STUDIES OF THE MECHANISM OF INDUCTION OF PULMONARY ADENOMAS IN MICE

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1. Introduction

The present paper is related to the frequently discussed question as to whether urethane tumorigenesis is a one stage or a multistage process. In either case, the tumorigenic process is assumed to begin with what may be called an *initial event*, a change in a single normal cell (*mutation*) resulting from a single *hit* by a tumorigenic molecule (one hit theory) or from several such hits (multihit theory). If the initial event is followed by the growth of the tumor studied, then the mechanism is described as a one stage mechanism. However, as explicitly suggested by Brues [5], the growth (of *first order mutants*) following an initial event may well be "benign" in the sense of being destined to disappear, except for the possibility of a second mutation in one of its cells creating *second order mutants*. If this second mutation in a cell of the benign growth turns into a tumor cell, then the process of tumorigenesis is called a two stage mechanism. It is easy to visualize three or four or, generally, multistage mechanisms of tumorigenesis. Naturally, there is the possibility that, with respect to some particular tumors, say pulmonary adenomas in mice, the tumorigenic process is a one stage process while, with respect to some other tumors, say pulmonary carcinomas, it is a multistage mechanism.

Some years ago a private communication from M. B. Shimkin to J. Neyman raised the question as to whether an experiment could be devised to decide whether a particular tumorigenesis, say of pulmonary adenomas in mice, is a one stage or a multistage phenomenon. The experiment contemplated was to consist of injecting mice with specified doses of urethane and counting adenomas. Briefly, the investigation by Neyman and Scott [18] resulted in the finding that, with a two stage mechanism, the fractionation of a given dose of urethane may influence the ultimate number of tumors. On the other hand, with a one stage mechanism, they concluded that the ultimate number of tumors must be independent of the time pattern in which the given fixed dose of the tumorigenic

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