Lung Cancer Model System Using 3-Methylcholanthrene in Inbred Strains of Mice


ABSTRACT

A model system has been established for studying lung carcinogenesis using intratracheal instillation of 3-methylcholanthrene in C3H/AnfCum and C57BL/Cum × C3H/AnfCum F1 (hereafter called BC3F1/Cum) mice. The animals in these studies were screened for adventitious agents and were free throughout their lifetime of two important lung viruses, Sendai virus and pneumonia virus of mice. Under these conditions, the occurrence of spontaneous and chemically induced lung cancers was determined over the lifetime of the animals. Data were analyzed by the actuarial method for lung tumor probability. Probability was found to be dose and time dependent. Over 95% of the 3-methylcholanthrene-treated BC3F1/Cum and over 88% of the C3H/AnfCum mice were found at death to have pulmonary carcinomas. Tumors observed in animals which died up to 40 weeks on test were almost always squamous cell carcinomas (~85%), while tumors which were observed in animals which died after 50 weeks were mainly alveolar adenocarcinomas (~80%). Both tumor types metastasized widely. Spontaneous lung cancers (only alveolar adenocarcinomas were observed) occurred in these two strains at low frequency and were expressed late in life. Thus, the system described affords a suitable model to study the induction, expression, and progression of lung tumors under conditions where a vast majority of animals develop neoplasia.

INTRODUCTION

Lung cancers have been induced in such diverse species as mice (6, 9, 12, 20), rats (1, 17, 18), hamsters (2, 4, 15, 16), rabbits (5), and dogs (13) following i.t. administration of poly-cyclic aromatic hydrocarbons. The types of tumors induced have included SCC, AAC, ASC, and PDC. The location of such tumors extended from the larynx to the trachea, the main bronchi, the terminal bronchioles, and the alveoli.

Of these species, the mouse presents several unique characteristics which make it a useful model to study the mechanism(s) for the induction of lung cancer. The advantages of using the mouse for such studies are: (a) availability of a large number of genetically diverse inbred strains; (b) economy of operation; (c) availability of colonies which are well defined in terms of their biological adventitious agents; and (d) availability of strains of mice in which susceptibility to lung cancer is genetically regulated (9, 10). To further enhance the utility of the mouse system for carcinogenesis studies, more information is required on the type, location, biological behavior, and the degree of spontaneous occurrence of lung carcinomas. Towards this end, experiments were initiated in 2 strains of mice to determine the occurrence of spontaneous and MCA-induced lung tumors.

MATERIALS AND METHODS

Animals. Female C57BL/Cum × C3H/AnfCum F1 (hereafter called BC3F1/Cum) and female C3H/AnfCum mice were purchased from Cumberland View Farms (Clinton, Tenn.) at 4 to 6 weeks of age. Mice were tested serologically for adventitious agents, inoculated i.p. with 0.1 ml Sendai vaccine (MA Bioproducts, Walkersville, Md.), and held in quarantine for a minimum of 3 weeks prior to chemical treatment. Five to 10% of the mice were tested for revirus type 3, pneumonia virus of mice, K virus, encephalomyelitis virus, polyoma virus, Sendai virus, minute virus of mice, mouse adenovirus, mouse hepatitis virus, lymphocytic choriomeningitis virus, and actromelia virus. The mice were negative in complement fixation and in hemagglutination inhibition tests for all viruses prior to Sendai vaccination, but they expressed detectable titers (by complement fixation test) to Sendai virus 3 weeks postvaccination. Positive antibody titers ranged from 1/20 to 1/160 serum dilutions. Mice were revaccinated after 6 months. The animals were housed 5/cage (stainless steel cages equipped with plastic fronts and filtered bonnets) on Bed-O-Cob corncob bedding (Chesapeake Feed Company, Beltsville, Md.). They were allowed free access to Purina laboratory chow and water from an automatic watering system. Racks containing the animal cages were kept in a room at 21–23.5° with a light cycle of 12 hr darkness and 12 hr light from fluorescent lights.

Preparation of Chemicals. MCA (Eastman Organic Chemicals, Rochester, N.Y.) was recrystallized from benzene and ground lightly for approximately 20 min using a mortar and pestle. It was suspended in a sterile GS solution at a concentration of 250 μg MCA per 0.02 ml GS. The suspension was stored at 4–6° in aliquots sufficient for use in one day. The MCA concentration was determined fluorometrically before use.

Chemical Treatment. Mice were 8 to 12 weeks old when first treated. The mice were lightly anesthetized with Metofane (Pitman-Moore, Inc., Washington Crossing, N. J.) and given 250 μg MCA in 0.02 ml GS or 0.02 ml GS alone via i.t. instillation according to procedures published previously (9, 10). A Hamilton Model PB-600 dispenser (Hamilton Co., Reno, Nev.) equipped with a 1.0-ml disposable syringe (Becton, Dickinson, and Company, Rutherford, N. J.) and
a 19-g, 1.5-inch Monoject blunt needle (Sherwood Medical Industries, Inc., St. Louis, Mo.) were used to assure precise delivery of the chemicals. Mice were treated every 14 days until the desired total dose was given. BC3F1/Cum mice were given 9 doses of 250 µg MCA per dose over 16 weeks (total dose, 2250 µg). C3H/AnfCum mice were divided into 3 groups. Group 1 received 3 doses of 250 µg MCA per dose over 4 weeks (total dose, 750 µg). Group 2 received 6 doses of 250 µg MCA per dose over 10 weeks (total dose, 1550 µg), and Group 3 received 9 doses of 250 µg MCA per dose over 16 weeks (total dose, 2250 µg). The vehicle controls in both strains received 9 doses of 0.02 ml GS over 16 weeks.

**Necropsy.** Mice were observed twice daily for evidence of illness or respiratory distress. Dates and circumstances of death were recorded for all mice. Nonautolysed tissues from mice found dead and those killed when moribund were examined microscopically. Lungs were fixed with approximately 1.5 ml of 10% buffered formalin by infusion via the trachea. The lungs were ligated at the trachea, and the thoracic viscera was removed as a single unit. Lung, trachea, esophagus, and thoracic lymph nodes were sectioned (6 µm) as a unit at 3 levels, using a frontal plane of section. Salivary gland, lymph nodes (cervical, bronchial), spleen, liver, kidneys, adrenal glands, large and small intestines, stomach, uterus, ovary, urinary bladder, heart, thymus, and head were also sectioned in 236 mice. All tissues were stained with hematoxylin and eosin and examined microscopically.

**Morphological Criteria.** A brief description of the lung tumors observed in these studies is presented below. A detailed description will be presented elsewhere.

SCC were nodular masses usually located in the peripheral portions of the lung. The masses were generally white to slightly yellow, often with depressed red centers. These masses were normally well vascularized, firm, and smooth with irregular margins. SCC were composed of squamous epithelial cells which produced varying amounts of keratin. Tumor invasion was a prominent feature. The tumors appeared to arise from the alveoli or terminal bronchioles. Metastases usually occurred in the heart, kidneys, and bronchial lymph nodes.

AAC occurred as discrete greyish-white, firm masses, located in the peripheral portions of the lung, and were often multiple. Some tumors occasionally showed pleural invasion and metastasis to tracheobronchial lymph nodes. Adenomas are not included in this category.

ASC contained elements of both tumors described above. Whether these tumors reflect a 'collision' of 2 different tumor types or represent a differentiation from one cell type to another was difficult to determine. Usually one component (squamous or glandular) was found in metastases.

A small number of other tumor types were observed in these studies. These will be described in detail elsewhere. These tumors were PDC and unclassified adenocarcinomas.

The most probable causes of death from these various tumors are: (a) lung infarctions; (b) renal infarctions; (c) congestive heart failure caused by obstruction of the left atrium; and (d) anoxia as the result of pulmonary insufficiency.

**Data Analyses.** Survival data are given as mean life span or mean survival time, defined as the sum of the number of weeks each animal lived, divided by the total number of animals. Tumor data are presented as the probability of an animal dying with lung cancer after a specific period of time following chemical treatment (11, 16).

The progression with time or the cumulative probability of an animal dying from a lung tumor was calculated by an actuarial method (7). Probabilities were calculated beginning the first week after completion of chemical treatment (11, 16).

Data are presented as the number of tumors for 2 experimental groups over any given time interval.

\[
P_n = 1 - \left( \frac{N_1 - T_1}{N_1} \times \frac{N_2 - T_2}{N_2} \times \cdots \times \frac{N_n - T_n}{N_n} \right)
\]

Statistical analyses were determined according to the method of Mantel and Haenszel (11). The procedure is briefly stated as follows. For 2 groups to be compared, the number of animals dead with tumors and the number of animals which are not dead of lung tumors are determined for each time interval and used to construct 2 x 2 contingency tables. The number of tumors expected and the variance of this number can then be determined for each week. The sum of the expected values is treated as an approximately normal random variable with known mean and variance. The \(\chi^2\) statistic, corrected for continuity, is then used to determine the level of significance of the difference between the expected number of tumors and the observed number of tumors for 2 experimental groups over any given time interval.

**RESULTS**

**Disposition of Animals.** The disposition of the animals in these studies is given in Table 1. Seven groups of mice were placed on test and were observed over their lifetime. Histological diagnoses were established for over 82% of all the animals on test. In the long-lived groups (shelf and vehicle controls), this number was lower (~62%) because these animals died of a variety of spontaneous causes over a longer period of time. Moribundity was difficult to predict from clinical signs in these groups. This is in marked contrast to those groups in which the animals died from chemically induced lung tumors, where moribund animals were often found to be hunched, lethargic, and clearly suffering from severe respiratory distress. Histological diagnoses were made in over 88% of the animals in the chemically treated groups.

**Survival.** The mean life span of untreated, shelf control female BC3F1/Cum mice was approximately 114 weeks, with a maximum life span of approximately 144 weeks. Survival of both BC3F1/Cum and C3H/AnfCum mice following the vehicle treatment period (16 weeks) was high and similar to the untreated, shelf control mice. Mean survival time posttreatment for BC3F1/Cum mice was approximately 102 weeks and for C3H/AnfCum mice was approximately 89 weeks. These correspond to approximately 114 and 101 weeks of age, respectively.

Survival times for MCA-treated mice were dependent on dose and were much shorter than vehicle or shelf control mice. Mean survival times posttreatment for BC3F1/Cum mice treated 9 times with MCA were approximately 36 weeks on test. Mean survival times posttreatment for C3H/AnfCum mice treated 3 times (750 µg), 6 times (1500 µg), or 9 times (2250 µg) with MCA were approximately 54, 46, and 40 weeks on test, respectively.

**Histopathology of Control Mice.** Observations from control BC3F1/Cum and C3H/AnfCum mice are presented in Tables 2 and 3, respectively. No differences were observed between

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presented for the major findings which could have been the cause of death. A total of 140 BC3F1/Cum mice was evaluated.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Treatment group</th>
<th>Treatment period (wk)</th>
<th>On test</th>
<th>Died during treatment</th>
<th>At risk after treatment</th>
<th>With tissues examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC3F1/Cum</td>
<td>Shell control</td>
<td>16</td>
<td>123</td>
<td>0</td>
<td>123</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>GS vehicle, 9 doses</td>
<td>16</td>
<td>111</td>
<td>16</td>
<td>95</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>MCA, 9 doses (total, 2250 µg)</td>
<td>16</td>
<td>431</td>
<td>26</td>
<td>405</td>
<td>374</td>
</tr>
<tr>
<td>C3H/AnfCum</td>
<td>GS vehicle, 9 doses</td>
<td>16</td>
<td>44</td>
<td>2</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>MCA, 3 doses (total, 750 µg)</td>
<td>4</td>
<td>98</td>
<td>3</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>MCA, 6 doses (total, 1500 µg)</td>
<td>10</td>
<td>100</td>
<td>23</td>
<td>77</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>MCA, 9 doses (total, 2250 µg)</td>
<td>16</td>
<td>148</td>
<td>31</td>
<td>117</td>
<td>104</td>
</tr>
</tbody>
</table>

* Deaths were categorized as either direct (death occurred within 24 hr of i.t. instillation) or indirect (mice were found dead in cage during treatment period).
* Number of mice alive at the end of the treatment period and from which survival curves were determined.
* Number of mice used for probability analysis.

Table 2
Histological observations found in control BC3F1/Cum mice
Mice were necropsied when found dead or killed when moribund. Data are presented for the major findings which could have been the cause of death. A total of 140 BC3F1/Cum mice was evaluated.

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Diagnosis</th>
<th>Wk on test</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 (29)*</td>
<td>Lymphosarcomas, reticulum cell sarcomas, and leukemias</td>
<td>47-131</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>10 (7)</td>
<td>Fibrosarcomas</td>
<td>91-128</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>10 (7)</td>
<td>Lung carcinomas</td>
<td>75-128</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>10 (7)</td>
<td>Neoplasms of the mammary gland, sebaceous gland, Harderian gland, ovari, and undetermined origin</td>
<td>73-133</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>4 (3)</td>
<td>Hepatocellular carcinomas</td>
<td>99-125</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>9 (6)</td>
<td>Adenomas of the lung*</td>
<td>71-127</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>19 (14)</td>
<td>Nephritis</td>
<td>93-138</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>9 (6)</td>
<td>Pneumonia, congestion, and lung inflammation</td>
<td>68-134</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>7 (5)</td>
<td>Spleen and liver necrosis</td>
<td>89-114</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>21 (15)</td>
<td>Died without observing a major disease, but such incidental findings were observed as myocarditis, atrial thrombosis, otitis media, otitis externa, uterine hydrodema, uterine hyperplasia, extramedullary hematopoiesis, uterine and ovarian cysts, chronic cystititis, and hematocysts</td>
<td>28-131</td>
<td>91</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage of incidence.

* Adenomas were benign alveologenic tumors, which lacked morphological evidence of cancer.

shelf control and vehicle control BC3F1/Cum mice, and the data from these groups were pooled (Table 2). No pulmonary tumors were observed in any control mice before 75 weeks. A total of 10 pulmonary AAC was observed in 140 BC3F1/Cum mice over the 138-week observation period (Table 2). The average expression time for these tumors was 105 weeks. One pulmonary AAC was observed at 91 weeks in 33 C3H/AnfCum mice (Table 3). No evidence of pulmonary SCC was found in any of these control animals.

Histopathology of MCA-treated Mice. BC3F1/Cum and C3H/AnfCum mice which died following MCA treatment had a variety of pulmonary carcinomas. Over 95% of lung tumors observed were SCC, AAC, PDC, and ASC. Table 4 presents a comparison of the distribution of pulmonary carcinomas as a function of time post MCA treatment of BC3F1/Cum mice. Three animals which died before the end of the treatment period were found to have SCC. The first SCC was observed at 12 weeks after initiation of MCA treatment after only 5 intratracheal MCA installations. Of the 224 animals which died during 17 to 40 weeks on test, 190 (85%) were observed to have SCC alone or in combination with other malignant tumors. During this same time interval, only 49 (22%) of the animals were observed to have any evidence of AAC. However, of the 74 animals which died after 50 weeks on test, 67 (91%) expressed AAC alone or in combination with other tumors, and 27 (36%) expressed evidence of SCC.

Analysis of the biological behavior of the MCA-induced SCC and AAC in 234 BC3F1/Cum mice showed that, of the 172 SCC observed, 90 (52%) were extensively invasive and/or metastasized to virtually all major organs, especially the heart, kidney, and bronchial lymph nodes. The most predominant route of metastasis was by direct invasion of the pulmonary vein with extension to the left atrium of the heart.

A total of 62 animals developed AAC alone or with cancer other than SCC, while 70 had both SCC and AAC. Of the 62 animals with AAC, 29 (47%) showed extensive evidence of invasion and/or metastasis to various organs. AAC most often invaded the pleura, mediastinum, and thoracic wall.

The distribution of lung cancers in C3H/AnfCum mice as a function of dose of MCA is shown in Chart 1. The animals which died of tumors early after MCA treatment (less than 40 weeks) were usually found with SCC (overall mean of 85% for all of these groups; Chart 1). Animals which died of late tumors after MCA treatment (greater than 50 weeks) were usually...
found with AAC (overall mean of 93% for all 3 groups; Chart 1). Different doses of MCA failed to alter this response. For all 3 MCA-treated groups, the mean expression time for SCC was 33 ± 4 weeks, and for AAC, it was 57 ± 6 weeks. A result of this difference in expression time of SCC and AAC was that the number of animals which died which moribund was given for each time interval. Conversely, as the dose of MCA increased, the number of animals dying with evidence of SCC over the entire treatment period is related to the dose of MCA. Analysis of these data showed that 9 doses of MCA resulted in a significantly higher lung tumor probability than did either 6 or 3 doses of MCA (p < 0.001). Animals treated with 6 doses had only a slightly higher lung tumor probability than did animals treated with 3 doses (p = 0.078). By only 28 weeks after treatment, the probability of lung cancer was significantly higher (p < 0.05) in the animals treated 9 times compared with those treated 3 times. By 38 weeks after treatment, animals treated with MCA 9 times were significantly higher in tumor probability than those animals treated 6 times.

Use of this method of analysis in C3H/AnfCum mice treated with either 3 (750 μg), 6 (1500 μg), or 9 (2250 μg) doses of MCA is presented in Chart 3. The probability of an animal dying of a lung tumor at any given time interval is related to the dose of MCA. Analysis of these data showed that 9 doses of MCA resulted in a significantly higher lung tumor probability than did either 6 or 3 doses of MCA (p < 0.001). Animals treated with 6 doses had only a slightly higher lung tumor probability than did animals treated with 3 doses (p = 0.078). By only 28 weeks after treatment, the probability of lung cancer was significantly higher (p < 0.05) in the animals treated 9 times compared with those treated 3 times. By 38 weeks after treatment, animals treated with MCA 9 times were significantly higher in tumor probability than those animals treated 6 times.

**DISCUSSION**

A lung cancer model system using inbred strains of mice requires knowledge about the: (a) natural life expectancy of the mouse strains; (b) natural or spontaneous level of expression of lung cancer; (c) types of pulmonary tumors which occur; (d) sensitivity to chemical carcinogen-induced lung cancer (especially carcinomas); and (e) biological behavior of the spontaneous and induced lung tumors. In this study, information concerning spontaneous and MCA-induced lung cancer in C3H/AnfCum and BC3F1/Cum strains of mice is presented. These studies were performed in mice free throughout their lifetime of infectious disease and of 11 adventitious agents. In particular, these animals were free from 2 agents which cause lung lesions, Sendai virus and pneumonia virus of mice. The effect of Sendai virus infections on pulmonary carcinogenesis studies has largely been ignored (14), despite the wide variety

**Table 4**

**Distribution of lung cancers in BC3F1/Cum mice as a function of time after 9 MCA treatments**

Mice were treated with 9 i.t. doses of 250 μg MCA in 0.02 ml GS at biweekly intervals for a total dose of 2250 μg MCA.

<table>
<thead>
<tr>
<th>Wk on test</th>
<th>Totala</th>
<th>No tumors</th>
<th>SCC</th>
<th>AAC</th>
<th>Both SCC + AAC</th>
<th>SCC + othera</th>
<th>AAC + othera</th>
<th>Other tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>17-19</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30-39</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50-59</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60-69</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>70-79</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>80-89</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>90-99</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a The diagnoses for 374 animals were individually arranged in 7 categories.
*b The number of animals which died or were killed when moribund is given for each time interval.
*c Includes one animal with SCC and lymphosarcoma (21 weeks), 3 with SCC and PDC (28, 43, and 48 weeks), and one with SCC and PDC (33 weeks).
*d Includes one with AAC and carcinoma of bronchogenic origin (37 weeks), one with AAC and unclassified adenocarcinoma (45 weeks), 4 with AAC and PDC (30, 46, 58, and 60 weeks), and 3 animals with AAC and ASC (51, 52, and 56 weeks).
*e Includes 5 animals with ASC (2 at 27 weeks, 2 at 45 weeks, one at 68 weeks), one with sarcoma (37 weeks), one with unclassified adenocarcinoma and PDC (45 weeks), and one with PDC (62 weeks).
*f Animals (26 mice) which died during the treatment period are not included in these analyses. Three animals which died during this period had SCC (12, 15, and 16 weeks).
*Includes one animal with SCC, AAC, and PDC (34 weeks) and one with SCC, AAC, and fibrosarcoma (36 weeks).
*g Includes one animal with SCC, AAC, and unclassified adenocarcinoma (43 weeks) and one with SCC, AAC, and PDC (48 weeks).
*h Includes one animal with SCC, AAC, and unclassified adenocarcinoma (53 weeks) and one with SCC, AAC, and sarcoma (57 weeks).
animals which died less than 40 weeks after carcinogen treatment were almost always SCC (Table 4 and Chart 1, 76 to 93%), while tumors in animals which died after 50 weeks were generally AAC (Table 4 and Chart 1, 92 to 100%). These results are very similar to the recent results of Yoshimoto et al. (20), who reported that 77 to 87% of the tumors observed early after i.t. treatment with benzo(a)pyrene were SCC, whereas 76 to 91% of the tumors were adenomas or AAC in the late period of observation (>50 weeks). The results suggest that the different neoplasms may arise from different cell types or that the expression of different neoplasms may be regulated by the carcinogen treatment.

The studies in which different dose levels of MCA were used, (see Chart 1) suggested that a larger dose of MCA was required for the induction of SCC rather than AAC. When the dose of MCA was lower, SCC were observed at a lower frequency, while AAC were observed at a higher frequency. SCC seemed to be initiated earlier and caused the death of the animal before AAC could be fully expressed. The mechanism by which higher dose levels of MCA (or longer exposure times) specifically induced the formation of SCC cannot be determined at this time; however, analysis of data from a parallel study suggests that multiple preneoplastic and neoplastic lesions are found in

Both of these strains of mice expressed a low spontaneous incidence of lung neoplasia, and these tumors appeared late in the life of the animal. The incidence of lung cancer in control mice is zero during the time at which chemically induced lung cancers appeared. Competing risks were apparent in the old-age animals. For example, the higher incidence of mammary cancers in the C3H/AnfCum strain, compared to the BC3F1/Cum strain, may have resulted in the C3H/AnfCum mice dying from mammary cancer before cancers of the hematopoietic tissues could be expressed. The latency of mammary cancer in the C3H/AnfCum strain was 15 weeks earlier than the latency for hematopoietic cancers in the BC3F1/Cum strain.

The lung tumors observed in these studies appeared to be similar in morphology to those reported by Nettesheim and Hammons (12), Ho et al. (6), and Yoshimoto et al. (20), who have studied MCA and benzo(a)pyrene-induced lung cancers in the inbred strains of mice. The most prevalent tumors observed in either strain were SCC and AAC, with smaller numbers of PDC and ASC (see Table 4 and Chart 1). The types of tumors observed were dependent upon the time at which the animal died after carcinogen treatment. Tumors observed in
animals sacrificed before 30 to 40 weeks on test.\(^6\)

The method of data analysis described here can be used to estimate the discriminating capacity of this lung cancer model system. For example, assuming a population of 50 animals on test, the cumulative probability of an animal dying with a spontaneous lung carcinoma in BC3F1/Cum mice is <0.02. A total of approximately 5 tumors or greater in the test group of 50 animals would be sufficient to yield a tumor probability which is significantly higher than control values \((p < 0.05)\).

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