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Dear Dr. Austin,

I much prefer the second draft of your report, which I have arbitrarily dated 8·8·81 on my copy. You have accomodated very nicely all of the comments and suggestions I sent previously. I think, however, there is still room for a couple more drafts before you would be ready to make this public. I am returning my copy with some editorial suggestions written in. Most of these are trivial.

My principal concern at this point is that the manuscript be made as clear as possible with respect to findings on the hypothesis that prompted the study - that there is an excess of brain tumors, and specifically glioblastoma. I have made some comments on this on the back of page 15, but I am not sure how useful they are. My difficulty is that I do not quite see myself how this matter can be tightened up.

One thing which I think might help is to emphasize the importance of comparing ICD categories as they are constituted in national statistics. Some of the thoughts that I would like to see in the Discussion (most of them are already there, but if I try to put them in my own order perhaps I will at least clarify my own views) are as follows:

(1) The most defensible comparison, from a scientific point of view is of the observed and expected categories in Table 5.

(2) With respect to Brains and CNS, we do have a significant excess for [redacted]oyees > = 6 months duration and latency 20 years + (O/E = 8/2.32, [redacted]0.003). I see no way around this. The fact that histologic evidence [redacted]not be found for one (case #5) does not rule him out, nor can case #6 be eliminated, since there are presumably similar cases among those from which population rates are estimated. Acknowledging the significant excess of brain tumors in this group, and asking whether it is likely to be

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occupationally related, the following points can be made:

(a) This is not a hypothesis-testing situation. You are only in fact finding that an excess does exist in a more formal evaluation of a situation which had been previously suspected to have such an excess on anecdotal grounds. This makes a very big difference to the interpretation of your p values. In fact, one could argue that p values are inappropriate altogether in such a situation. Considering that 44 causes of death have been examined, in 2 categories of duration of employment, 2 of hourly-salary status and 2 of latency (= 342 tests) it is not surprising that a few turn out to be "significant".

(b) Of the 8 cases, only 4 are glioblastomas. The original idea that glioblastomas were particularly in excess is therefore in error - they are in fact under-represented among the 8 (expected = 8 x .77 = 6.2) and do not significantly exceed their expectation based on general population rates (2.32 x .77 = 1.79, p ~ 0.1).

(c) An exhaustive review by both UC and NIOSH has failed to find any common work experience or exposure for these 8 cases which would make an occupational origin plausible.

(3) Of course it is possible to gerrymander an excess of glioblastomas by transferring the 3 cases from those coded as benign and unspecified brain tumors. One must recognize it as gerrymandering however and treat it with appropriate caution. Even the one that was miscoded should not really be recoded since such errors occur in general population data (although I would not want to be pressed on that).

In short, my own summary of the findings would be something like the following:

> There is a statistically significant excess of malignant brain tumors in this population which is confined to employees of 6 months duration or more and have latency of 20 years or more. The excess is not of any one form of tumor specifically and glioblastoma in particular is not significantly in excess. In view of the lack of specificity of tumor type and the failure to find any common link between cases in the working environment, it is not likely that this excess is occupationally related. The most obvious explanation of the excess is the initial observation of a small cluster arising by chance supplemented by intense efforts to identify these particular tumors specifically in this population.

I am sorry to toss this whole matter up in the air again, but I do think

this is a paper which will receive a lot of attention and is worth a little sweat. If you find any of these thoughts useful, please feel free to use them.

Best wishes,

Brian MacMahon, M.D.
Professor

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Encl.