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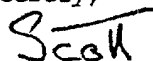
October 24, 1984

David E. Weil, Ph.D.
Project Manager
U.S. Environmental Protection Agency
Environmental Criteria and Assessment Office
(MD-52)
Research Triangle Park, NC 27711

Dear David:

Enclosed please find my response to the two specific questions posed in your letter of October 11, 1984. I was very favorably impressed by the Schwartz and Prickle presentation. I would like to get a copy of the Lead Criteria document. Could you please send one to me? I would also like to get Joel Schwartz' and Jim Prickle's addresses so that I could correspond with them further about this research. Thank you very much for your assistance with these matters. I enjoyed meeting you and hope that my input was of some help.

Sincerely,



Scott T. Weiss, M.D.
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Enclosures

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1. Do you find the relationship between blood lead and hypertension biologically plausible?

There are really two aspects to the issue of biologic plausibility. The first relates to possible physiologic mechanisms by which lead could influence blood pressure. The second relates to animal or human physiologic data that support one or another theory. There are several physiologic hypotheses that could be investigated further: vascular reactivity and an increase in circulating blood volume (1), increased adrenergic responsiveness (2), and competitive inhibition of divalent cation absorption (3). The only one of these hypotheses addressed by the current investigation of Prickle and Schwartz et al. is the third of these possibilities, i.e., competitive inhibition of divalent cation absorption. The inability of dietary calcium to enter the regressions when lead was excluded from consideration makes this possibility less likely. Another possible mechanism, not addressed by this work, is whether increased blood lead level leads to renal damage and hence to hypertension or whether increased blood lead level leads to hypertension which then leads to renal damage. Reanalysis of the NHANES data utilizing the serum creatinine will be interesting but probably will not answer this question definitively.

Animal data is certainly consistent with the epidemiologic study of Prickle and Schwartz, particularly the work of Victery et al. (2) and Webb (1). Much of the other work is with blood lead levels that are extremely high and, given the log dose response curve, less likely to show the effect and less likely to be applicable to humans.

Clearly, the investigation of Prickle and Schwartz is unable to answer the physiologic mechanism by which blood lead influences blood pressure. However, this work is consistent with existing animal data and

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More human physiologic studies should be done to define the pathophysiologic mechanism involved.

2. Is the relationship between hypertension and the increased incidence of stroke and heart attack accurately portrayed in this memo?

Before dealing directly with this question it is worthwhile to review briefly what Prickle and Schwartz et al. have done and whether there are any statistical or epidemiological flaws in their analysis. These investigators regressed blood pressure on age, body mass index, blood lead, and a variety of dietary variables in a cross-sectional analysis of males 40-59 years of age from NHANES II. They used a variety of regression analyses and procedures to insure that there was no confounding in the relationship between blood lead and blood pressure. They also considered a wide variety of demographic and historical variables as well. This part of the analysis is well done and up to this point there are only two relatively minor points, one statistical and one epidemiological, that deserve attention. One would like to see some sort of comparability analysis to see how the white males included in these regressions differ from the rest of the people in NHANES II; secondly, one would like to see a plot of residuals, a Cook's t statistic, or a cross validation to insure oneself that these regressions are not being driven by a few influential points. Having made these two minor suggestions, it seems clear that blood lead is a significant predictor of blood pressure.

The relationship between hypertension and cardiovascular disease (stroke and MI) is obtained from logistic regressions of the probability of cardiovascular disease on age, blood pressure, cholesterol, and cigarette smoking. The reduction in blood pressure due to reduction in blood lead is then used to estimate the decrease in cardiovascular

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even. This approach is valid and provides reasonable estimates. Although one would like to see longitudinal data supporting the blood pressure-blood lead relationship, the analysis completed by these authors is quite complete and without any obvious flaw.

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REFERENCES

1. Webb et al. In vivo and in vitro effects of lead on vascular reactivity in rats. Am J Physiol. 1981;241:H211-6.
2. Vickery et al. Hypertension and the renin-angiotensin system in rats. J Lab Clin Med. 1982;99:354-62.
3. Saltman P. Trace elements and blood pressure. Ann Int Med. 1983;98(2):823-7.

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