A STOCHASTIC MODEL FOR A TWO-STAGE THEORY OF CARCINOGENESIS

HOWARD G. TUCKER
UNIVERSITY OF CALIFORNIA, BERKELEY

1. Introduction to the theory

A two-stage theory of induced pulmonary carcinogenesis has been suggested by M. B. Shimkin and M. J. Polissar [6]. In brief, the preliminary evidence and the problem suggested by more detailed study are outlined as follows. Each mouse of a large collection of experimental mice is administered a dose of the carcinogenic agent, urethan. At certain times after administering the carcinogen a small group (5 or 10 or 15) of mice were selected from the large group; they were killed and their lungs were examined. In examinations undertaken shortly after administering the carcinogen, small distinct growths were noticed on the lungs which were not cancerous tumors and which Shimkin and Polissar call "hyperplastic foci." As time progressed these hyperplastic foci increased in both number and size. Eventually, the individual sizes of the hyperplastic foci became constant, while the total number of them per mouse lung began to decrease gradually. At about the same time, or shortly after the appearance of the first hyperplastic foci, tumors were observed on the lungs. For a while the tumors per mouse lung increased in both number and size. A time was reached, however, when the number of tumors on each mouse's lungs remained fairly constant, while continuing to increase in individual size. It was noticed at the early era of tumor formation that the smallest tumors observed were much larger in cross-sectional area than the smallest cross-sectional area of tumor that could still be observed with the microscopes. In their study, Shimkin and Polissar were thus led to consider that perhaps the hyperplastic foci and the tumors were not biologically independent of each other. It seemed to them that possibly the hyperplastic foci were precursors to the tumors and that as some hyperplastic foci attained a certain approximate age and size they changed into tumors. This is the two-stage theory of carcinogenesis as formulated by Shimkin and Polissar.

This paper is a preliminary attempt toward the verification or disproof of this theory. The method to be used is that of verifying (or, more accurately, not excluding) a particular theory by means of a mathematical model. This method is explained here for our particular problem. We first make the basic assumption that the number $X(t)$ of hyperplastic foci that can be counted on a mouse's lungs at time t after administering the carcinogen is a random variable. We make the

This investigation was supported (in part) by a research grant (No. RG-3666) from the National Institutes of Health, Public Health Service.