Tumors of the Salivary and Parathyroid Glands in Rats Fed with 2-Acetylaminofluorene

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Wilson (3) and his associates induced tumors in rats fed 2-acetylaminofluorene in a prepared diet. The tumors arose in many organs but none appeared in the salivary glands. Bielchowsky (1) reported similar findings with this compound and recorded tumors of the thyroid gland, also, after thiouracil had been added to the diet (2). No changes of any sort in the parathyroid glands were reported.

In our experiments, 36 female and 23 male Wistar rats 2½ to 3 months old were given an oily mixture (peanut oil) of 2-acetylaminofluorene with a syringe bearing a curved needle for introduction into the pharynx. Of this mixture, 1 cc. containing 10 mgm. of the drug was administered every other day, and later 20 mgm. were given every third day. The total amount given ranged between 250 and 650 mgm. during 111 to 227 days. The animals were fed on one part Purina dog chow checkers and two parts Rockland rat diet, allowed water ad libitum, and observed until death.

Twenty-two of the treated rats developed nodular swellings in one or both of the submaxillary regions. These swellings extended to the subcutaneous areas of the chest and axillae. Autopsy revealed enlarged submaxillary glands and many small discrete or large confluent cysts containing a yellowish oily fluid (peanut oil). The cystic nodular masses ranged in size between 1.5 x 1.6 x 2.4 cm. and 3.0 x 2.5 x 2.2 cm., and displaced or covered the submaxillary glands. By further dissection the swellings were traced to the mediastinum. Several animals showed white exudates on the pleura and pericardium, and effusions were noted in the pleural and pericardial spaces. The changes in the liver varied between passive congestion, cirrhosis, cysts, and adenoma. The adrenal glands and the thyroid also contained cysts, which, however, were not filled with yellow oily fluid. Four of the treated females, one having been fed 435 mgm. of 2-acetylaminofluorene in 213 days, had litters.

In addition to cystic swellings, 12 animals developed tumors, as follows:

<table>
<thead>
<tr>
<th>Tumor</th>
<th>No. of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma of submaxillary gland</td>
<td>2</td>
</tr>
<tr>
<td>Adenoma of submaxillary gland</td>
<td>3</td>
</tr>
<tr>
<td>Mammary adenocarcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Parathyroid adenoma</td>
<td>2</td>
</tr>
<tr>
<td>Adenoma of liver</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoma of neck</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid adenoma</td>
<td>1</td>
</tr>
</tbody>
</table>

Only neoplasms of the submaxillary and parathyroid glands not hitherto reported will be described. One tumor of the left submaxillary gland appeared in a female rat that had received 340 mgm. of 2-acetylaminofluorene in 4 months. Eleven weeks after the last dose of the drug the animal was sacrificed. The tumor, soft, purple, nodular, and not encapsulated, measured 2.8 x 2.6 x 1.5 cm. Microscopic section (Fig. 1) showed a cystic tumor adjoining normal salivary glands. This adenocarcinoma had distorted architecture which included large cysts containing papillary projections of epithelium. Many of the cystic spaces were completely filled with masses of epithelium. Fig. 2 shows invasion of the subcutaneous connective tissue by groups of cancer cells. The cells were irregularly cuboidal and the cytoplasm contained mucous secretion demonstrated by the mucicarmine stain. Numerous mitoses were evident.

The adenomas of the submaxillary gland appeared as isolated areas of hyperplastic ducts and acini, in which the normal cuboidal epithelium had been replaced by columnar epithelium (Fig. 3). These localized adenomas showed a transition from normal tissue to the adenocarcinoma previously described.

Serial sections of the thyroid revealed enlarged parathyroid glands lying in the substance of the thyroid tissue. In 2 animals the normal structure of the parathyroid, with its diffuse arrangement of cells and occasional cords, was replaced by an adenomatous structure with hyperplasia (Figs. 4, 5).

Twenty-four of the 59 animals had been given, in addition to 2-acetylaminofluorene, measured doses of aromatic amino acids ranging between 143 and 416 mgm. in 45 days. None of those fed with amino acids...
Fig. 1.—Papillary cystadenocarcinoma of submaxillary salivary gland. Normal gland, upper left. Mag. × 60.
Fig. 2.—Invasion of stroma by cancer. Mag. × 454.
Fig. 3.—Adenoma of submaxillary salivary gland. Mag. × 120.
Fig. 4.—Parathyroid adenoma. Mag. × 60.
Fig. 5.—Parathyroid adenoma. Mag. × 60.
developed any tumors after the administration of 2-acetylaminofluorene up to 650 mgm. The aromatic amino acids probably interfered with the carcinogenic activity of the acetylaminofluorene. The animals fed with aromatic amino acids and acetylaminofluorene did not develop cirrhosis of the liver as did those fed with the latter compound alone.

Thirty-six animals with transplanted mammary adenofibromas were fed acetylaminofluorene, which had no effect on their growth, and no malignant changes were noted in them.

CONCLUSION

The localization of cysts and tumors in the neck may be attributed to trauma of the pharynx and esophagus produced by the needle. The 2-acetylaminofluorene may therefore exert a local action if applied frequently to the same site. Wilson and his co-workers reported that no tumors appeared after subcutaneous injection of 2-acetylaminofluorene (3). In view of our observations it is suggested that this chemical may constitute an industrial hazard.

REFERENCES

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