EXPERIMENTAL PRODUCTION OF TUMOR IN A WHITE RAT

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Ever since the establishment by Virchow of an etiological theory of cancer due to irritation, cancer investigators have attempted to find a means of producing cancer experimentally by some form of irritation.

The first successful results were reported by Yamagiwa and Itchikawa in 1915, using rabbits, the ears of which were painted with coal-tar every second or third day.

In 1918 Tsutsui published the fact that by painting the skin of the interscapular region of mice repeatedly with tar he had succeeded in producing hyperkeratosis, papillomatous growth, and carcinoma. From the report of these experiments, it appears that out of 67 mice surviving more than 100 days after painting with tar was commenced, cutaneous carcinoma developed in 16 animals, and sarcoma in one. Metastatic nodules were found in the lungs of two mice.

Since then, Murray and Woglom, Block and Dreifuss, Roussy, Deelman, Fibiger and Bang, Caspari, Teutschlander, and Lippschutz have repeated this experiment with essentially the same results.

For painting, coal-tar was used. An investigation, recently undertaken by H. Jordan in the pathological laboratory of Teutschlander in Heidelberg, demonstrated that with Gasworks' tar it is possible to produce almost 100 per cent. carcinoma in white laboratory mice which survive the painting for four months. He also found that the specific agent that produced the precancerous warts seems to be contained in the sediment of coal-tar distilled at 400 degrees C. When this sediment is used for painting, results are obtained in one-half the time it takes for full tar.
Many of the tumors produced by tar painting are transplantable. Lipschutz and also Bang succeeded in producing carcinoma in a small number of animals by transplanting the precancerous warts, before carcinoma was demonstrable histologically.

Most observers have found that various strains of mice showed an average immunity of 10 per cent against tar cancer. It takes from 85 to 200 days of painting with tar before the precancerous warts appear,—the largest number appearing about the 120th day.

To determine which constituent of tar was the active factor in the production of tumors, carbolic acid, creasote, etc., were used for painting, with negative results. Bayet thinks that tar cancer is essentially arsenic cancer. For in the tar workers developing cutaneous cancer he was able to demonstrate arsenic in the tar (10–20 mg. per kilo) in all the cases. In his opinion tar cancer produced experimentally closely resembles arsenic cancer in man. Hence he believes that simple irritation is not sufficient in itself to produce cancer. There is required in addition a general toxic agent. Leitch and Kennaway fed rats
and mice on bread containing arsenic (Fowler's solution). The mortality resulting was too high. They then applied Fowler's solution in alcohol (0.12 per cent arsenic) directly to the skin of 100 mice, painting three times a week. In three months they

lost two-thirds of their mice, but observed a growing tumor in one survivor. This animal was killed after 162 days of painting, and a typical squamous-cell cancer infiltrating muscle and metastasizing in the lung was found.

On the other hand, H. Jordan and also Fibiger had the full tar which produced cancer in their experiments examined chem-

**Fig. 2.** Rat Tar Epithelioma × 200. Shows surface epithelioma with tumor cells apparently arising therefrom.
ically and found it to be free from arsenic, and in Bierich's opinion arsenic, while producing a proliferation of epithelium, also effects an increased resistance of the connective tissue preventing the down-growth of the epithelium. He believes that if the first effect of tar on the connective tissue is increased by arsenic, cancer formation can be arrested.

A careful search of the literature discloses that besides the production of tar cancer on the rabbit's ear and on the back of the mouse, there are publications of experimental production of tar cancer in the rabbit's breast and wall of the rabbit's stomach and lung by means of tar injection and tar inhalation; also in the lung and gall-bladder of the guinea-pig.
So far as attempts in the rat are concerned, Menetrier reports that by means of tar mixed in the food he succeeded in obtaining an adenocarcinoma of the stomach in a white rat.

Maisin and Picard state that by local application of paraffin, tar and scarlet red in equal parts, they succeeded in obtaining an epithelioma of the bladder in one rat out of ten tested. They remark on the extraordinary resistance of rats to all attempts to induce carcinoma in the skin by chemical means.

Russel injected tar into the flanks of 40 rats. After 12 months 4 rats were alive. One rat developed a metastasizing tumor, histologically a sarcoma.
Pappenheimer and Larimore observed that rats maintained on deficient diets tended to eat hair, and found in these animals ulcers of the stomach in which particles of hair were embedded. These ulcers, however, could also be produced experimentally in rats on a complete diet, when chopped hair was added to the diet. The ulcerative lesions were associated with papillary epithelial hyperplasia and the authors seem inclined to think that the ingested hair acted as a mechanical irritant resulting in the lesions.

Many attempts have been made to produce skin cancer by means of tar in the laboratory rat, among them the most determined effort of Bullock in this Institute, who used animals of a strain susceptible to cysticercus irritation. He painted the backs of 185 white rats three times weekly for over one year, until all animals had died. Fifty-seven of these animals were young (two and a half to five months). 128 were older (seven to eleven months). He began painting January 24, 1923, and the last rat died June 7, 1924. They were painted over the back of the ear and the pinna. For the first three months coal tar from Leggett & Bros. was used; Gas House Tar was then substituted. The last rat surviving showed minute nodules on the surface of the painted skin. In the other animals no pachydermia, hyperkeratosis, or warts were observed, the only effect being a temporary alopecia.

In the experiment described here 100 white rats were used. These animals were painted with a Gas-works tar which was known to produce cancer in mice, the tar being diluted to 50 per cent with glycerine and 1 per cent of arsenious acid being added. Painting was done on the interscapular region of the skin twice weekly. The experiment was controlled by painting a similar series of 100 rats with 1 per cent arsenious acid in glycerine. The painting continued for 226 days when alopecia, pachydermia, hyperkeratosis and a few papillomatous growths were observed in the tar-painted animals. The control series showed no changes whatever, except that the mortality among the animals was lower. At this point painting was suspended for five months. After this interval 16 of the tar-painted rats
were found surviving. Painting was recommenced, using the same skin area, the same intervals, and the same composition of tar, glycerine and arsenious acid. At this period 381 days had elapsed since the initial painting. The painting was continued for 63 more days, making a total of 444 days. Again painting was interrupted for two months. On the 511th day one rat was found to have a skin horn with an underlying tumor infiltrating the skin and presenting all the characteristic appearances observed in the tar cancers produced in the mouse. The base of the tumor was 2 cm. in diameter and presented a distinctly raised hard edge. Portions of the tumor were removed from the base for microscopic examination and also for transplantation. The results of the transplantation are still outstanding because of the short period of time elapsed. Unfortunately the animal itself succumbed and terminated efforts at autotransplantation. At autopsy there was no gross evidence of metastasis. The photograph of the animal, as well as the microscopic views of the tumor, illustrate the lesions described.

We are not ready to offer any conclusions at this time, as the experiment is being continued on a larger scale.

REFERENCES


