Experimental Brain Tumors

III. Tumors Produced with Dibenzanthracene*

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The unexpected success with benzpyrene in producing intracranial neoplasms in C3H mice (6), after many unsuccessful attempts by other workers, was a clear indication to try still another chemical carcinogen for its effect on brain tumor production. The carcinogen chosen was 1,2,5,6-dibenzanthracene.

In 1938, Weil (3) reported the result of injecting a lard solution of dibenzanthracene into the brain of a white rat. He stated that 7½ months after the injection he found a squamous epithelial carcinoma and surrounding the tumor a definite glial proliferation. In the summary of his findings Weil wrote, “One case was noted in which injection of the dibenzanthrace-lard mixture produced a malignant carcinoma besides granuloma.” No mention was made of a glioma produced with dibenzanthracene yet, in 1941, in discussing a paper by Sweet and Bailey (2) on the experimental production of intracranial tumors with methylcholanthrene, he referred to this animal as having both an epidermoid carcinoma and a glioma. The illustration (Fig. 1-A) in the original report of 1938 shows perhaps some glial proliferation but is decidedly not convincing as a glioma.

More recently Weil and Blumklotz (4) redescribed this case and stated that “In the midbrain, tissue posterior to this epithelial tumor shows neoplastic transformation into a glioma.” There is certainly evidence of glial proliferation in the illustrations (Figs. 5-C and 7) of this part of the brain but it is, nevertheless, questionable whether this constitutes gliogenous neoplasia.

The most extensive animal experiments with intracranial implantation of dibenzanthracene were performed by Peers (1), who employed cholesterol pellets containing 5 per cent of this carcinogen. Of 53 stock albino mice that survived 6 months or more, not a single animal developed a definite intracranial neoplasm. Peers stated “It is therefore concluded that the brain and meninges of the mouse respond only very slowly or not at all to the carcinogenic stimulus of 1:2:5:6 dibenzanthracene.”

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METHOD

Twenty-one female mice of the C3H strain received intracerebral implants of pellets of 1,2,5,6-dibenzanthracene obtained from the Edcan Laboratories, South Norwalk, Connecticut. The animals were all 7 weeks of age at the start of the experiment, which was concluded when the last mouse died spontaneously. The operative procedure, anesthesia, animal care, and diet were all similar to those previously employed in experiments with methylcholanthrene (5). Pellets of the carcinogen were prepared by heating the crystals gently in a beaker until they fused; when the solidified mass cooled, cubes were cut with a knife to a diameter of 1 mm. The pellets thus obtained, without further treatment, were implanted in the right cerebral hemispheres. It should be noted that no oily or fatty vehicle, such as lard or cholesterol, was employed.

RESULTS

The pertinent data are presented in Table I. Of the 21 mice in the experiment, only 2 developed
gliomas (No. 10, glioblastoma multiforme, and No. 11, ependymoblastoma). One animal (No. 8) had an intracranial (meningeal) sarcoma and another (No. 4) had both an intra- and an extracranial sarcoma. In this animal it could not be determined where the sarcoma arose—whether intra- or extracranially or whether, indeed, it did not represent two separate tumors. Eight mice (Nos. 3, 5, 9, 13, 20, 23, 25, and 26) had extracranial sarcomas only. One animal (No. 6) developed a squamous cell carcinoma of the scalp. Tumors failed to develop in 8 mice (Nos. 1, 2, 7, 16, 17, 18, 19, and 24).

In those animals in which intracranial neoplasms did not develop, the sites of pellet implantation were marked by slit-like spaces (Fig. 1). There was neither mesodermal nor gliogenous cellular proliferation. All signs of inflammation, foreign body reaction, and phagocytosis were lacking.

**Meningeal sarcoma.**—Mouse 8. This animal had a diffuse neoplasm in the meninges over the right cerebral hemisphere as well as a nodular tumor extension into the underlying cortex (Fig. 2). There was also an extension of the tumor through the trephine opening in the skull with the formation of a small nodule beneath the scalp. The spindle-shaped tumor cells were arranged in parallel rows or formed whorls. Each cell had bipolar processes that combined with those of other cells to form a delicate reticular stroma. Many cells were in mitotic division and a few had more than one nucleus.

**Intra- and extracranial sarcoma.**—Mouse 4. The head of this mouse became progressively deformed during the last 2 weeks of life. At necropsy the deformity was found to be produced by a tumor beneath the scalp. A neoplasm also replaced much of the right cerebral hemisphere, but no apparent connection was demonstrable between this and the extracranial new growth. The cells composing the tumor were elongated and had prominent oval nuclei with much chromatin and single nucleoli. They gave rise to interlacing fibrillary processes that formed a dense stroma. Numerous mitotic figures were present as well as occasional bizarre multinucleated elements.

**Glioblastoma multiforme.**—Mouse 10. A large portion of the right cerebral hemisphere was replaced by a partially hemorrhagic, infiltrating tumor (Fig. 3). The neoplastic cells varied considerably in size and shape. Many were in mitotic division and some were of giant size with more than one nucleus (Fig. 5). Parts of the neoplasm were necrotic, but there was no real pseudopalisading around these zones of necrosis. The ground substance was amorphous, granular, and pale pink (in hematoxylin-eosin stain), with no definite fibrillary structure. Wilder preparations for connective tissue reticulin were negative.

**Ependymoblastoma.**—Mouse 11. One week before this animal died, a tumor appeared in the scalp at the site of the craniotomy. At necropsy this mass was found originating in the right cerebral hemisphere, in which was discovered the pellet of dibenzanthracene. Tumor cells infiltrated the cerebral cortex and the overlying leptomeninges. Many of them were carrot-shaped and had unipolar processes. They were often arranged in acinar formation around empty spaces or formed pseudocysts around blood vessels (Fig. 4). Intracerebral transplants of this neoplasm in other mice of the same strain yielded tumors that grew in the ventricular system and infiltrated diffusely the nervous tissue and meninges. Pseudocysts were more numerous in the transplants than in the primary tumor. In both, many cells were in mitotic division and a few were multinucleated. The primary tumor also contained several small deposits of calcium salts.

**COMMENT**

Four animals only in this series of 21 C3H mice developed intracranial neoplasms following intracerebral implantation of pellets of dibenzanthracene. Of these tumors 2 were gliomas and 2 sarcomas. This incidence of carcinogen-induced tumors is considerably less than half that yielded by either methylcholangan-threne (5) or benzpyrene (6).

In view of the inability of Peers to induce brain tumors in stock albino mice into which were implanted cholesterol pellets containing 5 per cent dibenzanthracene, it should be emphasized that in the present experiments undiluted carcinogen was employed. This alone may account for the discrepancy in his and our results. The other difference in the two experiments was that whereas Peers employed albino mice, our animals were of the C3H strain. We have conclusive evidence (7) to show that the mouse strain is an important factor in the incidence of carcinogen-induced brain tumors.

With the single exception of the possible glioma produced by Weil with a lard solution of dibenzanthracene in a white rat, the two instances of glioma detailed in this communication constitute the first successful efforts to produce gliogenous neoplasia with this chemical carcinogen.

**SUMMARY**

Pellets of 1,2,5,6-dibenzanthracene were implanted in the right cerebral hemispheres of 21 female C3H mice.

Thirteen tumors developed, of which two were gliomas. One was an intracranial meningeal sarcoma. One sarcoma was both intra- and extracranial. Eight tumors were extracranial fibrosarcomas. One neoplasm
was a squamous cell carcinoma of the scalp. Eight animals failed to develop any type of tumor.

Of the two gliomas, one was a glioblastoma multiforme whereas the other was an ependymoblastoma.

REFERENCES


DESCRIPTION OF FIGURES 1 TO 5

Fig. 1.—Mouse 5. Slit-like spaces indicating site of pellet implantation in left half of interbrain of non-tumor-bearing animal. Note absence of all cellular proliferation. Mag. X 13. Specimens in Figs. 1 to 5 were stained with hematoxylin and eosin.

Fig. 2.—Mouse 8. Tumor nodule of meningeal sarcoma indenting cerebral cortex; neoplasm distinctly demarcated from nervous tissue. Meninges at right in photograph are infiltrated with tumor cells. Mag. X 30.

Fig. 3.—Mouse 10. Infiltrating tumor replacing most of right cerebral hemisphere. Mag. X 10.

Fig. 4.—Mouse 11. Tumor cells in right cerebral hemisphere showing pseudoacinar formation at top of photograph and perivascular arrangement at bottom. Mag. X 325.

Fig. 5.—Mouse 10. Pleomorphic tumor cells, some in mitotic division. Note giant tumor cell at bottom and amorphous stroma. Mag. X 325.
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