

THE INFLUENCE OF HIBERNATION ON THE DEVELOPMENT OF EXPERIMENTAL TUMORS IN CITELLUS MAXIMUS PALL.

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The genesis of malignant neoplasms caused by a solution of 9,10-dimethyl-1,2-benzanthracene (DMBA) was suppressed throughout $4\frac{1}{2}$ months of winter hibernation in Citellus suslica Gueldenstaedt [4,5] and the 10-week "summer" hibernation in C. erythrogenis Br. [3]. This influence was seen to be considerably stronger than in hamsters [1,2], since hibernation in the latter is not as deep as in the marmots.

In this work an attempt was made to clarify how a shorter but equally deep "summer" hibernation would affect the course of the same process in marmots of another species. For this purpose we used C. maximus Pall.

METHOD

All the animals were given a single injection of DMBA in a dose of 2 mg in 0.2 ml benzene subcutaneously, into the inner surface of the left thigh. When 72 days had elapsed after the injection all the animals participating in the experiment were divided into 2 groups. One group of 11 marmots, after initially being maintained for three days on dry food material (oats), was placed in a cellar, where the temperature was maintained within the range of 15-16°. The other group, with the same number of animals, remained in the normal animal quarters and served as control. In the course of the first week 3 marmots of the first group, having not entered into the hibernation state, were transferred to the regular quarters and added to the control group. The 8 marmots remaining in the cellar fell into a deep hibernation. At that time their rectal temperature dropped to 16.3-17°, while in the non-hibernating animals there (which were later removed) the temperature was 32-33°. In the marmots of the control group, residing in the normal quarters, the temperature was 33.5-35°.



Fig. 1. Sandstone marmot. Tumor at 2 years and 5 months after the injection of DMBA.

After a two-week period all the marmots were returned to the normal quarters and awakened from their hibernation. Subsequently, no member of that group returned to the deep hibernation. In April, 1957 there remained 7 animals in the experimental group and five in the control, the rest having died. Observations were continued up until the natural death of all the animals. The last marmot died on November 28, 1958. Thus, our observations lasted over a period of $2\frac{1}{2}$ years (the injections were carried out on June 12, 1956).

All the marmots were autopsied after their deaths, and the injection site—the skin and underlying tissue—was subjected to histological investigation. We employed the method of imbedding in paraffin and staining with Bemer's hematoxylin, eosin, and by the method of van Gieson.

In the course of the experiment we recorded minimal hair losses temporarily appearing in the marmots of both groups. We never observed neoplasms or pathological changes which could be interpreted as pre-tumors in the group entering the hibernation state.

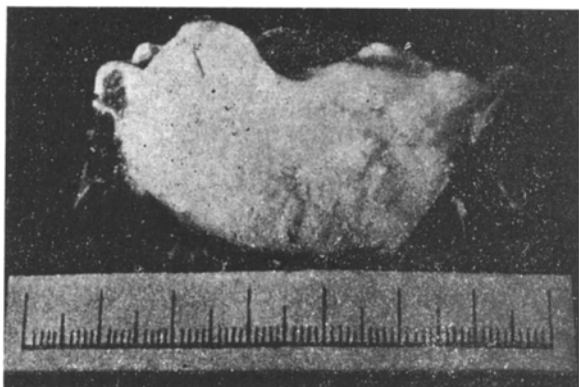


Fig. 2. The same tumor as in Fig. 1, in cross section. Above and to the left can be seen a portion of the spherical node situated on the medial protuberance.

was located on the external side and anterior, while the two others—smaller in size—were turned inward and posteriorly. The marmot died on November 28, 1958, 9 days after a biopsy was carried out on it; at that time a small scar remained at the site of the operative wound. Autopsy showed that the protuberances which were felt through the skin on the side of the peritoneal wall were also well defined. To a greater or lesser degree, fluctuation was felt in all three of the protuberances. On the medial protuberance at the level of the linea alba in the peritoneal cavity there was a spherical node of reddish-brown color. Lateral and anterior to this node at one place the mesenteric folds were loosely attached to the peritoneum overlying the tumor, the latter making the entire surface of the tumor appear lustrous. The weight of the tumor was 43 g.

On sectioning it could be seen that there were no borders between the protuberances: the entire tumor appeared as a uniform, dense mass, varying only in color. Its central portion was a grayish-brown color, the entire peripheral (larger) portion was pink, and in the region of the spherical node mentioned before it was a vivid red. A small number of white strands were threaded through the whole tumor; large blood vessels accompanied by parallel running nerves could be seen in places. No metastases were discovered. In Fig. 2 the tumor is presented in cross section (photograph taken after fixation of the material in a 10% solution of formalin).

With microscopic investigation of the sections from various portions of the tumor no essential differences could be found between them. The neoplasm turned out to be a spindle cell sarcoma with a large admixture of polymorphic cells. The tumor tissue contained a significant number of dilated thin-walled blood vessels. Mitotic figures were seen everywhere. Fibers, staining a pink color by van Gieson's technique, were present in very small number. The tumor cells infiltrated and destroyed the adjacent muscle and subcutaneous fat tissue, penetrating into the dermis. A portion of the tumor, with isolated adipose tissue cells retained, is presented in Fig. 3. Sites of necrosis were encountered in some areas of the visual field.

Biological proof of the malignancy of this neoplasm was also provided by the fact that transplantation of portions of it yielded a high percent of "takes", and no tendency toward a decrease in this figure was seen in the course of 4 passages of homo- and heterotransplants.

No final conclusions can yet be drawn from this experiment. However, it can be stated, in the first place, that we obtained an experimental malignant tumor from a sandstone marmot, a species in which a neoplasm had not yet been described; secondly, our data on the influence of deep hibernation (even of relatively short duration) coincides with previously obtained results from experiments on other species of marmots which enter into a deep hibernation—speckled and red-jawed marmots.

In conclusion, it should be noted that among different families of the rodent order the squirrel family, to which belong the marmots, is characterized by an exceptional infrequency of "spontaneous" tumors and by a low output of experimental neoplasms [3].

A neoplasm arose in one female in the group of animals that did not fall into hibernation. At the beginning of May, 1958, no pathological changes were observed in her. In the middle of May a thickening appeared, fixed to the underlying tissue, which was located to the left on the posterior portion of the peritoneal wall at the level of the articulation between the femur and the pelvis. The skin over the neoplasm was movable. The thickening had an imperfectly oval nodular form, and a dense consistency. By June 13th, 1958 its diameters were equal to 23 and 18 mm. Gradually, the skin over it became fixed, and the neoplasm, remaining just as dense and nodular, markedly increased in dimensions. By November 18th, 1958 it attained the proportions 50×46×23 mm. In Fig. 1 we see the marmot at that time.

It was now possible to establish that the neoplasm consisted of three fused protuberances. The largest of these

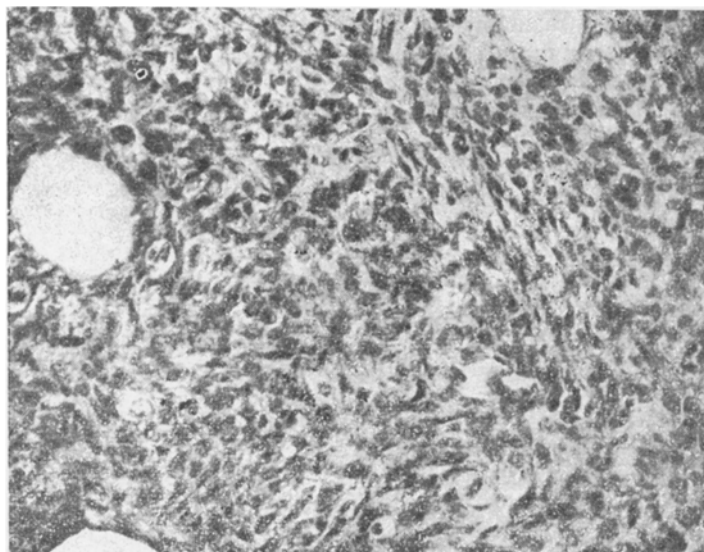


Fig. 3. The same tumor as in Figs. 1 and 2. Sarcoma. Projections of spindle-shaped cells can be seen, along with polymorphic cells, mitoses and remnants of adipose tissue. Magnification 150 \times .

SUMMARY

A tumor caused by the administration of 9, 10-dimethyl-1,2-benzanthracene developed in one Citellus maximus Pall. from the non-hibernating group in one year and eleven months. Within five months it reached the size of 50 \times 46 \times 23 mm. This neoformation proved to be a spindle cell sarcoma with considerable polymorphism. It is markedly transplantable. No signs of tumor growth were detected in the experimental group of animals which were in a deep summer hibernation for two weeks.

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