SUMMARY

Single or multiple plastic films (unplasticized vinyl chloride-vinyl acetate copolymer) of different sizes and shapes were implanted s.c. in female CBA/H and CBA/H-T6 mice. Tumor incidence increased and accelerated with increased total surface area of multiple implants or with increased size of single implants. Tumor distribution curves over time were generally multiphasic. The profiles changed in proportionate relation to implant size. These findings indicate class differences between tumors according to latency. Since latency is known to be a predetermined characteristic of foreign body-induced tumors, class differences seem to exist at the originator cell level, reflecting diversity of intrinsic carcinogenic factors.

INTRODUCTION

Several investigators of chemical carcinogenesis have reported nonuniformity of tumor distribution over time which was statistically significant (5, 6, 9). Multiphasic incidence curves seem also characteristic for tumors induced in mice by foreign body implantation (2). The present investigation was carried out to verify this observation on a larger scale and under varied conditions.

Incidence and latency of foreign body tumors are correlated with size and surface area of implants (3). The effect of this variable on the multiphasic pattern of foreign body tumor incidence curves was used to gain insight into the nature of the phenomenon.

MATERIALS AND METHODS

Mice

We used inbred CBA/H and CBA/H-T6 mice, which were obtained from Harwell, England, in 1964 and maintained in this laboratory under established breeding conditions. The 2 strains are fully histocompatible but can be distinguished karyologically on the basis of the T6 marker chromosomes (1).

Periodic examinations proved our mouse colonies were generally free of latent virus infections such as ectromelia, lymphocytic choriomeningitis, polyoma, and lactic dehydrogenase-elevating virus.

Animals were fed Purina laboratory chow and given water ad libitum. Only females were used in these studies.
months following film implantation while showing no signs of tumor development. These animals were excluded from the regular computations.

**Group A** (*n* = 15). Two curved films, 22 x 22 mm in size and with a total surface area of 1940 sq mm, were implanted. The capsule pockets around the curved films tended to be wider than those around flat ones because of the space caused by the concavity.

**Group B** (*n* = 36). Two double films, 15 x 22 mm in size and with a total exposed surface area of 1320 sq mm, were implanted. Capsule pockets around paired films appeared somewhat larger than those around single implants. Some cells were usually found to have migrated a few mm deep between the 2 films along the rims, but otherwise the adjacent surfaces of paired films remained cell free.

**Group C** (*n* = 75). Two single films, 15 x 22 mm in size and with a total surface area of 1320 sq mm, were implanted.

**Group D** (*n* = 53). One single film, 15 x 22 mm in size and with a total surface area of 660 sq mm, was implanted. (Two animals remained tumor negative at >30 months postimplantation.)

**Group E** (*n* = 33). Two single films, 7 x 15 mm in size and with a total surface area of 420 sq mm, were implanted. (Three animals remained tumor negative at >30 months postimplantation.)

**Group F** (*n* = 31). One single film, 7 x 15 mm in size and with a total surface area of 210 sq mm, was implanted. (Seven animals remained tumor negative at >30 months postimplantation.)

**RESULTS**

The tumor incidence data obtained from the various experimental groups are compiled as noncumulative frequency histograms in Chart 1. The curves differ from each other in several criteria. These differences seem attributable to 1 variable: size and total surface area of implants. Specifically, the following findings are evident.

1. With increasing surface area of implants, tumor incidence is generally accelerated. For example, the tumor incidence in 50% of the animals was reached at the 21st month postimplantation in Group F and at the 11th month in Group A.

2. Each curve shows several characteristic peaks indicating periods of higher and lower tumor frequencies. This multiphasic frequency distribution pattern was previously noticed among others by Iversen et al. (6) and Turusov et al. (9) while studying chemically induced tumor incidence. In both laboratories, the data were subjected to computerized statistical analysis, leading to the conclusion that the observed incidence pattern was not due to chance fluctuation but to the existence of several discrete subpopulations. This conclusion seems to be valid also for the present data which carry as much statistical weight.

3. With increasing surface area of implants, the late peaks of tumor frequency shrink or even vanish, whereas the early peaks rise in height. Furthermore, the peaks change their position to earlier points on the time scale while the troughs shorten proportionately.

4. If the tumor frequency curves are arranged as in Chart 1, all corresponding peaks and troughs come to lie on straight connecting lines as a result of the regular proportionate spacing of the frequency peaks.

5. By summation of corresponding peak and trough values from all 6 tumor frequency curves, a set of approximate normal distribution curves was obtained (top of Chart 1). These conform basically with the computations of Iversen et al. (6) and Turusov et al. (9). Evidently, the tumor incidence data are not homogeneous but segregate as statistical subpopulations.

**DISCUSSION**

The inhomogeneity of the tumor incidence data indicates that tumors fall into distinct latency classes. Iversen et al. (6) have discussed several possible explanations without reaching any specific conclusions. We were unable to relate the fluctuations of tumor incidence to seasonal factors, difference in age of animals, irregularities in animal care, or overt complications such as inflammatory reactions at implant sites. As has been shown in previous FB tumorigene-

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3 The abbreviation used is: FB, foreign body.
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sis experiments (4), latency is a tumor characteristic predetermined already in preneoplastic “parent” cells that appear within the 1st 4 to 8 weeks of FB reactions. Hence, it must be assumed that class differences exist already at the preneoplastic parent cell level. Since the predetermination of tumor characteristics is an intracellular event, it appears that the observed class differences reflect a diversity of the intrinsic factors primarily involved in the tumorigenic process.

This line of thought led to the question whether parent cells of different latency categories would show additional distinguishing criteria which might provide clues as to the basic nature of such differences. Some degree of correlation seems to exist with regard to sex of animals. As previously reported (2), early tumor incidence peaks are more pronounced in female than in male CBA/H mice. This explains the observation (1, 2) that female mice reach the FB-tumor incidence in 50% of the animals 2 months earlier than males. Karyological, histopathological (7), and kinetic tumor growth characteristics (unpublished data) have so far not been found to be significantly correlated with tumor latency class.

Other peculiarities of the tumor incidence curves can be explained readily on the basis of results from previous FB tumorigenesis studies. Of particular relevance is the fact that the process of FB tumorigenesis takes its origin from a single parent cell. The number of different parent cells emerging in an animal in response to a FB implant is small, depending on the size of the FB surface area (3). In a CBA/H mouse, 1 parent cell is most probably evoked by an implant with approximately 200-sq mm surface area. Each multiple of this unit adds 1 more parent cell to the most-probable number. If more than 1 parent cell is evoked in an animal, naturally the one with the shortest predetermined tumor latency will be expressed as tumor in that animal. The more parent cells emerge, the greater is the likelihood that cells with shorter tumor latencies are among them. Consequently, the tumor incidence curves of large-implant groups consist mostly of very high early peaks. In contrast, tumor incidence curves of small-implant groups show peaks of more equal height evenly throughout the observation time. Here, threshold conditions are reached in the sense that most animals produced no more than 1 parent cell which could belong to any of the different latency classes.

Increase of FB size or total surface area not only augments early tumor incidence peaks at the expense of later ones but also makes corresponding peaks shift to earlier points on the time scale. This latter observation points to a preneoplastic promotion stimulus which may quantitatively relate to the extent of an animal’s engagement in FB reaction (4, 8).

REFERENCES

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