The Malignant Melanoma of Hamsters

I. Pathologic Characteristics of a Transplanted Melanotic and Amelanotic Tumor*

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SUMMARY

The pathologic characteristics of the amelanotic and melanotic variants of the transplanted melanoma of hamsters (Fortner) are described. Outstanding differences between the two variants are the more rapid growth and invasiveness of the nonpigmented strain. Similarities between the Cloudman S91 tumor and the melanotic melanoma are pointed out.

In 1957 Fortner (1) reported on the occurrence of an assortment of spontaneous tumors in the golden Syrian hamster (Mesocricetus auratus), a laboratory animal introduced into the United States in 1938 by the Public Health Service laboratory at Carville, Louisiana. In a subsequent paper he described the characteristics of the primary malignant melanomas which he found in this animal (2). A total of ten such tumors were observed in a group of 523 hamsters. Fortner noted that: “Their gross and microscopic appearances, histogenesis and biologic behavior are counterparts of the human melanomas” (2). At least five of the ten malignant melanomas were successfully transplanted to other animals, and only rarely did the tumor fail to take on subsequent transplantation. It was also noted that many of the transplanted tumors which were originally pigmented soon developed amelanotic areas. The nonpigmented tumors contained dopa-positive cells, and on histologic examination appeared more anaplastic than did the pigmented neoplasms. An increased growth rate and capacity to metastasize also accompanied the loss of pigment production by the tumor cells.

In February, 1958, Dr. Fortner was kind enough to provide us with an opportunity to establish two transplantable melanomas in this laboratory. A melanotic (#1) and an amelanotic (#3) tumor have since been maintained here in an inbred colony of hamsters. The following study was designed to extend Fortner’s observations on the pathologic characteristics of the transplanted hamster melanoma. It is part of a larger investigation of the in vivo and in vitro growth and behavior of this tumor as a means of gaining insight into the biologic properties of the melanoma.

MATERIALS AND METHODS

The tumors studied were all originally transplanted into the subcutaneous or muscular tissues of the right femoral area by implantation of tumor fragments of melanoma measuring about 5 mm. in greatest diameter. This was found to produce a tumor which corresponded to one resulting from the injection of 0.5–1.0 ml. of a 50 per cent (w/v) tumor suspension. Anywhere from 100,000 to 400,000 cells obtained by trypsinization of tumor tissue, as for the preparation of an inoculum for tissue culture (7), also produced tumors of similar characteristics. Of the three methods used to transplant the tumor, the first of the above-mentioned was found most reliable. Under these circumstances we could confirm Fortner’s observa-
tion that only rarely did the tumor fail to take. With a 50 per cent tumor suspension, about an 85 per cent take of the amelanotic tumor was observed, and even lower per cent takes were found with the melanotic tumor. Less satisfactory results were obtained when trypsinized cell suspensions were used. In selecting fragments of tumor for implantation, an attempt was made to obtain the most viable-appearing and characteristic pieces of tissue available—i.e., the most pigmented and nonpigmented areas were used for the melanotic and amelanotic tumors, respectively. Under these conditions, there was little tendency for the melanotic tumor to become less pigmented. The latter phenomenon was seen when tumor suspensions made up of relatively unselected portions of the tumor were used.

The hamsters used came from several similar inbred strains of animals which were developed in this laboratory. These strains are now beyond their thirteenth generation. The age of the animals was generally greater than 4-5 months and their weight close to 100 gm.

The observations on the gross pathology of the tumor were accumulated from post-mortem examinations which were conducted on every animal that died (over 300 autopsies were performed in all). Only those untreated hamsters that died of causes which were clearly unrelated to another disease process were included in the tabulated data of the gross findings; i.e., the data given in the tables apply to animals that presumably died because of the tumor. In addition to the gross observations of the transplanted tumor and its metastases, histologic examination was made of sections of both the melanotic and amelanotic variants of the tumor. Sections were studied from the site of implantation and from the metastases in the lymph nodes, muscle, thymus, liver, adrenal, kidney, intestinal tract, heart, and lung. Some of the animals were sacrificed to obtain well preserved tumor. Studies were made of sections stained with hematoxylin and eosin and with Wilder’s reticulum stain, of sections mounted unstained, and of sections bleached with potassium permanganate. Stains for iron were also employed. A dopa-oxidase reaction was performed.1

**Gross Pathology**

**Survival following implantation of tumor.**—The hamster’s life span following implantation of the melanotic and amelanotic tumors differed (Table 1). Those that received the nonpigmented tumor lived for 38.7 ± 4.2 days (mean ± standard error), whereas those with thepigmented variant lived for 66.3 ± 9.3 days.

**Implanted tumor.**—The tumor which grew at the site of implantation was usually discrete, ellipsoidal to spherical in shape, and often attained an extremely large size, i.e., one-quarter to one-third the size of its host. At post-mortem examination, its surface was usually ulcerated and infected. Most of the hamsters demonstrated extreme cachexia as the tumor attained a large size (Fig. 1).

The central portion of both types of tumors was usually grossly necrotic. Necrosis was more prominent in the melanotic tumors; most of the central portion of this tumor was occupied by black, mostly liquefied material which contained a moderate amount of blood. Only a rim of viable tissue was present at the periphery. Smaller tumors were less necrotic. Blood vessels were readily seen coursing along the surface of the tumor. However, arteriographic studies revealed that both tumors were sparsely vascularized in the more central portions (Fig. 2).

The amelanotic tumor was usually not as well demarcated from the surrounding tissue as was the melanotic tumor. It had a firmer consistency than the melanotic tumors. Gross evidence of extensive direct extension was not generally seen at the site of the implanted tumor.

**Metastases.**—At death, 95 per cent of the hamsters with the amelanotic melanoma had metastases. Of the animals with the pigmented tumor, 89 per cent had metastases. The anatomic distribution of the metastases found in a small

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<table>
<thead>
<tr>
<th>Measurement</th>
<th>Melanotic</th>
<th>Amelanotic</th>
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<tr>
<td>Survival (days):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>32-118</td>
<td>22-88</td>
</tr>
<tr>
<td>Mean</td>
<td>66.3</td>
<td>38.7</td>
</tr>
<tr>
<td>Standard error</td>
<td>±7.4</td>
<td>±4.2</td>
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<tr>
<td>Hamsters dying with</td>
<td>59</td>
<td>95</td>
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<tr>
<td>metastases (%)</td>
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<tr>
<td>Sites of metastases (%)</td>
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<tr>
<td>Lymph nodes</td>
<td>11</td>
<td>95</td>
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<tr>
<td>Liver</td>
<td>6</td>
<td>52</td>
</tr>
<tr>
<td>Kidney</td>
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<td>Lung</td>
<td>72</td>
<td>0</td>
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<tr>
<td>Subcutaneous tissues</td>
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</tbody>
</table>
group of animals studied separately is indicated in Table 1. Not all the sites of metastases which occurred are indicated in this table because of the small sample size used for this particular phase of the investigation (21 hamsters with the amelanotic tumor and eighteen hamsters with the melanotic tumor). Nonetheless, a striking difference was noted in the metastatic pattern of the two tumors, and it is this point which we seek to demonstrate here. All the animals with amelanotic tumor metastases had lymph node involvement (Fig. 3). In contrast to this 95 per cent involvement is the 11 per cent lymph node involvement observed in the animals with melanotic metastases. A further contrast in the distribution of metastases is seen when the percentages of animals with metastases to the lungs are compared. No animals with amelanotic tumor had metastases to the lung (except for occasional instances of direct extension from lymph nodes), whereas 72 per cent of the hamsters with melanotic tumor did show definite metastases (Fig. 4). Cardiac metastases were occasionally seen in both types of melanoma, but metastasis to the brain, spleen, or osseous tissues was rare.

Metastases from the amelanotic tumor were of the same general appearance as the primary tumor. The distribution of the lymph node metastases in a group of 29 animals is shown in Table 2. Of the periaortic nodes, the group located at the level of the renal arteries was most commonly enlarged (Fig. 3). Next in frequency was the group of nodes present in the retro-sternal area. The thymus was included under this designation. This organ was frequently replaced with tumor. Mesenteric nodes containing tumor were usually accompanied by spread of tumor to the gastrointestinal tract. The hepatic metastases found were either diffusely distributed throughout the organ, to produce a finely speckled appearance to the cut surface of the liver, or present in the form of larger tumor nodules. When spread to the liver occurred, hepatomegaly was common.

Metastases from the melanotic tumor never attained the large size that the amelanotic metastases did, nor were they ever as large as the implanted tumor. They were usually confined to the thorax and appeared less pigmented than the implanted tumor. In addition to pulmonary metastases, deposits of melanotic tumor were found on the diaphragm and parietal and mediastinal pleura.

**Histopathology**

The histologic appearance of the transplanted tumors and their metastases was similar in most respects to that described in the primary and metastatic tumors by Fortner and Allen. The melanotic tumor and the amelanotic variant were recognizable as arising from the same origin and showed more similarities than differences.

In both types of growth, the tumor was generally formed of solid sheets and masses of cells which were more polygonal than fusiform. There was little tendency to form fascicles or whorls, and the characteristic alveolar clusters of human melanomas were almost completely lacking. There was little fibrous stroma, and the tumors were not remarkably vascular. A perivascular arrangement was seen only in otherwise extensively necrotic areas. There was often extensive degeneration and necrosis, making observations of pattern difficult.

**TABLE 2**

<table>
<thead>
<tr>
<th>Regional lymph nodes</th>
<th>Per cent of animals showing involvement</th>
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<tr>
<td>Periaortic</td>
<td>97</td>
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<tr>
<td>Pelvic</td>
<td>90</td>
</tr>
<tr>
<td>Axillary:</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>84</td>
</tr>
<tr>
<td>Contralateral</td>
<td>57</td>
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<tr>
<td>Mediastinal</td>
<td>76</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>64</td>
</tr>
<tr>
<td>Cervical:</td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>41</td>
</tr>
<tr>
<td>Contralateral</td>
<td>28</td>
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</table>

* 29 animals received 0.8 ml. of a 50 per cent tumor suspension subcutaneously in the right inguinal area and were autopsied when they died with tumor metastases.

The melanotic tumor was histologically the more uniform in cellular appearance (Fig. 5). It was formed of polygonal melanocytes with scattered, more irregular or elongated melanophages. The nuclei were somewhat oval but rarely spindle-shaped. Variation in nuclear size was only moderate, the largest cells generally measuring only up to twice the diameter of the smallest. Nucleoli were easily seen but were generally small and basophilic and occasionally multiple. The chromat in had a finely stippled appearance with distinct nuclear membranes.

The amount of pigment varied from one area to another but was present in all the tumors classified as melanotic on gross examination. In general, pigmentation was not as extensive in the secondary growths as has been reported in the spon-
taneous tumors. It was not usually necessary to depigmentize the sections to examine the cyto-
logical detail. In the melanocytes, the pigment could generally be seen as a fine, diffuse granula-
tion of the cytoplasm. In the melanophages, the pigment granules generally formed coarser aggre-
gates, filling the cell (Fig. 6). Pigment was particu-
larly evident around areas of necrosis and in the vicinity of fibrous trabeculae and vessels, where phagocytes were more numerous.

Other occasional sites of pigment deposition were the regional lymph nodes and the glomeruli (Fig. 7). Pigment was not seen within the renal tubules, nor were the changes characterized as "melanuric nephrosis" observed (6). The numbers of mitotic figures seen in the tumors were variable. In some areas of cellular uniformity there might be none to one per high-power field. Elsewhere, particularly at margins of tumor nodules, or where there was more irregularity, there might be four to six or even more mitoses per high-power field. Giant forms or multinucleate cells were not encountered in the melanotic tumors, even in those areas having high mitotic activity.

In contrast, the amelanotic variant produced tumors with greater cellular pleomorphism. Degenerative changes were more frequent, and the tumor architecture less well preserved. The arrangement was again in broad sheets of cells without specific pattern. The cells were nearly always polygonal in shape without any significant tendency to develop spindle forms. While the average cell size did not seem to differ remarkably from that of the melanotic tumor, nuclear and cell size were generally variable. There were scattered giganto forms with bizarre nuclei. The largest nuclei were several times the diameter of the smallest. Large, often eosinophilic, nucleoli, sometimes occupying half the diameter of the nucleus were common. Nucleoli were sometimes multiple. Multiple nuclei or irregular masses of chromatin were observed. The chromatin pattern, however, was generally finely stippled or reticular. These large cells did not appear to be the same as those which were observed in tissue culture by Rosenberg et al. (7) but did resemble those described by Symeonides (9) in amelanotic melanomas of humans (Fig. 8).

The mitotic activity was fairly equal from area to area, and mitoses might average 1 to 3 per high-
power field. They were found without difficulty in all areas. No areas of spindle-celled, sarcomatous appearance were found as described by Greene (3), and no pigmentation occurred. The dopa reaction was negative.

A reticulum framework was found which varied with cell size and density. It generally surrounded individual cells or small groups of two to ten cells in the amelanotic tumors. The reticulum seemed somewhat less uniform in the melanotic tumor. Larger groups of cells and irregular nests or fascicles were marked off by thin strands of fibers, often paralleling vessels. This contributed to a fasciculated appearance which was not consistently observed and which was not apparent in hematoxylin and eosin preparations (Fig. 9).

Of particular interest was the apparent difference in manner of growth of the melanotic and amelanotic tumors. The melanotic tumor generally formed a discrete nodule within an organ or tissue and appeared to grow by expansion, maintaining a distinct solid boundary with the adjacent normal tissue (Fig. 10). The amelanotic variant, on the other hand, frequently grew as infiltrating columns or strands of cells within the invaded tissue, preserving the architectural framework, at least in the early stages. This was particularly evident in liver (Fig. 11), kidney (Fig. 12), heart muscle, and lymph nodes. Whereas the infiltrating mode of growth might resemble that of a malignant lymphoblastoma, the infiltration of the sinuses of lymph nodes did not.

DISCUSSION

Aside from the more rapid growth and greater metastasizing capacity of the amelanotic mel-
oma, there is also a difference in the metastatic pattern of these tumors. The amelanotic tumor

Fig. 1.—Hamster with amelanotic melanoma. The tumor was injected into the right inguinal area 70 days prior to the time this photograph was obtained. Note the large ulcerating, partially infected growth which has replaced the entire lower extremity.

Fig. 2.—Arteriogram of a hamster that has had both the melanotic (left) and amelanotic (right) tumors implanted at the same time. Note the larger size of the amelanotic tumor and the sparse arterial network within the tumor, particularly at its center.

Fig. 3.—Same animal as in Figure 1. The tumor has been cross-sectioned. Note the necrotic and infected areas at the distal end of the extremity. Below this portion of the tumor is the shriveled remnant of the foot. Periarterial nodes can be seen situated between the kidneys (upper arrow). A large pelvic node is present over the fundus of the bicornuate uterus (lower arrow). These nodes are completely replaced with tumor tissue.

Fig. 4.—Metastatic nodules of melanotic melanoma in the lung. These subpleural deposits are most characteristic for this tumor.
was impossible to evaluate specific differences in cytotoxic responses as described for individual specimens apparently were not re-
tent of migration and growth. There was no detectable correlation between the prior growth rate of 30 culture series of primary melanoma and car-
ticles. They responded, in the main, as individual tissue specimens. Cells were either sensitive or resistant to each agent individually, except in a few cases which responded in a similar manner to thioTEPA and phenylalanine mustard. All five agents under investigation produced direct objective cytological changes. All three alkylating agents, thioTEPA, methotrexate, and phenylalanine mustard, produced direct objective cytological changes. All five agents under investigation produced direct objective cytological changes. All three alkylating agents, thioTEPA, actinomycin D, and chlorambucil, methotrexate, and phenylalanine mustard. The antimetabolite, metho-
resembled changes seen after x-radiation--namely, aberrant chromosome structures and giant cells.

**DISCUSSION**

The relation of prior therapy to cellular changes in a wide variety of human benign and malignant tumors and normal tissues was impossible to evaluate specific differences in cytotoxic responses as described for individual specimens apparently were not re-

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The compounds in decreasing order of effective-

Whereas tumor types in general responded indi-

Of interest was the absence of a relation between --ch ECM and drug response based on primary or metastatic lesion type. A more definitive analysis awaits a study of drug effects based on the 

Normal treated tissue cultures never displayed severe cytotoxic changes that were observed in some cultures of tumor tissues exposed to identical drug concentrations. These data may be useful in predicting treatment outcome.

**Tables**

- **Table 1:** Summary of drug effects on tumor types.
  - a) the sensitivity of lymphosarcomas, Hodg-
  - b) the sensitivity of lymphomas to thioTEPA;
  - c) the sensitivity of fibrosarcomas to direct ex-
  - d) the sensitivity of certain carcinoma types to
  - e) the sensitivity of melanomas to methotrexate and phenylalanine mustard;
  - f) the resistance of breast carcinomas to chlor-
  - g) the resistance of all melanomas tested to

**Figures**

- **Figure 1:** Photograph of a mouse with a scale indicating metric measurements.
- **Figure 2:** Radiographic image of a human organ.
- **Figure 3:** Macroscopic view of a surgical specimen.
- **Figure 4:** Close-up view of a specific tissue section.
Fig. 5.—Spherical melanocytes from the amelanotic cultures. Note similarity to pigmented melanocytes. May-Grünwald-Giesma, X1500.

Fig. 6.—Spindle-shaped fibrocytes with pigment aggregated around nucleus. Giesma, X1500.

Fig. 7.—Wandering macrophage containing much ingested pigment. Giesma, X800.

Fig. 8.—Living unstained giant cell with an ingested melanocyte. The melanocyte is beginning to disintegrate, X800.
was impossible to evaluate specific differences in cytotoxic responses as described given before or between biopsies, in relation to lesions of the same type. This group did not include any primary and metastatic tumors from the same patient. There was no significant difference in response of 154 specimens 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 administered at the tissue site.

It was thought that the drug response was related to growth rate, and that both primary and metastatic tumors from the same patient would respond similarly. The seven drugs tested were: thioTEPA, actinomycin D, chlorambucil, methotrexate, and phenylalanine mustard. All agents tested produced direct objective cytological changes. All five antimetabolite agents caused mitotic inhibition and cytolysis. The antibiotic, actinomycin D, produced nuclear changes resembling changes seen after x-radiation--namely, nuclear pyknosis or nuclear elimination, and nuclear chromatin clumping. The compounds in decreasing order of effectiveness were: thioTEPA, actinomycin D, chlorambucil, methotrexate, and phenylalanine mustard.

The five agents under investigation produced certain trends in the cellular changes in a wide variety of human benign and malignant tumors and normal tissues. They responded, in the main, as individual tissue types to each agent individually, except in a few cases where responses were apparent:

- a) the sensitivity of lymphosarcomas, Hodgkin's, and lymphomas of undetermined type to di-thio-ethidium bromide;
- b) the sensitivity of lymphomas to thioTEPA;
- c) the sensitivity of fibrosarcomas to direct exposure to actinomycin D, chlorambucil, and thioTEPA;
- d) the sensitivity of certain carcinoma types to treatment and subsequent response for all normal, malignant, and benign neoplastic tissues tested.

Whereas tumor types in general responded individually to the test agents, certain trends were observed in some cultures of tumor tissues exposed to identical drug concentrations. These data may be useful in selection of agents and drug concentrations for future therapy, and in planning of experimental protocols, such as the addition of agents at predetermined drug concentrations to tumor cultures prior to drug addition or methods of culturing tumors in vitro or in vivo. Studies based on a large group of malignant neoplastic tissues, lymphatic leukemia, fibrosarcoma, and carcinomas, showed that these tumors and normal tissues were handled and cultured in an identical manner, regardless of the tissue type. There was no detectable correlation between the rate and exposure to any test agent other than that expected due to chance. All responses were of primary versus metastatic tissues, the responses of 311 specimens from patients with no prior therapy were compared with the responses of 30 randomly selected culture series of metastatic melanoma lesions were compared with the responses of 30 culture series of primary melanoma and carcinoma lesions. No significant difference in response was observed.

The relation of prior growth rate and treatment and subsequent response for all normal, malignant, and benign neoplastic tissues tested was not significant. It was apparent that only certain tumors could respond under these experimental conditions. Support for this conclusion was provided by the consistent responses to drugs of the same patient. Of interest was the absence of a relation between migration and growth in tissue culture and cellular changes in vivo, as supported by the consistent responses to drugs of the same patient.

A comparison was made between rate and exposure to actinomycin D, chlorambucil, and thioTEPA; and methotrexate and phenylalanine mustard. All three alkylating agents, thioTEPA, actinomycin D, and thioTEPA, produced changes that were qualitatively similar and resembled changes seen after x-radiation. The antimetabolite, methotrexate, caused pyknosis to form narrow, elongated, and often fragmented nuclei. The six normal treated tissue cultures never displayed mitotic inhibition or cytolysis. These data may be useful in the study of drug effects based on the lesion type in the group evaluated. Therefore, differences in cytotoxic responses as described given before or between biopsies in relation to lesions of the same type were impossible to evaluate.
Fig. 9.—Giant cell with an ingested melanocyte. Note the clear area surrounding the melanocyte and the second binucleate cell beside it. May-Grunwald-Giemsa, X600.

Fig. 10.—Giant cell with many ingested heavily pigmented melanocytes. Smaller pigment granules are seen in the periphery of the giant cell cytoplasm. Note the nucleus at the lower right corner of the giant cell. Giemsa, X800.

Fig. 11.—Unstained fixed preparations of two giant cells. Many melanocytes have been ingested, and many small clumps of ingested cytoplasm and pigment are to be seen, X400.

Figs. 12, 13.—A giant cell which has partially engulfed a spherical melanocyte. Pseudopodial extensions have nearly surrounded the melanocyte. Note the large size of the nuclei of these giant cells. May-Grunwald-Giemsa, X1000.
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individual specimens apparently were not re-

prior growth rate

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treatment and subsequent response for all normal,
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t type in the group evaluated.
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therapy within 7 months prior to biopsy. The re-
sponse in sensitivity or resistance to any agent based on
experimental data failed to reveal over-all sensi-
tory or resistance as a result of prior therapy.

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in vitro. on October 3, 2017. © 1961 American Association for Cancercancerres.aacrjournals.org Downloaded from
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DISCUSSION

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prior therapy seems to be more

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in vitro. in vivo.

according to the observations of Cobb and

in vitro, in vivo. in vitro.
seems to have a greater affinity for the lymphatic tissues, which may result from a predominantly lymphogenous mode of spread. On the other hand, the less active pigmented tumor may metastasize by a hematogenous route, explaining its more frequent occurrence in the lungs. This difference in the melanotic and amelanotic tumor may be related to the more invasive character of the growth of the amelanotic tumor.

The question arises whether or not the amelanotic tumor should be considered a true melanoma. The cells of the nonpigmented melanoma are dopa-negative, and its behavior is that of an undifferentiated neoplasm. It would appear, however, from morphologic and tissue culture studies, that the amelanotic tumor is similar to its pigmented counterpart and that they are variants of the same tumor. The origin of this amelanotic tumor, as described by Fortner, also supports the concept that this is a true melanoma. Characteristic junctional changes were present at the site of the tumor. Nonetheless, we believe that the pigmented tumor should be used in experiments designed to investigate the biologic characteristics of the hamster melanoma.

A comparison of the pathologic characteristics of this tumor, with its counterpart in mice, reveals that the transplanted hamster melanotic melanoma is similar to the Cloudman S91 melanoma which has been intensively studied in recent years (4, 5, 8). Most striking is the affinity of the metastases for pulmonary tissue.

When compared with the pathologic characteristics of the human melanoma, it can be seen that the hamster tumor is more similar than the mouse melanoma. Nonetheless, significant differences exist. The unpredictable metastatic pattern of the melanoma of man is in sharp contrast to the uniform behavior of these transplanted hamster melanomas, thus compromising the use of this tumor as an experimental tool in the investigation of human melanomas.

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The Malignant Melanoma of Hamsters I. Pathologic Characteristics of a Transplanted Melanotic and Amelanotic Tumor

J. C. Rosenberg, C. Assimacoupoulos, P. Lober, et al.