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*C.T.R.
Special Projects
(Enslin)*

Re: Kurt Enslein's Analysis of Doll Data

I enclose Kurt Enslein's final summary report of his analysis of the Doll data. Enslein has summarized the purpose of the analysis, the procedures performed, and what he considers the significant findings. This summary is cross referenced to the three progress reports sent to you earlier.

Our comments follow. We specifically invite your attention to the recommendation that we be authorized to discuss the preparation of an article with one or more statisticians (e.g., Alvan Feinstein, Alexander Brownlee). No additional funding is requested at this time.

The use of "pure" cigarette smoking categories by Enslein in his analysis instead of the "mixed" categories used by Doll does not appear to have resulted in any significantly different smoking-disease associations than Doll reported.

Enslein's analysis does, however, confirm some of the criticisms of Doll's study which have been raised in the past and these criticisms together with Enslein's confirming findings may be useful in questioning Doll's studies. Some of the criticisms which are reported in Enslein's summary are as follows:

(a) Doll reported that there had been a 7% decline in the lung cancer rate over the 10-year period of his study among his sample of physicians whereas there had been a 22% increase over the same period of time among the general population

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Page 2
Feb. 4, 1970

in England and Wales. The decline in physician lung cancer rates is attributed by Doll to the reported large scale cessation of cigarette smoking among the physicians during this 10 years. This reported finding is often cited against us. For example in *The Health Consequences of Smoking* (1967), p. 24, Doll's study is cited as "The best available example of a controlled cessation experiment with reduction of risks resulting from reduction of smoking". Doll has been criticized for drawing the conclusion that there has been a reduction in physician lung cancer rates during this 10-year period because the difference in the number of lung cancer deaths is not statistically significant. Enslein performed calculations to determine if the decline reported by Doll from the first five years of his study to the second five years was statistically significant. He found that the difference in mortality rates reported by Doll was not statistically significant. See Point 1(c), p. 6. Using "pure" smoking categories Enslein found that there had actually been an increase in lung cancer rates in the second five years.

(b) Doll's reported decline in lung cancer rates discussed above is referred to constantly by anti-cigarette spokesmen. But Doll did not report what happened to coronary heart disease rates among his physicians during this same time period. At our request Enslein has investigated this and found that coronary heart disease rates were rising among the physicians much faster than in the general population. This is evident from the graph on page 12 of Enslein's summary. This finding may provide the basis of an explanation for a decline in lung cancer rates among physicians if in fact there was a decline: If physicians are dying at an early age from coronary heart disease, fewer of them may survive long enough to get lung cancer. Further, the increase in coronary heart disease rates among physicians is occurring during the period that smoking amounts are claimed to be reduced.

Note: Although requested to do so, Enslein has apparently not age adjusted his "pure" doctor

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population to that of the general population. Without such correction, lung cancer and heart disease rates would be expected to show an increase in the later years of the study due to the increasing age of the fixed doctor population. The extent of this needs to be determined before reliance is placed on the results reported by Enslein.

(c) Doll reported in his 1964 paper that only 69% of the male physicians and 60% of the female physicians had answered his questionnaire. The large percentage of nonresponse itself raises questions about the validity of Doll's study. In addition, Doll conducted a follow-up analysis on a sample of the nonresponders and, as Enslein points out on page 14, this analysis revealed that there is a gross difference in the smoking habits of the nonresponders and responders. It is difficult to predict what effect this would have on Doll's results but it does indicate that his population is biased as to smoking habits and that his conclusions are therefore questionable.

Enslein discusses a number of criticisms of Doll's study in his summary which appear to be of interest but about which we have certain reservations. For example:

(a) On page 5, Enslein states that it is difficult to see how Doll could have drawn valid conclusions as to lung cancer rates because of the presence of large fluctuations in the death rate from year to year. Some statisticians would view the fluctuations shown in Figure 1 on page 7 as attributable to chance.

(b) On page 6, Enslein compares the average lung cancer death rate for the first five years of Doll's study with the second five years and finds that there has been an increase in the lung cancer death rate. This is contrary to Doll's 1964 article

which reports a 7% decline in the lung cancer death rate between these two periods and is therefore worth further investigation. However, many statisticians believe that a questionnaire population such as this will have unusually low mortality rates for the first years in the study because extremely ill people probably will not answer questionnaires. The effect of excluding the first two years of the study is shown in Part A of the Table on page 9 where a comparison of lung cancer death rates for the two 4-year intervals reveals a slight decrease in the second period. [Another criticism of Doll's conclusions which has been made in the past, but which Enslein does not make, is that the number of lung cancer deaths in each year is so small that the rates calculated are almost meaningless and therefore any comparison is not justified.]

(c) In Section 2(b) on page 11, Enslein reports the results of a statistical significance test on Table 20 in Doll's report which Doll interprets as showing a rising gradient of coronary heart disease with increased smoking. Enslein's analysis of the statistical significance of the smoking gradients reveals that they are not significant. There is some question as to whether or not an evaluation of the statistical significance of all of these gradients pooled together in such a table is really relevant.

(d) In Section 3 on page 13, Enslein criticizes Doll's method of lumping all age groups together to calculate standardized rates. There may be some question as to whether or not this is a valid criticism. In any event, Enslein's observation would not apply to the disease categories most often associated with smoking such as lung cancer and coronary heart disease since Doll calculated age specific rates for these diseases.

(e) In Section 4 on page 13, Enslein deals with

Doll's procedure of sampling nonresponders. As pointed out above, Doll's study is questionable because of the large rate of nonresponse and the obvious difference in smoking habits of the nonresponders as compared to the responders. However, statisticians may differ in opinion on whether or not Doll's procedure of sampling the nonresponders was proper.

(f) In Section 5 on page 14, Enslein states that various statistical problems make the conclusions as to 19 of the 20 diseases studied unreliable. This is essentially a subjective interpretation of the numerous calculations made and others might differ as to the proper conclusions.

(g) In Sections 6 and 7, Enslein discusses the finding that certain disease categories show lower mortality rates among smokers than among nonsmokers. No one would contend that smoking prevents these diseases. This is just another way of stating the axiom that statistical association alone does not prove causation.

(h) In Section 8 on page 16, Enslein points out that in certain categories Doll included deaths from an 11th year of his study. It is questionable whether or not this is really an important criticism of Doll's study.

(i) In Section 9 on page 16, Enslein states that Doll's population had a much better mortality record than the general physician population. This indicates that the physicians who did not respond to Doll's questionnaires probably had a much higher mortality rate than those who did respond and reinforces the position that Doll's study is questionable because of the large nonresponse factor. The difference could be attributable to several factors and deserves further attention.

Page 6
Feb. 4, 1970

In working with Kurt Enslein it has become obvious to us that he has a capability in the computer field. However, we have found that considerable supervision of his work is advisable in directing the areas which should be investigated, and in the interpretation and presentation of the results generated. We feel that his major value is in assisting on specific projects which require computer data analysis.

Enslein's work has raised several questions about the procedures Doll used in his study. The answers to these might lead to additional criticisms of Doll's study. We believe consideration should be given to the possibility of someone approaching Doll about these questions. Such action would probably only be worthwhile if a decision was made to pursue the possibility of an article based on this work. It would be preferable if someone of recognized status consulted with Doll either alone or with Enslein.

We do not believe that Enslein's findings alone are sufficient to provide the material necessary for an article in one of the scientific journals. We are doubtful that Enslein (or any other person at Genesee Computer Center, Inc., with whom we are acquainted) has the requisite academic background and standing to author an article which would be accepted for publication in one of the more prestigious scientific journals. Confidential consultation with others indicates that Enslein's major value may be in working with someone of recognized status in the academic world. Enslein's present work on the Doll data might be used as a departure point for such an article.

Our specific recommendation is that we be authorized to pursue such a possibility further.

Yours truly,

William W. Shinn
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