The Induction of Melanotic Tumors Resembling Cellular Blue Nevi in the Syrian White Hamster by Cutaneous Application of 7,12-Dimethylbenz[a]anthracene

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SUMMARY

Melanotic tumors resembling cellular blue nevi of man were induced in the Syrian white hamster by single and multiple applications of 7,12-dimethylbenz[a]anthracene (DMBA). Histologically they resembled the melanotic tumors produced under similar experimental conditions in the Syrian golden hamster. They showed great variations in pigment content from almost nonpigmented to heavily pigmented tumors. Study of early lesions suggested origin of the melanotic tumors in the Syrian white hamster from amelanotic perifollicular melanocytes. None of the induced tumors metastasized. One of the poorly pigmented tumors was transplanted into both golden and white Syrian hamsters. One of the transplants gave rise to metastases to lymph nodes, lungs, and kidneys. The capacity to produce pigment was retained in the transplanted tumors. The study confirms our previous observation that cutaneous application of a single dose of DMBA to Syrian hamsters induces a high incidence of melanotic tumors which differ morphologically and biologically from the melanomas known to occur spontaneously in the Syrian golden hamster.

In a previous communication we reported the induction of blue nevus-like melanotic tumors in the Syrian golden hamster by single and multiple application of DMBA (1). These findings were subsequently confirmed by Homing (4) and Ghadially (3). Recent experiments conducted in our laboratory in several additional series of hamsters showed that these lesions could be produced in up to 100 per cent of the animals with a single application of approximately 800 μg. of DMBA in mineral oil. The transplantability of these tumors was also demonstrated (5). Histologically, the melanotic tumors differed from the spontaneous malignant melanomas described in the Syrian golden hamster (2) but closely resembled cellular blue nevi of man (1). To investigate the possible relationship between tumor growth and pigment formation in response to a specific chemical carcinogen, it was decided to study the effects of DMBA upon the skin of the Syrian white hamster.

This variant of the Syrian hamster is not a true albino (pigmentation of the pinnae and the scrotal skin appears when the animal reaches sexual maturity about the 5th week of age), but the absence of melanin-containing cells in the hair bulbs and the lack of pigmentation of the hair indicate that a pigment-producing melanocytic system as it occurs in the golden hamster is not present in the skin of the white variety, except in those few areas which appear grossly pigmented.1

MATERIALS AND METHODS

Eighteen female and 29 male Syrian white hamsters obtained at 10-12 weeks of age from Abrams Small Stock Breeders, Chicago, Ill., were used. The animals were housed in plastic cages and

1 Since submission of this manuscript it has been shown that the skin of the white hamster is devoid of the perifollicular collections of pigmented melanocytes which are found in the golden hamster around some of the pilosebaceous follicles (O. Illman, and F. N. Ghadially, Coat Colour and Experimental Melanotic Tumor Production in the Hamster. Brit. J. Cancer, 14: 483-88, 1960). Using repeated applications of DMBA, these authors were able to induce tumors identical with those described in our report in the white Syrian hamster but not in the cream-colored variety.
fed Rockland mouse diet and tap water ad libitum.

The carcinogen used was 7, 12-dimethylbenz-[a]anthracene (DMBA) (Eastman Organic Chemicals). The DMBA was purified by column chromatography on magnesia and used as a 1 per cent solution in fluorescence-free mineral oil U.S.P. (Superla 34, Standard Oil Co. of Indiana). The carcinogen was given with a standard glass dropper, each drop measuring approximately 20 μl. The drops were applied evenly to the skin of the middle line of the back, kept free of hair with an electric clipper. The hamsters were divided into two groups and treated as follows: Group 1 (nine female and fourteen male animals) received one death or killed when in terminal condition. The animals were necropsied except for five females and two males lost through cannibalism. Histologic studies were performed on the skin, lungs, liver, spleen, kidneys, adrenals, and any additional organs which showed gross pathologic changes. Sections from these tissues were stained with hematoxylin and eosin. The Snook modification of the Maresch-Bielschowsky stain was employed for the demonstration of reticulin fibers in the tumors. The dopa reaction was performed according to the method of Laidlaw on frozen sections of selected tumors. Bleaching of melanin pigment was carried out by exposing the section to

TABLE 1

RESULTS OF THE APPLICATION OF 7,12-DIMETHYLBENZ[a]ANTHRACENE TO THE SKIN OF THE WHITE HAMSTER

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NO. ANIMALS</th>
<th>SURVIVORS AT:</th>
<th>MAXIMAL SURVIVAL TIME (WEEKS)</th>
<th>TOTAL NO. ANIMALS WITH MELANOTIC TUMORS/NO. MELANOTIC TUMORS*</th>
<th>PER CENT ANIMALS WITH MELANOTIC TUMORS</th>
<th>AV. TIME OF APPEARANCE OF MELANOTIC TUMORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% DMBA in min. oil 4 drops once</td>
<td>9♀</td>
<td>8 8 8 6 4 1 0</td>
<td>68</td>
<td>7/32</td>
<td>87.5</td>
<td>24.7 (11-59)</td>
</tr>
<tr>
<td></td>
<td>14♂</td>
<td>15 13 12 12 8 3 3</td>
<td>79</td>
<td>15/46</td>
<td>100</td>
<td>28.0 (19-76)</td>
</tr>
<tr>
<td>1% DMBA in min. oil 4 drops once weekly for 3 weeks</td>
<td>9♀</td>
<td>9 9 8 3 3 0 0</td>
<td>56</td>
<td>9/31</td>
<td>100</td>
<td>91.6 (11-35)</td>
</tr>
<tr>
<td></td>
<td>15♂</td>
<td>13 13 12 10 8 5 0</td>
<td>63</td>
<td>12/39</td>
<td>92.3</td>
<td>97.3 (19-36)</td>
</tr>
</tbody>
</table>

* Based on no. animals alive when first tumor appeared.
1 In parentheses are given weeks in which the first and last tumor appeared.
2 Each drop had a volume of approximately 20 μl. (0.000 μg). The drops were given on the middle line of the back evenly spaced in cranio-caudal direction.
3 An additional ulcerated tumor was lost through cannibalism.
4 An additional ulcerated tumor was lost through cannibalism.

RESULTS

Incidence.—The incidence of melanotic tumors is summarized in Table 1. It ranged from 87.5 to 100 per cent. There was no significant difference between those animals receiving one and those receiving three applications of DMBA. The percentage figures are computed on the basis of the animals alive at the time when the first tumor appeared. These figures do not differ significantly from those obtained in the Syrian golden hamster under similar experimental conditions. None of the control animals developed melanotic tumors.
Gross findings.—The appearance of the skin of one of the tumor-bearing animals is illustrated in Figure 1. Heavily pigmented tumors similar to those produced in the Syrian golden hamster are readily apparent. In addition there were tumors which varied in color from pink to light brown. They were designated as “poorly pigmented.” Localization of both heavily pigmented and poorly pigmented tumors is illustrated in two composite diagrams (Charts 1, 2), indicating a predilection of the tumors for the lower back and the flanks. However, occasional tumors were observed as high as the base of the ear. None arose in the area occupied by the dorso-lateral scent glands, and none were found on the ventral skin of the animal. The tumors varied in size from 0.2 to 1.5 cm. in diameter. Only few exceeded 1.0 cm. There was no apparent difference in the average size of heavily pigmented and poorly pigmented lesions. On sectioned surface the tumors appeared well demarcated. The heavily pigmented tumors were dark brown to black; the poorly pigmented ones were greyish white to pale brown. Some showed an uneven distribution of the pigment. No gross me-
tastases to lymph nodes, lungs, or other organs were seen.

In addition to the pigmented tumors, the skin of all carcogen-treated animals exhibited pigmented spots which were not appreciably elevated and usually measured less than 0.2 cm. in diameter. Some of them were so small as to be barely visible to the naked eye.

**Histologic observations.**—The melanotic tumors produced in the Syrian white hamster were morphologically similar to those previously reported in the Syrian golden hamster. They were located in the deeper layers of the dermis and in the subcutaneous tissue (Figs. 2, 3), often extending to the cutaneous muscle, but rarely beyond it. Spindle-shaped cells with ovoid or fusiform nuclei predominated (Fig 4). These cells were often arranged in interlacing bundles which imparted upon the tumor a morphologic pattern similar to that of neurofibroma (Fig 5). In some tumors clusters of globular cells with abundant clear cytoplasm were present. These "clear" cells gave a negative reaction for neutral fat and were dopa-negative by the method employed by us. Further studies to determine their nature are in progress.

The melanotic tumors of the white hamster exhibited a wide range of variation as to both the relative number of pigmented and nonpigmented cells and the intensity of pigmentation of the individual cells. In some tumors pigmented cells were abundant, in others they were scarce or completely absent at the levels sectioned. Often there was close intermingling between heavily pigmented cells and those in which the pigment was scant or absent. In general, cells with light brown pigment were more abundant than those with dark staining granules. Even in cells with abundant pigment the complete visual obliteration of nucleus and cytoplasm previously noted in the melanotic tumors of the golden hamster was not observed.

Of particular interest is the finding of pigmented tumor cells with one or two, occasionally several, delicate, pigment-containing cytoplasmic processes. They had the appearance of dendritic melanocytes (Fig. 6). Other pigmented cells with more abundant cytoplasm and without demonstrable processes resembled macrophages, and it was in some instances difficult to decide whether they represented melanocytes or melanophages. In general, melanophages were more numerous in the heavily pigmented tumors than in the poorly pigmented ones. They were never conspicuous in the early lesions.

As previously reported, the pigment granules were readily removed with potassium permanganate and gave a positive Fontana stain and a negative iron reaction (1). Dopa-positive tumor cells were few in number and gave a weak dopa reaction by comparison with the intensely dopa-positive perifollicular melanocytes which were observed in the vicinity of the tumors.

Silver impregnation for argentaffine fibers showed an abundant fibrillar reticulum surrounding almost every cell. There was little mature collagen in Van Gieson stains. Bodian stains for nerve fibers revealed occasional small nerve branches or isolated nerve fibers or both within the tumors.

Of great interest was the histological appearance of some of the small and presumably early lesions which were seen only microscopically. They were composed of perifollicular aggregates of nonpigmented spindle-shaped cells (Fig. 9). This picture corresponds to the perifollicular melanocytic proliferations observed in DMBA-treated golden hamsters (Fig. 8) and strongly suggests origin of the melanotic tumors of the white hamster from perifollicular amelanotic melanocytes.

Cytologic features of malignancy were observed only occasionally. They consisted of variation in size and shape of the neoplastic cells and their nuclei and the presence of mitoses, some of them atypical. Metastases were not observed in this series.

**Transplantation studies.**—One of the poorly pigmented tumors which arose in a male white hamster receiving three applications of DMBA was implanted successfully into white and golden hamsters. The transplants were done by implantation of a small tissue fragment measuring 2–3 mm. into the subcutaneous tissue of the back. The tumor grew rather slowly in the first generation and reached double the size of the transplanted tissue fragment in approximately 16 weeks. In subsequent generations the rate of growth was slightly accelerated. The tumor is now carried in the ninth generation. It metastasized to the regional lymph nodes, lungs, and kidneys. Grossly it appeared nonpigmented. Microscopically it resembled malignant neurilemmoma; however, on careful search some of the tumor cells contained melanin pigment (Fig. 10) and had the morphologic appearance of dendritic melanocytes (Fig. 11).

**DISCUSSION**

The present study of melanotic tumors in the Syrian white hamster confirms and supplements the experiences gained with the production of these neoplasms in Syrian golden hamsters by single application of DMBA (1). Melanotic tumors
are as readily produced in the Syrian white hamster as they are in the Syrian golden hamster. In addition, it has been demonstrated that the carcinogen DMBA has two effects that are not necessarily interdependent. In the first instance, it has been found that DMBA can convert amelanotic melanocytes in the white hamster's skin into melanin-producing cells, possibly by activating an enzyme system which normally remains inactive over the entire life span of the animal. In the second instance DMBA can give rise to tumors which originate from melanocytes but which may be either amelanotic or pigmented. It is apparent, therefore, that the capacity of this compound to induce the formation of melanotic tumors is not necessarily dependent upon its capacity to bring about the formation of melanin pigment from its nonpigmented precursor.

In the melanotic tumors of the white hamster, the pigment did not obscure the cellular structure to the extent that bleaching was necessary for study of cellular details. It thus became readily apparent that many of the tumor cells had delicate pigment-laden cytoplasmic processes which made it possible to recognize them as dendritic melanocytes. Restudy of sections from the melanotic tumors of the golden hamster after bleaching enabled us to demonstrate cells with similar dendritic processes.

Pigment-containing macrophages (melanophagides) were much less abundant than in the melanotic tumors of the golden hamster. They were absent in the nonpigmented tumors, and their relative number appeared to be dependent upon the degree of pigmentation. Since macrophages appear in response to extracellular deposition of pigment either from intact or necrotic cells, a rough correlation between degree of pigmentation and relative abundance of melanophages is to be expected. In this connection it is worthy of note that necrosis, a common feature in the melanotic tumors of the golden hamster, was rare in those of the white hamster. The reason for this difference is difficult to explain, since growth of the tumor was equally slow in both. However, in the golden hamster all tumor cells were “choked” with pigment granules which obscured the nuclei and cytoplasm completely. It is conceivable that such extreme pigmentation may have interfered with the normal metabolism of the tumor cells and thus played a primary or contributory role in the causation of cell death.

The resemblance of the tumor pattern to that of neurofibroma, previously noted in bleached sections of melanotic tumors of the golden hamster (1), was even more striking in the white hamster, since it was readily apparent without bleaching of the sections. Equally impressive was the fact that the metastasizing transplant had the histologic appearance of malignant neurilemmoma and that only the demonstration of occasional pigmented dendritic melanocytes in the metastases established the nature of the tumor (Figs. 10, 11). We tried to find morphologic evidence of origin of the tumor cells from perineural or endoneural cells of small cutaneous nerve fasciculi by studying numerous early pigmented lesions both in the golden and the white hamster. Occasionally we found melanocytes in cutaneous nerve branches; because of the rarity and inconsistency of this finding its significance is not clear. Nerve fasciculi and individual nerve fibers were incorporated in the larger tumors, but this could be fortuitous and would not necessarily indicate origin of the tumors from the neurilemma of cutaneous nerve branches. More convincing observations with regard to the histogenesis of the melanotic tumors were reported recently by Ghadially and Barker, who traced their origin to a network of melanocytes which surround some of the pilosebaceous structures in the skin. Our own studies of early lesion in the golden hamster are in accord with the interpretation of these authors. Corresponding nonpigmented perifollicular cells which we believe to be amelanotic melanocytes apparently give rise to the melanotic tumors in the white hamster.

Cytologic features suggestive of malignancy are observed only rarely. Regional and distant metastases were found only in hamsters carrying the transplant, but not in any of the animals with the induced tumors. These observations tend to confirm our previous impression that the carcinogen-induced melanotic tumors of the Syrian hamster are of low-grade malignancy and differ from the spontaneous malignant melanomas reported in this species (2) not only histologically but also biologically.

The very high incidence of melanotic tumors that can be obtained in both golden and white Syrian hamsters by means of a single application of DMBA tends to make this a model experiment for the study of pigment-cell growth.

REFERENCES


Fig. 1.—White female Syrian hamster with pigmented cutaneous tumors. The skin over these tumors is intact. Note the pigmented ears, indicating that the white hamster used in this experiment is not a true albino. The animal died 50 weeks after the first of three consecutive weekly applications of DMBA in mineral oil.

Fig. 2.—Poorly pigmented melanotic tumor measuring approximately 0.3 cm. in diameter and 0.1 cm. in depth. It is well below the epidermis but approaches it in one area in which a hair follicle is surrounded by tumor tissues. The tumor was composed of both nonpigmented and pigmented cells. The former predominated. The pigment was light brown and did not obscure the cellular details. This was the smallest of four tumors in a white male hamster which had received three consecutive weekly applications of DMBA in mineral oil. The animal died in the 50th week of the experiment. Hematoxylin and eosin, X75.

Fig. 3.—Melanotic tumor composed of heavily pigmented, poorly pigmented, and nonpigmented cells, most of which are spindleshaped. The pigment was dark brown to black. The tumor measured 0.3 cm. in diameter and 0.1 cm. in thickness. White male hamster painted with DMBA in mineral oil 3 times at weekly intervals and killed 63 weeks after the first application of the carcinogen. Hematoxylin & eosin, X180.
was impossible to evaluate specific differences in cytotoxic responses as described
prior to drug addition or methods of culture. The compounds in decreasing order of effective-
ness or resistance as a result of prior therapy. All specimens were excised from patients treated with one or several of the drugs
administered at the tissue site as, for example, in clinical procedures involving the use of agents ad-
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in vitro, in vivo, and response to any test drug concentrations. These data may be useful in
todays of malignancy, and benign neoplastic tissues tested. There was no detectable correlation between the
growth rates of primary versus metastatic tissues, the responses of 154 specimens excised from patients with no
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A comparison was made between rate and exposure to actinomycin D, chlorambucil, and thio-
TEPA, caused pyknosis to form narrow, elongated cells. All three alkylating agents, thioTEPA,
methotrexate, actinomycin D, and thioTEPA; and phenylalanine mustard. All agents tested pro-
duced direct objective cytological changes. All five agents under investigation produced
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FIG. 4.—Poorly pigmented melanotic tumor composed predominantly of spindle-shaped cells. Relatively few of the cells were pigmented. The pigment was light brown and was contained in the more darkly staining cells with abundant cytoplasm. There were also clusters of large cells with abundant optically clear cytoplasm near the right upper corner of the illustration. The tumor is from the animal illustrated in Fig. 1. Hematoxylin & eosin, X300.

FIG. 5.—Poorly pigmented portions of a melanotic tumor of a white female hamster painted once with 4 drops of 1 per cent DMBA in mineral oil. This was the largest of ten melanotic tumors and measured 1.0 × 0.8 × 0.3 cm. Note the interlacing bundles of spindle-shaped cells with abundant intercellular matrix. This area closely resembles the pattern of neurofibroma. The pigment in the few pigmented cells was so pale that it was not demonstrable in black and white photographs. Hematoxylin & eosin, X150.

FIG. 6.—Melanotic tumor of white hamster following three applications of DMBA in mineral oil at weekly intervals. It is composed of heavily pigmented, poorly pigmented, and nonpigmented spindle-shaped cells. Note the dendritic melanocytes with cytoplasmic processes containing a finely granular brown to black pigment. Hematoxylin & eosin, X1,000.

FIG. 7.—Same tumor as illustrated in Fig. 3. A reticulin stain shows an abundance of argentaffin fibers. Silver impregnation for reticulin, X100.

was impossible to evaluate specific cytotoxic responses as described prior to drug addition or methods of culture response based on primary or metastatic lesion type in the group evaluated. There was no detectable correlation between the prior growth rate and response to any test agent other than that expected due to chance. All responses of 154 specimens excised from patients with identical drug therapy included administration of carcinostatic agents and apparent: a) the sensitivity of lymphosarcomas, Hodgkin's, and lymphomas of undetermined type to di-rect exposure to chlorambucil; and b) the sensitivity of lymphomas to thioTEPA; c) the sensitivity of fibrosarcomas to direct exposure to chlorambucil; and d) the sensitivity of certain carcinoma types to methotrexate, actinomycin D, and thioTEPA; e) the resistance of lymphosarcomas to methotrexate, actinomycin D, and thioTEPA; f) the resistance of all melanomas tested to phenylalanine mustard. Apparently, tissues which survive therapy and grow in vitro, are able to respond like untreated tissues of primary and metastatic tumors from the same patient. There was no significant difference in sensitivity or resistance to any agent based on tissue type in the group evaluated.

Normal treated tissue cultures never displayed cellular changes in a wide variety of human benign tumors and normal tissues tested. They responded, in the main, as individual tissue of 30 randomly selected culture series of metastatic carcinoma lesions were compared with the responses of 311 specimens from patients with no prior therapy. All specimens were excised from patients with identical drug therapy, cancer research. Of interest was the absence of a relation between migration and growth in tissue culture and response to drug. This conclusion was further supported by the consistent responses to drugs of melanoma, sarcoma, and malignant, and benign neoplastic tissues tested. The effect of prior therapy seems to be more closely related to success or failure of growth than to the severity of cancer. The five agents under investigation produced direct objective cytological changes. All five produced direct objective changes that were qualitatively similar and resembled changes seen after x-radiation--namely, aberrant chromosome structures and giant cells. The compounds in decreasing order of effectiveness were: thioTEPA, actinomycin D, chlorambucil; and phenylalanine mustard. All agents tested produced direct objective cytological changes. All five agents caused mitotic inhibition and cytolysis. The antibiotic, actinomycin D, produced nuclear pyknosis to form narrow, elongated cleolar reduction. The antimetabolite, methotrexate, caused pyknosis to form narrow, elongated cleolar reduction. The antimetabolite, methotrexate, caused pyknosis to form narrow, elongated cleolar reduction. The antimetabolite, methotrexate, caused pyknosis to form narrow, elongated cleolar reduction. The antimetabolite, methotrexate, caused pyknosis to form narrow, elongated cleolar reduction.
FIG. 8.—Early melanotic lesions in a golden hamster treated with a single application of DMBA in mineral oil. Note the perifollicular arrangement of the proliferating melanocytes which contain a black pigment completely obscuring cellular and nuclear details. In some areas the pigmented cytoplasmic processes of some of the melanocytes can be made out. Hematoxylin & eosin, X150.

FIG. 9.—Perifollicular proliferation of amelanotic melanocyte near the tumor illustrated in Fig. 2. Note that in both the white and the golden hamster (Fig. 8) the early lesions do not have the histologic appearance of a tumor but consist of a more or less circumscribed proliferation of perifollicular melanocytes. Hematoxylin & eosin, X150.

FIG. 10.—Pulmonary metastasis of first transplant of poorly pigmented melanotic tumors of white hamster. The transplant as well as the metastases were almost entirely composed of nonpigmented spindle-shaped cells. An occasional small focus of pigmented cells is illustrated in the upper half of the picture. Hematoxylin & eosin, X100.

FIG. 11.—Higher magnification of part of the field illustrated in Fig. 10. Most of the tumor cells are nonpigmented. The pigmented cells have the morphologic appearance of dendritic melanocytes. Hematoxylin & eosin, X1,000.
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treatment and subsequent response for all normal, solid tissues were handled and cultured in an iden-
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A comparison was made between rate and ex-

DISCUSSION

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