 38, 39, 62), electrolyte status (31, 35, 37, 40, 54, 62, 65, 66), renal stress (1, 15, 37, 40, 41, 44, 50, 52, 53, 55), muscle trauma (21, 22, 27, 30, 32, 37–40, 48, 60), and/or general markers of clinical health in athletes (5, 6, 16, 29, 36, 37, 40, 42, 51, 55–57, 59). Furthermore, recent studies in which the incidence of injury among football players, baseball players, and soccer players during training and competition have been monitored carefully have indicated that creatine users experience a similar or decreased incidence of dehydration, heat-related disorders, muscle cramping, and musculoskeletal injuries compared with athletes who do not use creatine (21–23, 25–28, 30, 32, 36–39, 43, 48, 57). Given this large body of evidence, our view is that associating creatine supplementation with recent heat-related fatalities is scientifically insupportable, inappropriate, and misleading.

It is our view that commentary about the safety and efficacy of training methods, athletic care, and/or nutritional supplementation should be based on a thorough examination of the scientific literature so that informed decisions and policies can be made. This editorial has served to infer that dietary supplementation with ephedra and creatine increases the risk of heat intolerance without providing data to show that such a relationship exists. As a result, instead of stressing the importance of properly educating athletes, coaches, and trainers about proper conditioning to decrease the risk of heat-related illness when exercising in hot and humid environments through heat acclimatization, proper hydration, training of coaches, and medical supervision of athletes, this editorial may mislead some readers to conclude that simply prohibiting athletes from taking supplements will eliminate the risk of heat-related fatalities. In addition, it may serve to misinform the public about the safety of a supplement such as creatine, which has been studied extensively and has been shown to have ergogenic and therapeutic benefit for healthy, athletic, orthopedic, and diseased populations (including people with a number of neuromuscular disorders). Although we think that it is important for athletes to inform their athletic trainers and team physicians about any over-the-counter drug or supplement that they take and that this information should be considered in the care of athletes, the truth is that athletes who play football are at greater risk for injuries by participating in their sport than by taking nutritional supplements. This is particularly true when athletes are required to train in hot and humid environments without adequate medical supervision and/or intervention when heat-related illness occurs.

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In Reply:

We appreciate the interest of and comments by Kreider et al. concerning our editorial (5). Although they argue that dietary supplements that contain amphetamines such as ephedrine compounds and creatine are safe, they miss the point of the editorial.

Statistical analysis of fatalities in sports in the United States has always been difficult, because there is no central or governmental reporting agency responsible for monitoring such events. The National Center for Catastrophic Sports Injury Research data that we reported represent our best attempt to gather and collate data concerning all deaths on the football field, but they are incomplete because of the inaccessibility of much information. It was not our intent to compare or contrast the numerous causes of death in contact sports such as football. We certainly acknowledge the inherent risk of death as a result of head and cerebrospinal injuries or cardiac dysrhythmia (4). In contrast to the recognized risk of death as a result of catastrophic central nervous system injury, which is widely appreciated by neurosurgeons, we wished to emphasize that there seems to be a recent trend toward an increasing number of deaths that are a result of heat-related illness. This small but important increase in the years after the deregulation of dietary supplements has occurred despite what we think is adequate and effective knowledge of the clinical science of dehydration and its treatment by physicians, athletic trainers, coaches, and players (16). This increase in heat-related fatalities has transpired while the number of direct injury-related football deaths has generally remained level (9). Although we also acknowledge that numerous factors may be operative in causing nontraumatic deaths in athletes the use of dietary supplements, among other variables, should at least be considered in conjunction with training in extreme heat.

As we stated in our editorial, we recognize that several factors potentially contribute to this apparent increase, including the additional body weight of modern football players. However, an increase in players' weight did not occur just within the past several years. We appreciate the authors' pointing out that misdiagnosis or medical mismanagement may occur in the heatstroke setting, and we are acutely aware of the necessity of accurate and proper health care delivery on a daily basis. We want instead to stress that changes in ath-

letes' behavior, in particular the widespread use of exogenous substances, may lead to an increased risk of dehydration and heat-related illness in select or vulnerable individuals while exercising in a heat-stressed environment.

Kreider et al. criticize us for failing to cite clinical studies indicating that amphetamine compounds including ephedra alkaloids can safely promote weight loss in healthy individuals. We did not think that it was our obligation to document that these substances are, in fact, well tolerated by most people; instead, we thought it important to emphasize that amphetamines do occasionally generate unwanted physiological responses. Numerous studies have purported to demonstrate the safety and effectiveness of these substances as aids for weight loss in obese and trained individuals (7, 23). However, more than 3300 cases of adverse effects involving all dietary supplements have been reported to the U.S. Food and Drug Administration in 8 years; 1400 (42%) of them were associated with ephedrine alkaloids, including 81 deaths (3). A recent review covering a 3-year period showed 926 cases of possible herbal ephedrine toxicity in which stroke, myocardial infarction, and death were temporally related in 16, 10, and 11 individuals, respectively (1, 20). In addition, the concomitant ingestion of large amounts of caffeine, a common practice among athletes, has been shown to lead to significant increases in both systolic blood pressure and heart rate (11).

We agree that creatine is generally a safe and efficacious dietary supplement, and although numerous studies have demonstrated its positive effects as an ergonomic aid, the question remains regarding whether or to what extent any athlete who is about to be subjected to an extreme heat stress environment should continue to consume exogenous substances. The studies mentioned by Kreider et al., many of which were published in abstract form, indicate that during football, soccer, baseball, and cycling trials with creatine, there were no observed trends toward abnormalities in renal, metabolic, muscular, or fluid maintenance function. With regard to the relative rarity of heat-related football deaths, which annually occur in only several players among 1.3 million participants, it is unlikely that a controlled study could account for the multiple factors that must be in place for circulatory insufficiency to progress to multiorgan failure and thermoregulatory death. In addition, analysis of the potential role of an exogenous substance with metabolic actions would be difficult. These multiple other factors include the relative dehydration of the athlete before participation, heat acclimatization, the amount of heat and humidity exposure, the intensity of exercise, the design of the athlete's clothing and/or uniform, fluid replacement, the athlete's underlying medical or cardiac status, the simultaneous ingestion of substances or medications that may interact, excessive dosage, genetic predisposition, medical management, and other possible variables.

Notwithstanding the considerable investigations reported by Kreider et al. and the supplement industry, controversy nonetheless remains, which is highlighted by the numerous conflicting reports in the literature concerning perceived untoward effects of creatine use (10, 14, 15, 17, 19, 21). Long-term effects of creatine supplementation also are unknown (12, 18, 22). In one referenced article, for example, we are not certain that cycling for 1 hour in a 37°C environment by 75-kg individuals at 60% of maximum oxygen consumption, with no concomitant ingestion of other drugs or caffeine, necessarily recapitulates the extreme environmental stresses that many football players endure in preseason summer football sessions and ensures the categorical safety of creatine use (13).

The mechanism of action of creatine seems to result in increases in total body water by enlarging intracellular water content, but whether increased intracellular water content can be mobilized adequately or in a timely manner in select individuals to be available for intravascular volume support during acute heat illness is unclear (18, 22). This is especially true for the small number of athletes who may have ingested concomitant medications or herbal or dietary supplements, as well as those with recent dehydration; those athletes who are not heat-acclimated, who may experience individual variability; or athletes with unrecognized medical co-morbidities. In addition, physiological attempts to compensate for heatstroke-induced impending circulatory failure have never been studied with regard to the role and interaction of exogenous substances (8).

Athletes today face tremendous pressure to compete and win. The clichéd "win at any cost" attitude is far too common in modern sports training and performance (1, 2, 26). It is known that current athletes often not only consume numerous substances but do so in more than the recommended amounts. Because of deregulation, it is suspected that there is an increased tendency to consume more than the recommended amounts of dietary supplements, and it is easier for many athletes to use these supplements. Creatine has been reported to have been consumed by athletes in greater than recommended doses. Studies have not been performed, however, to measure the effects of larger doses, particularly in a heat-stressed environment. In addition, athletes often consume a cornucopia of exogenous substances, including not only anabolic steroids but also caffeine, human growth hormone, erythropoietin, and salbutamol (24). Another new and fashionable substance is clenbuterol, a $\beta 2$ and $\beta 3$ agonist that has not been studied or analyzed in environmental stress conditions such as extreme heat. Also, the potential for drug-drug interactions is a ubiquitous concern that is difficult to assess fully in any experimental design (6).

Our emphasis is not on the individual safety profile of each of the above-mentioned substances or dietary supplements but rather to warn of a possible link between the behavior of modern athletes and the use of exogenous agents that they may think give them an edge in preparation for competition. Although the number of nontraumatic or heat-related fatalities in U.S. football is small, these deaths are not insignificant. We think that the apparent increase in recent years is not due to misdiagnosis, water intoxication with resultant hyponatremia, medical mismanagement or nonsupervision, or faulty on-field care by athletic training staff, as Kreider et al. assert.

Instead, heat-related illnesses may be influenced, in selected instances, by the consumption of exogenous substances. In no manner did we attempt to mislead those involved in the care of athletes and their training methods, as Kreider et al. state, as supported by our collective 70 years of experience in attempting to emphasize education and understanding of the pathophysiology of athletic injuries. Instead of issuing an indictment of all dietary supplementation, we tried to emphasize the constant risk—albeit small—of heatstroke in athletes who train and compete in heat-stressed conditions and that the symptoms of heatstroke are often of subtle but rapid onset and constitute a medical emergency.

Accurate, educated, and thorough approaches to the medical aspects of athletic training and sports medicine are universally supported. In fact, discussions with the majority of current athletic trainers will yield the response that one of their greatest concerns today is the uncertainty surrounding their athletes' exploding use of exogenous substances. Just as others have recently suggested regarding the use of selected dietary supplements, we recommend the cessation of use of all such substances before engaging in training sessions during hot conditions, especially by individuals who are not heat-acclimated (25).

The prevention of serious adverse medical events involves the elimination of any potentially controllable factors. Rarely, if ever, can the ingestion of a foreign substance be described as safe across the full spectrum of all human and athletic activities. Hence our message: the use of any foreign substance for the sole intention of enhancing athletic performance may have untoward and unanticipated consequences in some individuals.

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