

EFFECT OF NITROSOETHYLUREA ON INDUCTION
OF SARCOMAS BY A FOREIGN BODY

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The possibility of obtaining sarcomas experimentally at the site of introduction of whole disks of cellophane and other chemically inert materials aroused great interest initially and has been repeatedly confirmed [2-5, 7]. Meanwhile, introduction of the same materials in the form of a powder of perforated disk did not lead to the development of neoplasms. All workers agree that induction of sarcomas in this case depends more on the shape than on the chemical nature of the foreign body. In an attempt to explain this phenomenon it has been postulated that endogenous carcinogenic substances are deposited on the disks or in the capsules surrounding them [6].

Recent data on the possibility of synthesis of carcinogenic nitroso compounds from their precursors (nitrites and nitrates) [8] confirm the view that endogenous carcinogens, causing cell transformation, may accumulate around a foreign body.

The object of this investigation was to study the possibility and characteristics of development of neoplasms as a result of the combined action of nitroso compounds and implantation of disks.

EXPERIMENTAL METHOD

A cellophane disk measuring 2×3 cm (animals of group 1) or shredded cellophane (animals of group 2) was implanted subcutaneously in the dorsal region into male noninbred rats aged 6 weeks. On the 3rd and 4th days after the operation half of the animals from each group was given an intraperitoneal injection of nitrosoethylurea (NEU) in a dose of 60 mg/kg (groups 3 and 4 respectively). The tumors were fixed in 10% formalin and sections were stained with hematoxylin-eosin and by Van Gieson's method.

EXPERIMENTAL RESULTS

Group 1, into the animals of which cellophane disks were implanted, consisted of 20 animals at the time of appearance of the first tumor (9.5 months). Tumors developed around the disks in 12 of these animals, i.e., in 60%, after a mean latent period of 16.5 ± 0.9 months (Fig. 1). These results coincide with data obtained previously [3, 4]: in rats into which a whole cellophane disk of the same size was implanted subcutaneously, sarcomas appeared in 51.1% of cases after a mean latent period of 15 months.

In the 15 rats of group 2, into which shredded cellophane was implanted, not a single tumor appeared.

In the rats of group 3, into which a cellophane disk was implanted and NEU injected, tumors appeared at the site of implantation of the disk in 11 of 15 animals which survived longer than 9 months, i.e., in 73.3%. The mean latent period of development of the neoplasms was shorter, namely 13.7 ± 0.87 months (Fig. 2).

In the rats of group 4, into which shredded cellophane in five of 15 animals (33.3%) after a mean latent period of 13.2 ± 0.81 months (Fig. 3).

The cellophane disk or shredded cellophane was found inside all the tumors at autopsy. The tumors were solid in consistency, white in color, with hemorrhagic cysts. Around the cellophane disk the hemorrhagic cysts were small, but after injection of NEU they were much larger, and sometimes the whole tumor consisted of a thick-walled cyst. The tumor tissue around the shredded cellophane contained small cystic cavities.

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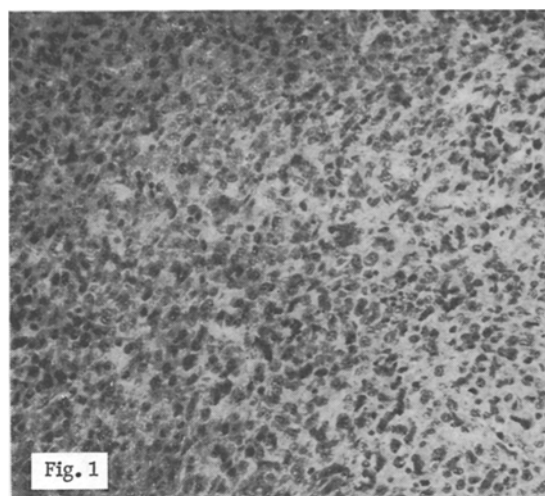


Fig. 1. Round-cell sarcoma induced by implantation of cellophane disk. Here and in Figs. 2 and 3, magnification 200 \times .

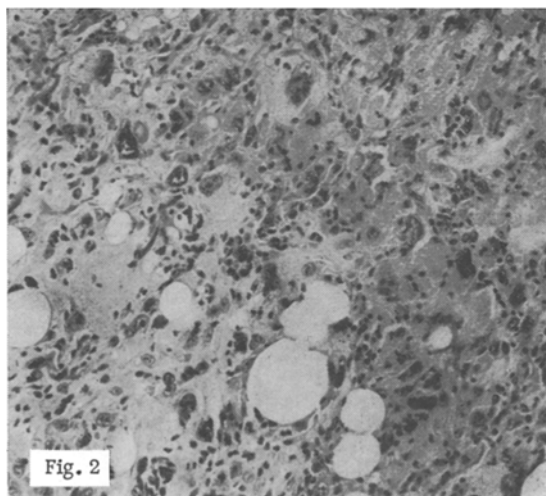


Fig. 2

Fig. 2. Polymorphocellular sarcoma around cellophane disk after injection of NEU.

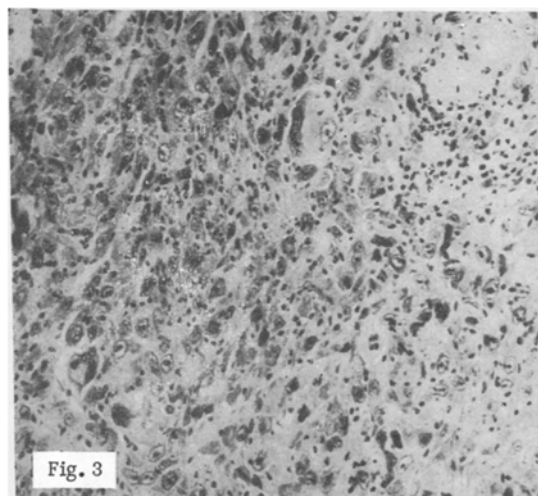


Fig. 3

Fig. 3. Polymorphonuclear sarcoma around shredded cellophane after injection of NEU.

After histological examination the tumors around the cellophane disk were classified as round-cell sarcomas, and one as a spindle-cell sarcoma, rich in collagen fibers. Few collagen fibers were present in the round-cell sarcomas. Uniformity of structure of these tumors and infrequency of their blood vessels were noteworthy.

Tumors in rats of groups 3 and 4, which received NEU, differed in cellular composition from those in rats of group 1, but were similar to one another. They were polymorphocellular sarcomas with many giant cells, polynuclear cells with hyperchromic nuclei. Polymorphic cells with pale, large nuclei also were present. Cells with curiously shaped mitotic figures were found. A special feature of these tumors was the large number of blood vessels of different diameters.

The investigations showed that intraperitoneal injection of NEU in the period of acute inflammation developing around a foreign body implanted into the loose connective tissue leads to an increase in the frequency of development of tumors around a disk and also to the appearance of tumors around shredded material. Tumors appeared around shredded cellophane, in animals receiving NEU (group 4), in 33% of cases, whereas in rats not receiving NEU (group 2) no tumors appeared, i.e., the development of neoplasms in this case must be entirely attributed to the injection of NEU. The frequency of development of tumors around the cellophane

disk in these experiments was 60%. In animals of group 3 tumors appeared in 73.3% of cases, and this can be attributed to the action of two carcinogenic agents (the disk and NEU) combined.

The latent period was shortened from 16.5 months in the animals of group 1 to 13.7 months in those of group 3. This last time is very close to the period of development of neoplasms observed in group 4 (13.2 months), indicating the influence of NEU.

Potentialization of the carcinogenic effect was not found with a combination of etakril (a Soviet acrylic plastic) disks and nitrosomethylurea (NMU), in the experiments of Eliseev and Zabezhinskii [1]. After implantation of an etakril disk measuring 2×2 cm tumors appeared in 30% of the animals, after injection of NMU in 44.8%, and after a combination of these two agents — in 41.7% of animals. Injection of the nitroso compound into the site of the focus of inflammation thus did not potentiate carcinogenesis due to implantation of the disk, but acted as a chemical carcinogen, as can be judged from the roughly equal numerical data obtained by these workers. They injected NMU inside the capsule around the disk 1 week after its implantation. Their experimental conditions thus differed from our own. Injection of NMU inside the capsule may perhaps have prevented the development of carcinogenesis due to the disk itself, because of disturbance of the integrity of the collagen capsule.

The present writers postulated [6] in 1962 that endogenous carcinogenic substances may participate in carcinogenesis induced by a foreign body, and consequently, in surgical practice it was recommended that possible combinations of foreign bodies with chemical carcinogens should be avoided. The results of the present investigation provide experimental confirmation of this hypothesis and of the suggested recommendations.

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