

KEY WORDS: foreign bodies; induction of sarcomas; initiation and promotion.

Subcutaneous implantation of certain foreign bodies into animals leads to sarcoma formation close to the implant. It has been shown that even chemically inert foreign bodies may possess carcinogenic activity of this kind. The carcinogenic effect of the foreign body depends on its physical shape. Smooth continuous laminae, if sufficiently large in area, are the most carcinogenic, whereas perforated or fragmented laminae from the same materials are virtually noncarcinogenic [1, 3].

The aim of this investigation was to study the role of the shape of a foreign body in different stages of carcinogenesis.

EXPERIMENTAL METHODS

Smooth continuous polyvinyl chloride laminae measuring 22×15 mm were used as highly carcinogenic foreign bodies, and laminae from the same material and of the same size, but with frequent perforations (50 to 60 holes per square centimeter, diameter of each hole 0.3 mm), and also Millipore filters with a pore diameter of 0.45μ (of the HA type, of U.S. manufacture) [1, 2] were used as weakly carcinogenic foreign bodies.

The smooth laminae were implanted subcutaneously in the dorsal region of CBA mice, one per animal. After 1.5 and 3.5 months the laminae were removed through an incision in the capsule from the tail end. Immediately after this, a perforated lamina or piece of filter

TABLE 1. Appearance of Tumors in Response to Injection of Various Foreign Bodies and to Their Removal

Expt. No.	Experimental conditions	Index	%
1	Continuous lamina	16/30	53,3 $P_{1-2} < 0,001$
2	Perforated lamina	2/29	6,9 $P_{2-3} < 0,005$
3	Replacement of continuous lamina by perforated after 3.5 months	10/27	37,0 $P_{1-3} > 0,1$
4	Replacement of continuous lamina by perforated lamina after 1.5 months	2/35	5,7 —
5	Filter	0/40	0 —
6	Replacement of continuous lamina by filter after 3.5 months	6/28	21,4 $P_{5-6} < 0,001$
7	Continuous lamina for 6.5 months	1/28	3,6 —

Note. Numerator indicates number of mice with tumors, denominator total number of mice surviving until 12 months.

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of the same size was introduced into the interior of the capsule to replace the smooth lamina. The skin was sutured and painted with alcohol. In some mice, only the continuous lamina was removed after 6.5 months. In the remaining mice, only continuous or only perforated laminae or only filters were implanted. The animals were under observation for 20 months if they survived. The results were subjected to statistical analysis by Student's *t* test.

RESULTS

It will be clear from Table 1 that continuous laminae made of polyvinyl chloride were highly carcinogenic: Tumors appeared in more than half of the mice and the minimal latent period of their appearance was 12 months. For a tumor to appear, a lamina had to be present at the site of implantation for a considerable part of the latent period: Removal of the lamina, even 6.5 months after implantation, almost completely prevented the appearance of a tumor. Implantation of perforated laminae made of polyvinyl chloride and of Millipore filters with a pore diameter of 0.45 μ caused hardly any tumor formation. These results are in agreement with those obtained previously [1].

Replacement of the continuous lamina by a perforated lamina or filter of HA type after 3.5 months gave a significantly higher yield of tumors than implantation of noncarcinogenic laminae only. These differences are statistically significant. Replacement of the lamina at an earlier stage, after 1.5 months, had no such effect: There was no increase in the percentage of tumors. The results of these experiments showed that the process from the time of implantation of the lamina to tumor formation can be divided into two stages. The first stage proceeds only in the presence of a continuous lamina. After 3.5 months, for the process to continue the presence of a lamina is also necessary, but in this case any kind will do — either continuous or perforated.

The existence of two qualitatively different stages (initiation and promotion) was demonstrated previously for certain types of chemical carcinogenesis [4]. The present experiments indicate that these stages also exist for carcinogenesis induced by foreign bodies.

The mechanisms taking place at each stage of the processes are not yet clear. Many workers consider that the formation of a collagen capsule of a definite structure is essential for tumor development. If a perforated lamina is introduced into such a ready made capsule, this probably maintains its existence during the second phase of the process.

LITERATURE CITED

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