Reply to Drs. Lemmer and Pickering

Subsequent to Dr. Tom Pickering's article on white coat hypertension in the Journal, Dr. Lemmer wrote to point out that Hellwig may have reported the phenomenon as long ago as 1738. Actually, when the Reverend Stephen Hales first noted blood pressure by intraarterial measurement in 1711, he demonstrated "office" or white coat hypertension in the horse he studied. Figure 1 is an artist's conception of the scene which took place in Hales' barn (laboratory or "office") during the experiment. The artist prepared this sketch for me from the description of the procedure as written by Hales in his original treatise, as follows: 4

"I caused a mare to be tied down alive on her back . . . having laid open the left crural artery . . . I inserted a brass pipe . . . (to which) I fixed a glass tube . . . the blood rose . . . 8 feet 3 inches perpendicular above the left ventricle . . . (later) "it would fall 12 to 14 inches." (It is of note: that 8 ft 3 inches converts to 183 mm Hg and a fall of 14 inches would reach a level of 155 mm Hg.) "The pulse of a horse that is . . . not terrified . . . is about 36 beats in a minute . . . this mare's pulse was 55 to 100 in a minute . . . she being in pain."

I have used this illustration for many years to demonstrate that Reverend Hales elicited the "pressor response to a noxous stimuli" (183 mm Hg is high even for a hotel) at the very first time he demonstrated the hydraulic force of the circulating arterial blood. Furthermore, he showed the liability of blood pressure when he described the fall that occurred with "relaxation" and then later with blood loss (after removal of 7 quarts of blood, the column fell to 48° or 104 mm Hg).

There is almost always a predecessor who precociously noted a phenomenon, and Pickering acknowledges Lemmer's comments as well as the 1940 contributions of Asman and Goldshliss. But does deserve credit for promulgating and clarifying the "white coat" observation in recent years and its importance in decisions concerning blood pressure management.

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A. C. P. Graduate

From the Internal Medicine Residency Program, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213.

FIGURE 1. Sketch of scene in Dr. Hales' barn. Reprinted with permission from Shapiro AP."

The 1993 Treatment Guidelines: More Criticisms

The criticisms aired in your columns of the various 1993 guidelines for treating hypertension, and of JNC-V in particular, are welcome. The ensuing debate has provided a much healthier scientific atmosphere than prevailed earlier. I have reviewed the guidelines critically and in some detail elsewhere. However, several points arising from the more recent exchanges require further comment and correction.

Dr. Moser repeats in his recent letter an assertion made earlier in JNC-V that "diuretics and β-blockers..."
... are the only two classes of drug that thus far have been tested and shown to reduce morbidity and mortality in long-term hypertension treatment trials.\footnote{13} He then goes on to state, not entirely consistently, that methyldopa, clonidine, or reserpine were added in some of the earlier studies. This is not an accurate description of the situation. There is of course considerable dispute concerning which trials should be evaluated when making such assessments: several, including Hypertension Detection and Follow-up Program (HDFP),\footnote{14} have for example been rated as being of low quality.\footnote{15} Rightly or not, the trials most often considered by the guidelines papers were the 13 of the Collins et al metaanalysis,\footnote{16} plus the Systolic Hypertension in the Elderly Program (SHEP), the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension), and the second Medical Research Council (MRC) trial.\footnote{17} Of these 16 studies, \(\beta\)-blockers featured in fewer than half, only 7.\footnote{18} By contrast, centrally-acting agents (methyldopa, rauwolfa, or clonidine) were employed in 14 of the 16. Diuretics were used in all 16, albeit in varying types and doses, and with widely differing attempts at potassium conservation. The New Zealand discussion document, which so worried Drs. Nicholls and Richards, takes this misappraisal further, stating "Low dose diuretics and low dose \(\beta\)-blockers should be considered as first line treatment ... These are the only classes of drugs which have been shown in randomized clinical trials to reduce the risk of cardiovascular events."\footnote{19} I have been told that this erroneous statement partly reflects unfortunate wording. Even so, to compound a misconception with a non sequitur remains a misfortune of some magnitude.

The much-quoted, much denigrated, but remarkably persistent HDFP study\footnote{20} has plagued interpretation in this field since 1979. It still clearly colors the thinking of JNC-V. A major fault in the HDFP design was that it did not assess simply antihypertensive drug therapy, but compared two entirely different systems of health care, in one of which was included a stepped-care program (SC) of antihypertensive drug treatment. However, the SC patients also received substantial financial assistance, and more ready access to diagnostic and therapeutic facilities, for whatever reason, than did the comparison (RC) group. Almost certainly the lower morbidity and mortality in the SC group, which was shown for a range of noncardiovascular, as well as cardiovascular, causes, reflected these differences in health care.

There is a further confounding aspect of HDFP that is frequently overlooked, even by some usually well-informed members of JNC-V.\footnote{21} The protocol of HDFP\footnote{22} prescribed for the SC patients multiple risk factor interventions, including, where indicated, antismoking counselling and dietary attempts to lower body weight and serum cholesterol. Strangely, one of the coauthors of a metaanalysis\footnote{23} of hypertension treatment trials much quoted in the guidelines has stated\footnote{24} that the Multiple Risk Factor Intervention Trial (MRFIT) was excluded from that metaanalysis "because of the potential confounding likely to result from the concurrent interventions for smoking cessation and cholesterol lowering." Why HDFP,\footnote{25} which likewise possessed these potential sources of confounding, was allowed to remain has not, so far as I am aware, been explained. JNC-V is strangely silent on this point. It would be opportune to rectify this anomaly now, since the incorporation of HDFP in such analyses must inevitably erode confidence in any derived conclusions.

Moreover, HDFP, in which there was concurrent prescription of diuretics with dietary attempts to lower serum cholesterol, cannot provide a secure base for evaluating long-term effects of diuretics on cholesterol, even though it might be pointed out that, as usually implemented, such dietary interventions are largely ineffective.

It is unfortunate that the 1993 guidelines exude a defensive authoritarianism more suited to medieval theologians than to contemporary clinical scientists. Neither the motives nor the intentions of the committee members are impugned. However, inaccuracy is not excusable. There is much danger that real and substantial benefits in the drug treatment of hypertension could be discredited, or that very necessary future research will be inhibited.

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How Should Circadian Blood Pressure Variation Be Determined?

I read with great interest the recent editorial by Dr. Pickering entitled "How Should Diurnal Changes of Blood Pressure Be Expressed?" He notes that two techniques are used most often to determine the period of nocturnal decline in blood pressure (BP): 1) the diary method; and 2) arbitrarily defined time periods, such as recommended by Scientific Committee of the International Conference on Ambulatory Blood Pressure Monitoring. Dr. Pickering makes a case for the diary method. However, I would suggest that the method chosen should depend on the purpose of the study.

I agree with Dr. Pickering that the diary method is preferable if the purpose of the study is to examine behaviorally-induced changes in BP, including sleep, as in the work of Dr. Pickering and his colleagues. However, my 17 years of experience of personally entering diary information for BP recordings from over 2,000 diaries in Dr. Pickering's laboratory and my own has taught me the limitations of this technique, particularly in pediatric studies. Many subjects considered the diary a nuisance and provide only minimal entries, including sleep times. This was true particularly for youths who often provided less than five entries. The diary method requires that the subject reliably reports the time of sleep onset and the time of awakening. Clearly, the former is not possible and in many cases neither is the latter, particularly for myopic individuals. Third, inherent in this approach is the assumption that the subject remains in bed and asleep for the entire nighttime period. Often, this was not the case, but subjects rarely recorded this in their diary.

Specified time intervals are preferable for studies measuring the BP changes or load over a defined period. In addition, this method is preferable for studies examining the influence of long-term BP control systems. It does not have the difficulties or make the assumptions indicated above for the diary technique. It simply provides an estimate of the BP over that period of time, independent of the activity of the individual. This is an important point, because it is the BP that is the focus of these studies, not the activity cycle. However, it is important not to refer to these periods as "awake" and "asleep" for the reasons pointed out by Dr. Pickering. In our studies, we now define periods of "daytime" and "nighttime."

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From the University of Tennessee, Memphis, The Health Science Center, Room 336, 877 Madison Ave, Memphis, TN 38163.

Fluoxetine’s Effect on Biochemical Screening for Pheochromocytoma

The biochemical diagnosis of pheochromocytoma is made by screening for an increased urinary excretion of total metanephrines (metanephrine and normetanephrine) and confirmation with measurements of the excretion of fractionated catecholamines (norepinephrine, epinephrine, and dopamine) and other metabolites (vanillyl mandelic acid, VMA). Unfortunately there are situations and drugs that can interfere with this biochemical diagnosis. One class of drugs known to alter catecholamine metabolism is tricyclic antidepressants, possibly by decreasing whole-body norepinephrine turnover. Little is known definitively about the effects of newer antidepressants, such as fluoxetine, on the excretion of catecholamines and their metabolites. Therefore, we decided to evaluate the effects of fluoxetine on screening laboratory tests used to diagnose pheochromocytoma.

METHODS

Individuals 18 years and over who were being seen for the evaluation of psychiatric problems were recruited to participate in this study. These individuals had received recommendation to either take fluoxetine for their psychiatric problems or withdraw from fluoxetine due to side effects or ineffectiveness in the treatment of their psychiatric problems after a minimum of 1 month exposure.

After agreeing to participate, these individuals were instructed to collect an acidified 24-h urine sample (beginning after the first morning void through the

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