Environmental Health Perspectives
Vol. 81, pp. 107-108, 1989

Commentary

Quantitative Models for Lung Cancer Induced by Cigarette Smoke

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This discussion paper gives a limited history of work done at this Institute on quantitative modeling relating to lung cancer and cigarette smoking, a health hazard whose study has been given much encouragement by Norton Nelson. It first starts with the proposal that life shortening be considered as a measure of the impact of lung cancer using log normal and Weibull types of distributions of time to occurrence; second, it continues with an examination of the fits of the log normal and Weibull distributions to the Doll and Hill data on smoking and lung cancer in British physicians and a systematic review and development of mathematical models of carcinogenesis; and third, it reports on the current work that points out inconsistencies in the Armitage-Doll multistage model with the Doll and Hill data and suggests a two-stage clonal growth model that assumes promotion of clonal growth is restricted to cells initiated by the smoke. This proposal and related work support a current trend in risk assessment to adopt a two-stage clonal growth model that incorporates birth and death rates of cells and the transitional probabilities of the stages.

This paper focuses on work done at the Institute on lung cancer induced by cigarette smoking and its relevance to quantitative models used in risk assessment. In the beginnings of the Institute, the health effects of cigarette smoke were identified as a critical and promising area of research by Norton Nelson, and this has led to considerable experimental and theoretical work being done. Indeed, much of the success of the Institute stemmed from guideposts for research that have been erected by Nelson. They have been most valuable to me in pointing out problems having considerable significance and productive potential.

In a personal way, I am indebted to Norton Nelson for having helped me stop smoking back in the fifties, early enough so that it has extended my expected lifespan considerably. Nelson participated in the first authoritative report declaring cigarette smoke to be a major health hazard. This was written by a study group on smoking and health for the principal national health organizations (*1*). I have great respect for all of the study group, but it was my direct appreciation and esteem for Nelson's insight and judgment in scientific matters that precipitated my decision to quit smoking.

Early in the seventies, Roy Albert advanced the concept that life shortening be used for measuring the impact of lung cancer on the individual as well as on the population as a whole. In the published paper (*2*), much stress was given to what was called the Blum-Druckrey model, which assumed time of occurrence is log normally distributed, with the median time t being related to the dose d by the equation $t^n d$ = constant where $n \geq 1$ is a constant. A generalized form of the Weibull model was also considered (recall that the Weibull model assumes incidence rate to be a product of a power of dose and a power of time).

In the mid-seventies, Alice Whittemore arrived at the Institute. She was sponsored by the SIAM Institute for Mathematics and Society (SIMS) as a participant in its program to encourage mathematicians to shift their careers to societal problems. Norton Nelson's good judgment encouraged her to join us and this action was reciprocated by SIMS who, in recognition of his insights and broad perspectives, asked him to join its Board of Directors.

The first project undertaken by Alice Whittemore was to extend Doll's analysis of the data he obtained with Hill relating smoking to lung cancer in British physicians and, in particular, to examine the fits of the log normal and Weibull distributions (*3*). The issue was important for high-to-low dose extrapolation, both for frequency response and for the life-shortening criteria proposed by Albert. However, as is often the case, the analysis did not discriminate between the two distributions, both of which were found to give a reasonable fit in each of several age and dose groups (*4*). Whittemore went on to review and develop quantitative models in a systematic way (*5*). A particularly important case for risk assessment, and one that is most frequently used, is the Armitage-Doll multistage model, which assumes that a cell must undergo several discrete sequential transitions in order to be

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transformed into a cancer cell and that there is no preferential proliferation in the intermediate stages (*6*).

A few years ago, as part of his thesis work at the Institute (*7*), Michael Gaffney examined in more detail the implications of the Armitage-Doll multistage model. He related these implications to the Doll and Hill data on cigarette smoking and lung cancer in British physicians. As others have done, he assumed that there were five or six transitions, that smoking affected the initial and penultimate transitions, and that increases in transition rates were linearly related to the amount of smoking. The following is a description of the work of Gaffney which is being prepared for publication.

In comparing the implications of the Armitage-Doll model to the gross features of the Doll and Hill data, Gaffney found four discrepancies that motivated him to look for a better conforming model:

a) Although incidence for continuous smoking is consistent with an increase in the initial transition and incidence after stopping smoking is consistent with an increase in the penultimate transition, both incidences cannot be fitted simultaneously if it is assumed that smoking increases both transitions.

b) Excess incidence after stopping smoking is predicted to increase with time, but the data are generally described as showing no change.

c) The dose-response relation is predicted to be linear-quadratic with the quadratic contribution becoming more dominant as smoking duration becomes greater, but no change in dose-response is indicated by the data.

d) Background incidence is predicted to increase with age by a power which is one more than the power of the increase in incidence with smoking duration, but the data suggest that both incidences increase to the same power.

To remove these discrepancies and match the gross features of the cigarette data, Gaffney has proposed a two-stage model with clonal growth that depends on a power of time. It assumes, as a key special feature, that promotion of cell proliferation is restricted to cells that have been initiated by smoking and that there is no promoting effect on background initiated cells. Without this special feature, the two-stage clonal growth model is equivalent quantitatively to the multistage model with dose affecting the initial and penultimate transitions, and so the discrepancies would still remain.

An interesting aspect of the equivalence relation between the multistage model and the two-stage clonal growth model is the identification of an increase in the penultimate transition with an increase in clonal growth. Thus, the characterization of agents as late-acting carcinogens could be explained by their acting as promoters of clonal growth. Examples of this would be cigarette smoke, nickel, arsenic, and chloromethyl ethers (*8–10*).

Finally, it is to be noted that Gaffney's result agrees with a current trend in risk assessment modeling. In the recent past, the multistage model of Armitage and Doll has had the widest preference for risk assessment. It leads to a polynomial dose expression for the cumulative incidence function called hazard in statistical terminology, which is a well-accepted basis for high-to-low dose extrapolation. The 95% upper confidence limit for the coefficient of the first-degree term has been adopted by the EPA for their linearized extrapolation procedure (*11*).

Currently there are new voices that advocate a two-stage clonal growth model that is more complex than the proposal of Gaffney (*12,13*). It incorporates birth and death rates of the cells and transitional probabilities of the stages. The model has the advantage of having a more realistic biological foundation with components that can be referred back to the biologist who can then play a more important role in risk assessment. In this context, it is appropriate to refer to work by Fredric Burns, who has studied cell proliferation for many years at this Institute and has been an advocate of a clonal growth model (*14*).

Supported by Center grants ES 00260 from the National Institute of Environmental Health Sciences, CA 13343 from the National Cancer Institute, and SIG-00009 from the American Cancer Society.

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