INDUCTION OF SARCOMAS BY A NONCARCINOGENIC FORM OF FOREIGN BODY AND GLUTARALDEHYDE

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The formation of subcutaneous sarcomas following implantation of a foreign body into animals is known to depend on the physical shape of the material and not on its chemical structure [1, 5]. A complete lamina of a chemically inert substance exerts a carcinogenic action, whereas the same lamina, if shredded, will not induce tumor formation. The development of a tumor around a lamina is connected with the formation of a collagen capsule. However, it is not yet clear why the collagen capsule around the lamina contributes to tumor formation.

The writer previously showed a difference in the absorption time of primarily synthesized collagen in the connective-tissue capsule around carcinogenic and noncarcinogenic forms of foreign body. The earlier resorption of collagen around the noncarcinogenic shape was associated with the structural features of its granuloma. Since the process of collagen resorption begins in the connective tissue surrounding it, and around shredded fragments contact with it is greater (for collagen infiltrates between them), the process of collagen resorption, once begun, naturally will end sooner [2].

It was concluded from these observations that resorption of collagen in the connective-tissue capsule plays a role in the development of sarcomas. The aim of the present investigation was to test this conclusion.

The aim was to discover whether tumors can develop under conditions inhibiting collagen resorption in the connective-tissue capsule around a foreign body of noncarcinogenic form (a shredded lamina). To create this type of experimental model we used glutaraldehyde, which is a tissue fixative, and shredded cellophane. Glutaraldehyde reacts with the lysyl amino groups of collagen protein and increases the number of cross-linkages in it. This collagen becomes resistant to the action of collagenase and is less easily resorbed [6].

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male rats weighing 200 g. A lamina of ordinary cellophane measuring 2 × 3 cm^2, divided into fragments each measuring 0.1 cm^2, was used as the foreign body and was implanted beneath the skin of the animal's left flank. Daily for 5 days, 3 weeks after implantation, 0.5 cm^3 of a 2.5% solution of glutaradehyde was injected subcutaneously near the capsule with cellophane.

There were three control groups of animals: only shredded cellophane was implanted into the 18 rats of group 1, the 16 rats of group 2 received the same dose of glutaraldehyde only, and the 15 animals of group 3 (control) received five daily injections of 0.5 ml of physiological saline near the implanted shredded cellophane.

The animals remained under observation for 2 years.

Morphological investigations were carried out 2 months after implantation of the cellophane and at the end of the glutaraldehyde injections.

EXPERIMENTAL RESULTS

No tumors appeared in animals of the control group. The results of the experiments with shredded cellophane agree with data published previously [1, 2]. No information on the carcinogenic action of glutaraldehyde could be found in the literature.

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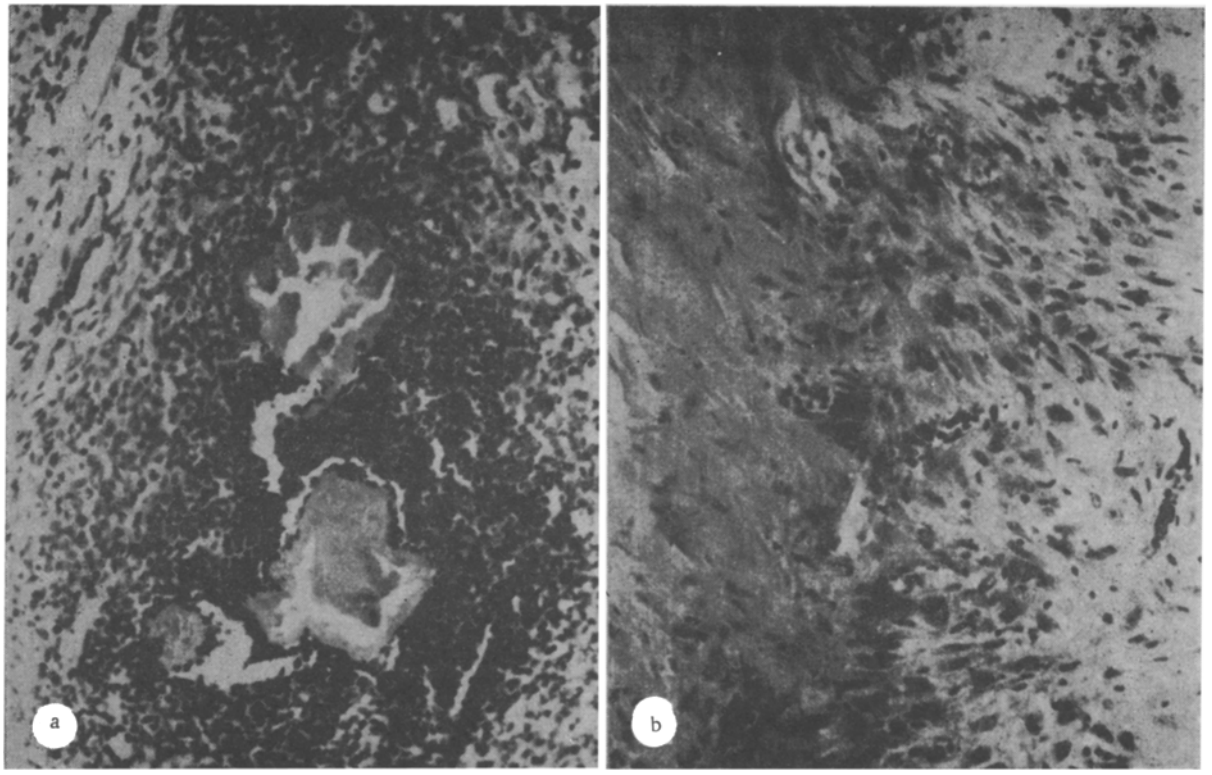

Fig. 1. Sarcoma appearing at site of implantation of shredded cellophane and injection of glutaraldehyde. a) Small-cell proliferation visible around shredded fragments of cellophane in depth of sarcomatous tissue; b) tumor tissue consisting of polymorphic cells surrounded by a thick layer of collagen of amorphous type. 200 ×. Hematoxylin and eosin.

In the experimental group of 33 rats which survived 8 months until the time of appearance of the first tumor, malignant neoplasms appeared in 21 (63.6%) animals. The mean latent period was 15.7 months.

All the tumors were polymorphocellular sarcomas, rich in blood vessels, and with preserved fragments of cellophane visible in the depth of the tumor tissue (Fig. 1a), surrounded by active proliferation of small cells. Around the periphery of the tumor tissue there were extensive areas of collagen of amorphous type (Fig. 1b).

Morphological investigations of the collagen capsule in the early stages of development, 2 months after implantation of cellophane, revealed the formation of amorphous collagen masses in it.

The results thus showed that sarcomas may form around a noncarcinogenic form of foreign body if glutaraldehyde, which increases the number of cross-linkages, also is injected. This "tanned" collagen is preserved around the periphery of the tumor nodule (Fig. 1b). As a result of these physicochemical changes in the collagen in the granuloma, the same microenvironmental conditions are created around the shredded cellophone as are observed around the complete lamina, and they lead to sarcoma development.

After implantation of a whole lamina measuring 2 × 3 cm^2 tumors arise in 50% of animals with the same length of latent periods. The similarity of many parameters, such as the frequency of development of sarcomas, the duration of the latent period, and the morphology of the tumors may indicate similarity of the mechanisms of development of sarcomas around a complete lamina and shredded cellophane accompanied by injection of glutaraldehyde. One of the main microenvironmental factors induced in tumor development is inhibition of resorption of surplus masses of collagen, which was initially synthesized by fibroblasts of young connective tissue in the course of their maturation. The masses of collagen formed initially undergo slow resorption because of their large number. Later, as the animal increases in

age, the surplus collagen also ages, for the number of cross-linkages in it increases. This, in turn, aggravates the aging process even more, for this kind of collagen becomes resistant to enzyme action. All these disturbances create the conditions for the long existence of surplus masses of collagen around the foreign body, inhibiting synthesis of new collagen molecules, which is dependent on the amount of collagen in the intercellular space. As a result, differential mechanisms in young connective tissue cells are disturbed during morphogenetic processes and sarcomas develop.

The induction of sarcomas around a foreign body of noncarcinogenic form was demonstrated by the writer also after intraperitoneal injection of ethylnitrosourea [4], and also on the addition of a shredded lamina to a whole lamina, when the frequency of tumors increased from 50 to 72% [2], evidently on account of an increase in the number of initiating cells. In the investigation cited, it was shown that induction of sarcomas may also take place due to a change in the microenvironment, which acts as a promoting factor.

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