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DASH-Sodium Trial: Where Are the Data?

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A recent *New York Times* editorial[1] suggested that medical research may suffer the same loss of society's confidence that we have witnessed recently in other sectors of our society. Two medical issues reported in the preceding week precipitated the article. One was the discontinuation of the hormone replacement therapy (HRT) limb of the Women's Health Initiative,[2] raising the possibility that one of the "absolutes" of women's health management was not scientifically verifiable. The second was an investigative commentary in its own Sunday Magazine[3] that asked "what if fat did not make you fat?" That article generated heated debate in letters to the *Times* editor, a commentary in the *Wall Street Journal*, and lively exchanges on national TV and radio. As with the HRT episode, the article on dietary fat challenged one of the most widely held beliefs in U.S. preventive medicine policy.

Several common factors created the conditions leading to the emotional conflicts these two issues have generated. First, both HRT and dietary fat policies were established long before properly controlled randomized trials produced data to support them. Second, our nation's research establishment led by the National Institutes of Health (NIH) is heavily invested in each policy, trumpeting them as broadly applicable to all at risk, postmenopausal women in the former case and essentially all individuals in the latter. Third, these challenges to conventional medical wisdom emerged at a time when our society is repeatedly confronting the reality that leaders of respected institutions and corporations have manipulated and misrepresented data at tragic expense to us all. Implicit in the *New York Times* editorial was the proposition that some medical research and the public policy derived from it might be subject to these same questionable forces.

In the area of hypertension research there is currently an unfortunate example of compromised data reporting from an important federally funded trial. Equally disconcerting is that senior members of our research community are currently using the inaccurate interpretation of data to influence national nutrition policy and practice guidelines related to hypertension management. With full disclosure of the facts involved, it could reasonably be argued that elements of this situation are disturbingly similar to those that have become all too familiar in big business. These include: withholding information that the public has the right to know; auditing mechanisms that fail to detect improprieties, electing to remain silent when issues arise; reluctance by colleagues to challenge misleading promotion of the data; and presentations to federally constituted panels that fail to disclose requested data.

In question is the NIH-funded Dietary Approaches to Stop Hypertension (DASH)-Sodium Trial,[4] which was an important and logical study following the impressive results seen in the original DASH Trial.[5] In the words of the DASH investigators, a diet rich in fruits and vegetables and dairy foods low in fat had an impact on blood pressure (BP) equivalent to single drug therapy. These findings were particularly noteworthy given the Trials of Hypertension Prevention (TOHP) report[6] of the same year. TOHP demonstrated that limiting sodium intake at levels consistent with current U.S. nutrition policy was substantially less effective than the DASH diet in reducing BP. As earlier studies have suggested, these carefully executed studies provide clear evidence that nutrition policy for preventing and managing hypertension could be more productively directed at improving overall diet quality, as defined by the DASH Trial, rather than restricting sodium.

DASH-Sodium Trial offered an unprecedented opportunity to assess whether sodium restriction offered additional BP benefits to an at-risk population that was already consuming the DASH diet. The potential outcome suggested by prior research[7–10] was that once at-risk persons improved the quality of their diet, principally by increasing intakes of dairy foods, fruits, and vegetables, sodium restriction would have little or no further effect. The initial public presentation of the DASH-Sodium Trial results occurred in May 2000 at the American Society of Hypertension (ASH) Annual Meeting, the day *after* they were announced in a National Heart, Lung, and Blood Institute (NHLBI) press conference that featured NHLBI Director, Dr. Claude Lenfant, and received widespread media coverage.

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Before formal presentation of the data, the media was told that DASH-Sodium Trial demonstrated that even normotensive individuals would benefit from dietary sodium restriction and that the national nutrition policy recommendation for sodium intake should be lowered from 2400 to 1500 mg/day. These claims were strongly reinforced by Dr. Frank Sacks' presentation and comments at the ASH meeting. Although the study was powered to allow for subgroup analysis—the data necessary to support the contention that normotensive subjects benefited from sodium restriction—these were not presented nor provided when directly asked at ASH.

Although the primary publication was under review at the *New England Journal of Medicine*, quotes from Sacks were prominently featured in cover stories in two national health publications. Articles in *Hippocrates*[11] and the *Nutrition Action Healthletter*[12] appeared in September 2000 and December 2000, respectively. The statements from Sacks strongly reinforced the aggressive interpretation of the data as promoted in the NHLBI press release and at the ASH meeting. However, data to support these claims were still not provided. This author had several communications with the editors of the *New England Journal of Medicine* before the article's publication in which I expressed concerns regarding the widespread media coverage the authors' conclusions were getting before the data were publicly available. I also emphasized the importance of publication of the subgroup analysis—the only means of determining the truth of the claims that everyone would benefit from reduced sodium and that national intake guidelines should be further lowered.

Published in the *New England Journal of Medicine* in January 2001,[4] the DASH-Sodium Trial article concluded that: "Our results should be applicable to most people in the United States" and ". . . our results provide support for a more aggressive target for reduced sodium intake." Remarkably, nowhere in the article was there exposition of the data that are fundamental to such an intervention study, ie, the means, standard deviations, and sample sizes for the subgroups specified in the study protocol on the two diets (control and DASH) at three levels of sodium intake. Without these data, it is simply not possible to determine whether the authors' conclusions are valid. The impact of these unsubstantiated statements was amplified by the accompanying editorial by Dr. Philip Greenland who stated: "the main message of this new trial stated forcefully by the authors . . . is the results appear to be applicable to most people in the United States," and he advocated "widespread adoption by all persons with and without hypertension."[13]

The *Journal* subsequently published several letters from scientists who questioned various aspects of the DASH-Sodium Trial report.[14–17] This author wrote that: "Even the very limited data provided in figures 1 and 2 of the article indicate . . . any effect of sodium restriction was limited . . .Thus, the authors' statement that these findings are broadly applicable to the entire population, are not true. To prove otherwise, the authors are obligated to report . . . the analyses of subgroups."[14]

Sacks et al's response[18] was telling in its word selection ". . . the DASH-Sodium Trial findings are *qualitatively* the same amongst all subgroups, but differ *quantitatively*" [italics added]. Once again the actual data were not provided, although it was stated that the "full subgroup results" would be published soon. That publication appeared in December 2001 in the *Annals of Internal Medicine*,[19] and despite the title "Subgroup Analysis of DASH-Sodium Trial," the promised full subgroup results were still not reported. In fact, the analysis was based on a model that eliminated the 2400 mg/day sodium intervention and "used generalized estimating equations to fit linear models." That statistical maneuver precluded, once again, any possibility of clearly determining whether the authors' prior conclusions and recommendations were justifiable.

To put this in perspective, envision a pharmaceutical intervention that used three "doses," in this case sodium levels, in a comparable hypertensive population and then attempted to gain approval for the use of the stronger dose (in this case 1500 mg/day of sodium) based on an analysis that excluded the intermediate dose (2400 mg/day of sodium). The response of the Food and Drug Administration (FDA) and informed scientists would be vigorous and preemptive, forcing full exposition of all the data. What the DASH-Sodium Trial authors did in the *Annals* article would not meet the standard that would have been applied to the pharmaceutical company by the FDA or one of its review panels. It certainly did not fulfill the published assurance of Sacks et al[18] that the full subgroup analysis would be published. The analysis in the *Annals* did, however, provide clear evidence that only full presentation of the data would settle this issue. Table 4, "Multivariate Regression Analysis . . . in Selected Subgroups," documents that normotensive persons less than 45 years of age who were consuming the DASH diet experienced no further significant improvement in BP with sodium restriction below 3300 mg/day.

This finding is incompatible with the conclusion and interpretation of the trial repeatedly advanced by NHLBI and the DASH investigators in their press releases, presentations, and publications. The findings of DASH-Sodium Trial are not broadly applicable and they do not warrant a lower target for sodium intake for most Americans. Only older hypertensive persons exhibited BP benefit; 2.8 mm Hg reduction when sodium was restricted from 3300 to 1500 mg/day. Because the 2400 mg/day sodium diet was excluded from the analysis, one can only speculate how truly limited the group is that would benefit from further sodium restriction in the US (current recommendations being 2200 mg/day), provided their diet is otherwise adequate in terms of dairy, fruit, and vegetable intakes.

The answer to that question is central to a process

currently underway under the auspices of the Food and Nutrition Board (FNB) of the Institute of Medicine and the National Academy of Sciences. The FNB is currently considering revision of the Daily Recommended Intakes (DRI) for sodium, potassium, and other electrolytes, in the context of a diet adequate in all other nutritional factors. This report will have broad impact in public and private health agency recommendations, medical practice guidelines, and health claim and food labeling regulations. Reviewing the DASH-Sodium Trial results at an FNB meeting in June, Dr. Sacks repeated the conclusions set forth in the original publication and editorial,[4,13] again without providing the subgroup analysis in either his presentation or in response to specific queries about it by audience and panel members. Dr. Sacks simply referred to the *Annals* article.

Summarizing many of the concerns and implications surrounding the DASH-Sodium Trial authors' failure to provide this fundamental data, this author called upon the *New England Journal of Medicine,* as publisher of the original article and editorial, to request the data necessary to support the authors' conclusions. The request for full disclosure of the DASH-Sodium Trial data was made in hope that it "occur in a manner that reflects best on the peer-review process." The editor's response was that "after lengthy discussion we have been unable to define a publication strategy that would address your concerns" (GD Curfman, 8/20/02).

It is unfortunate that despite reasonable, appropriate, and extensive efforts, critical data from a federally sponsored trial have been withheld. With this summary of these efforts, it is hoped that the DASH-Sodium Trial Research Group will provide the missing data. That simple, responsible action would allow the scientific community on its own to determine whether the conclusion and recommendations of the DASH-Sodium Trial investigators are truly valid.

The good news is that DASH-Sodium Trial may well be the key to achieving something rare in science–resolution of an issue that has been hotly debated for decades. As suggested a few years ago, in the sodium controversy we could all be right.[20] Dietary salt does elevate BP in certain individuals if they consume a poor diet. If the quality of the diet is adequate, salt intake has little relevance to BP control for the vast majority of individuals. It follows that the focus of national nutrition policy directed at hypertension should be on overall diet quality. To finally determine whether resolution is within reach, we do not need statistical maneuvering or personal interpretations; rather, to borrow the words of that great American investigator Sgt. Joe Friday, "we just need the facts, just the facts."

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