The Epidemiology and Virology of C-type Virus-associated Hematological Cancers and Related Diseases in Wild Mice

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Summary

In several different populations of wild mice, observed over a 35-month period in laboratory geriatric colonies, a direct correlation was found between the prevalence and titer of spleen complement-fixing gs (p30) antigen and C-type particles in newly trapped healthy mice and a predilection to lymphoma and a hind leg paralytic disease upon aging. Other studies have established the indigenous C-type virus as the essential etiological determinant of both diseases in wild mice. An increased incidence of breast carcinomas, hepatomas, and pulmonary adenomas associated with C-type virus also occurred in the lymphoma-paralysis-prone colony as compared with the tumor-resistant colony.

Introduction

As a potentially useful model for understanding the etiology of cancer in humans, we have been carrying out natural history studies on spontaneous cancer and on C-type virus expression in wild house mice (Mus musculus) in southern California. Because of their feral outbred nature and lack of exposure to laboratory-adapted viruses, wild mice might be considered less of an artifact and a more relevant model for human cancer than laboratory mice. We have trapped mice in several different locations and observed them in the laboratory over their remaining life-span for spontaneous tumors, other diseases, and C-type virus expression. We initially reported a low prevalence (<20%) and titer (≤1:4) of C-type virus gs (p30) antigen detectable by CF⁴ and of C-type particles detectable by EM in the spleens of wild mice from certain of these locations (10). Several hundred mice from these same areas that were observed, without treatment, into old age showed a low frequency (9.5%) of spontaneous tumors, mostly lymphomas (7). However, mice from particular trapping areas, LC and LP, were found to exhibit an unusually high prevalence (>80%) and titer (1:4 to 1:16) of spleen CF gs antigen, C-type particles, and infectious virus at the time of trapping (4, 6). Upon aging in the laboratory, LC and LP mice showed an increased incidence of lymphoma (4) and a lower limb paresis resembling amyotrophic lateral sclerosis (6). Virus transmission and neutralization studies established the indigenous C-type viruses of LC and LP mice as the essential etiological factor in the lymphomatous and paralytic diseases (6, 14, 21).

We have now followed, in the laboratory, more than 5400 wild mice from 6 trapping areas, including LC, over a period of 35 months. We describe here the cumulative total mortality and cumulative specific tumor and paralysis mortality rates in relation to the low or high activity of the indigenous C-type virus characterizing mice from these different areas.

Materials and Methods

The locations of the wild mouse trapping sites are shown in Chart 1; their description, indigenous virus characteristics, and spontaneous tumor predilection are summarized in Table 1. Trapping Site 1 is a squab farm in a semirural area of northwest Los Angeles County (Bouquet Canyon). Mice from this site are heavily infected with indigenous polyoma and LCM viruses and show a low incidence of spontaneous lymphoma and low degree of C-type virus activity (5). Trapping Site 2 is a pool of 3 semirural trapping areas [(a) an egg ranch (Munneke); (b) a birdseed plant (Hartz Mountain); and (c) a squab farm (Soledad Canyon)], in which the mice are free of polyoma and LCM viruses and show a similar low degree of C-type virus activity and similar low tumor rates (7, 10). Trapping Site 3 is a squab farm in an isolated rural area in southwest Ventura County (LC) and Trapping Site 4 is a duck farm in the semirural west San Gabriel Valley (LP). Mice from these latter 2 locations are free of polyoma and LCM viruses but show an increased degree of C-type virus activity and a proneness to lymphoma and paralysis (5, 6, 21). Latent subclinical cytomegalovirus infection has also been found in equally high prevalence in wild mice from the 3 trapping areas sampled (Areas 1, 3, and 4) (9).

Most of the mice were relatively small (5 to 15 g) when trapped and were assumed to be of young adult age (6 to 12 months). A few healthy mice from each trapping area were killed soon after trapping and their spleens assayed for CF

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2 Presenter.

3 The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

4 The abbreviations used are: CF, complement fixation; EM, electron microscopy; LC, Lake Casitas; LP, La Puente; LCM, lymphocytic choriomeningitis.

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gs antigen. The remaining mice from each trapping area were individually housed in Mason jars in 3 corresponding colonies for lifelong observation. Each colony was isolated from the others on separate floors (Colonies 2, 3, 4) or in a separate building (Colony 2), but all were maintained under similar dietary and environmental conditions. All ill, dead, or tumor-bearing mice were necropsied with microscopic study. The maintenance of the laboratory geriatric colonies, serological screening for indigenous murine viral antigens; necropsy procedure; and processing of tissues for histopathology, EM, and CF gs antigen testing have been reported (4, 6, 7, 10). Briefly, 10% disrupted aqueous extracts of tumor and spleen from the necropsied mice were tested by CF for mouse gs antigen at 1:2 and 1:4 antigen dilutions. A 1:20 dilution of sera pools from Fischer rats bearing Moloney sarcoma virus-induced tumor transplants was used as antisera (13). Based on a close similarity of CF reaction compared to those given by guinea pig sera prepared against electrofocus-purified murine gs antigen (11), the several sera pools (Moloney sarcoma virus 30, 322, 3490) were highly sensitive for the murine C-type virus gs antigen. The routine screening procedure on those specimens reported as "negative" for virus particles consisted of a thorough scan at x15,000 of 3 grids from each of 2 different blocks of tissue. The data on each mouse were coded, keypunched, and stored for computer analysis.

The results on occurrence of deaths from various causes were analyzed by an extended actuarial approach. The cumulative incidence curves for each cause of death of interest were first calculated and plotted using the actuarial life table approach, with each animal dying of another cause simply being regarded as lost to follow-up at the time of its death. Then, to calculate statistical significance levels and to provide an easy grasp of the data, the observed numbers of deaths in each colony from the particular cause of interest were compared to their expected numbers, calculated on the assumption of no difference between the colonies for this cause of death (23). An insufficient number of mice

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**Table 1**

Identification and description of trapping sites, indigenous virus profile, and occurrence of spontaneous tumors in wild mice aging in the laboratory

The prevalence of PY and LCM virus infection in these colonies was based upon the detection by CF or hemagglutination tests of specific antibodies in the sera of recently trapped mice (6). The presence of latent CMV infection was determined by virus isolation from the saliva of 60% of normal wild mice and by the induction of virulent disseminated CMV infection in over 50% of wild mice given antithymocytic sera (10). The level of indigenous C-type virus activity was determined by the prevalence and titer of GS antigen and C-type particles in the spleens of recently trapped wild mice. The spontaneous tumor occurrence is based upon the actual number of tumors observed over a 35-month observation period (Table 2). Only mice from Colonies 3 and 4 developed spontaneous hind leg paralytic disease (7, 27).

<table>
<thead>
<tr>
<th>Colony</th>
<th>Trapping site, location</th>
<th>Habitat</th>
<th>Indigenous viruses</th>
<th>Indigenous C-type virus activity</th>
<th>Spontaneous tumor occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bouquet Canyon, semirural northwest Los Angeles County</td>
<td>Squab farm</td>
<td>+</td>
<td>+</td>
<td>Low</td>
</tr>
<tr>
<td>2a</td>
<td>Munneke, semirural southwest Los Angeles County</td>
<td>Egg ranch</td>
<td>–</td>
<td>–</td>
<td>NT</td>
</tr>
<tr>
<td>2b</td>
<td>Hartz Mountain, urban south central Los Angeles City</td>
<td>Birdseed plant</td>
<td>–</td>
<td>–</td>
<td>NT</td>
</tr>
<tr>
<td>2c</td>
<td>Soledad Canyon, semirural northwest Los Angeles County</td>
<td>Squab farm</td>
<td>–</td>
<td>+</td>
<td>NT</td>
</tr>
<tr>
<td>3</td>
<td>Lake Casitas, rural southwest Ventura County</td>
<td>Squab farm</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>La Puente, semirural southeast Los Angeles County</td>
<td>Duck farm</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

<sup>a</sup> PY, polyoma; LCM, lymphocytic choriomeningitis; CMV, cytomegalovirus; NT, not tested.

<sup>b</sup> PY virus antibodies detected in 40% newly trapped mice (6).

<sup>c</sup> LCM virus antibodies detected in 20% newly trapped mice (6).

<sup>d</sup> PY virus T- and V-antigens were not found in these tumors, nor was there any seroepidemiological evidence incriminating PY virus in their pathogenesis (6).
Epidemiology of Spontaneous Tumors and Paralysis. The cumulative total mortality and cumulative specific tumor and paralysis mortality as calculated, assuming the absence of nonrelevant deaths, by life table methods (23) for mice from Colonies 1, 2, and 3 are shown in Chart 2. The actual numbers observed, numbers expected if there were no differences between colonies, and probabilities derived are shown in Table 2. The study was terminated after 35 months of observation when the last mouse from Area 3 died. At this time, 7 mice from Colony 1 and 41 mice from Colony 2 were still living. The total mortality was increased in Colony 3 mice (Chart 2a); this increase was mainly due to an excess of tumors and paralysis. If deaths from these causes were excluded, the mortality rates in Colony 3 became quite similar to those in Colony 1 but were still slightly increased compared with those in Colony 2 (Chart 2b). In mice from each colony, lymphomas were the most common tumor; breast carcinomas, hepatomas, sarcomas, and lung adenomas occurred less frequently. The excess of total tumors in Colony 3 mice (Chart 2c) was primarily due to an excess of lymphomas (Chart 2d) and, to a lesser extent, of carcinomas, mostly breast, (Chart 2e), hepatomas (Chart 2f), and lung adenomas (Chart 2g). The sarcoma incidence rates (Chart 2h), by contrast, were more nearly equal and remained low in mice from all colonies. A combination of 2 tumors, usually lymphoma and lung adenoma, in the same mouse occurred in 14 mice from Colony 3 and in only 1 mouse from each of the other 2 colonies (Table 2). The spontaneous hind leg paralytic disease was observed only in mice from Colony 3 (Chart 2i), and in a few surviving mice from Colony 4.

The cumulative lymphoma rate in Colony 3 mice, after a hiatus of 5 to 6 months, progressed linearly throughout the remaining 30-month-period of observation with about 2% of the surviving mice dying with lymphoma each month (Chart 2d). The lymphoma rates in mice from Colonies 1 and 2 were comparable to each other but at least 10-fold less than in mice from Colony 3. Not until the mice from Colonies 1 and 2 had been observed for about 30 months did they show an appreciable cumulative incidence (5 to 10%) of lymphoma. Lymphomas were 2 to 3 times more common in females from all 3 areas. In Colony 3 mice the increased incidence of breast carcinoma was noticeable within 12 months after trapping and it progressed linearly (Chart 2e). The increased incidence of hepatomas (Chart 2f) and lung adenomas (Chart 2g) in Colony 3 mice did not become clear until after about 30 months of observation. Apart from breast carcinomas, the nonlymphomatous tumor types did not show any sex predilection. The cumulative paralysis rate in Colony 3 mice kept pace with the lymphoma rate for the 1st 15 months of observation, after which it leveled off markedly as relatively few mice became paralyzed after this time (Chart 2i). The paralytic disease was equally common in both sexes.

Spleen CF gs Antigen and C-type Particles. The prevalence of spleen gs antigen detectable by CF in non-tumor-bearing mice from the different colonies after various periods of observation is shown in Table 3. In newly trapped mice from Trapping Areas 3 (LC) and 4, and in mice from these areas observed in laboratory colonies over longer periods of time, the prevalence of detectable spleen CF gs antigen was consistently greater than 70% and the titer was usually equal to or greater than 1:4. Numerous C-type particles were seen by EM in 14 of 14 spleens from newly trapped mice from these areas. By contrast, in mice from Areas 1 (Bouquet Canyon) and 2, again regardless of observation time, the prevalence of spleen CF gs antigen was less than 30% and the positive titers tended to be lower. C-type particles, few in number, were seen by EM in only 1 of 21 spleens from newly trapped mice from these areas. There is a suggestion that, in those few non-tumor-bearing mice from Colonies 1 and 3 that survived beyond 30 months, the prevalence of spleen CF gs antigen was somewhat less than that detected following shorter periods of observation.

Pathology of Spontaneous Tumors. The gross and microscopic features of the spontaneous lymphomas, breast carcinomas, lung adenomas, sarcomas, and hind leg paralytic disease in wild mice have been described (4, 6, 7). However, the difference in lymphoma type and pattern between mice from Colonies 3 and 4 and mice from other colonies deserves reemphasis. In mice from Colonies 3 and 4 the lymphomas were almost entirely of a poorly differentiated lymphocytic type with a diffuse pattern and an accompanying leukemia. They generally involved spleen, liver, and systemic lymph nodes but spared the thymus. They are apparently composed of a "null" population of lymphoid cells bearing neither T- nor B-cell surface markers (1). The lymphomas in mice from Colonies 1 and 2, as in mice from several other colonies previously described (7), were of a more heterogeneous make-up. They were mostly reticulum cell type B (3) or poorly differentiated lymphocytic type with a more nodular pattern and without leukemia. A few were well-differentiated lymphocytic lymphomas or type A reticulum cell sarcomas (3) involving mainly the spleen, liver, and mesenteric lymph nodes. The lung adenomas, even in Colony 3 mice, were single and small, seldom over 5 mm in maximum dimension. The hepatomas were usually multicentric in origin and generally well differentiated without detectable metastases.

C-type Virus Expression in Spontaneous Tumors. The prevalence of gs antigen detectable by CF and of C-type particles detectable by EM in spontaneous tumors and corresponding spleens of aging wild mice from the different colonies is shown in Table 4. In mice with lymphoma from all of the colonies, there was a high prevalence of detectable gs antigen and C-type particles in the tumors and spleens. This prevalence was greater (nearly 100%) in mice from Area 3 than in mice from Areas 1 and 2 (60 to 75%). The prevalence of detectable gs antigen and C-type particles in the tumors and spleens of mice bearing other types of tumors was also much greater in mice from Colony 3 (about 90%) than in mice from Colonies 1 and 2 (less than 30%). The number of C-type particles observed was also generally much greater in the tumor and spleen tissues from Colony 3 mice.

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(only 55) were followed from Colony 4 (LP) to allow for computation of these cumulative incidence rates.

Results
Chart 2a, cumulative total mortality from all causes; b, cumulative total mortality excluding deaths from tumors and paralysis; c, cumulative incidence rate for all tumors; d, cumulative incidence rate for lymphoma; e, cumulative incidence rate for carcinoma, excluding hepatoma; f, cumulative incidence rate for hepatoma; g, cumulative incidence rate for lung adenoma; h, cumulative incidence rate for sarcoma; i, cumulative incidence rate for paralysis.
Table 2

Spontaneous tumor and paralysis occurrence in aging wild mice

The observed numbers of deaths in each colony with a particular type of tumor or paralysis are compared to the expected numbers calculated on the assumption of no difference between the colonies for this cause of death (23).

<table>
<thead>
<tr>
<th>Colonies</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td>Observed</td>
</tr>
<tr>
<td>Total mice at start</td>
<td>2676</td>
<td>743</td>
<td>2008</td>
</tr>
<tr>
<td>Mice alive after 35 mos. observation</td>
<td>7</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>45</td>
<td>193</td>
<td>16</td>
</tr>
<tr>
<td>Other tumors</td>
<td>19</td>
<td>72</td>
<td>15</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>4</td>
<td>15.8</td>
<td>2</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>6</td>
<td>10.5</td>
<td>7</td>
</tr>
<tr>
<td>Hepatomas</td>
<td>8</td>
<td>15.7</td>
<td>6</td>
</tr>
<tr>
<td>Lung adenomas</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combination of 2 tumors</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

There are no statistically significant differences between any tumor rate in Colonies 1 and 2. The rate in Colony 3 is different from that in the other 2 colonies (p < 0.001) for lymphomas, carcinomas, hepatomas, and lung adenomas. There is no statistically significant difference between the 3 colonies for sarcomas.

b Breast carcinoma.

† Ten breast carcinomas, 2 skin carcinomas, 1 pancreatic carcinoma, 1 undetermined.

ι Five fibrosarcomas, 1 liposarcoma.

‡ Six fibrosarcomas, 1 angiosarcoma.

§ Six fibrosarcomas, 1 osteosarcoma, 1 carcinosarcoma of the breast.

* Combinations included in the above figures: 7 lymphoma and lung adenoma; 3 hepatoma and lung adenoma; 2 lymphoma and hepactoma; 1 lymphoma and breast carcinoma; 1 carcinosarcoma of the breast.

Table 3

Spleen CF gs antigen in non-tumor-bearing aging wild mice

Ten % aqueous spleen extracts from necropsied mice were tested by CF for mouse C-type virus gs antigen at 1:2 and 1:4 antigen dilutions using as antisera a 1:20 dilution of pooled sera from Fischer rats bearing Moloney sarcoma virus-induced tumor transplants (17).

<table>
<thead>
<tr>
<th>&lt;6 mos.</th>
<th>6-17 mos.</th>
<th>18-29 mos.</th>
<th>30+ mos.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. positive/no. tested</td>
<td>%</td>
<td>No. positive/no. tested</td>
</tr>
<tr>
<td>Colony 1</td>
<td>1:2</td>
<td>35/108</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>≥1:4</td>
<td>18/108</td>
<td>17</td>
</tr>
<tr>
<td>Colony 2</td>
<td>1:2</td>
<td>5/51</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>≥1:4</td>
<td>3/51</td>
<td>6</td>
</tr>
<tr>
<td>Colony 3</td>
<td>1:2</td>
<td>154/193</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>≥1:4</td>
<td>127/193</td>
<td>66</td>
</tr>
<tr>
<td>Colony 4</td>
<td>1:2</td>
<td>36/50</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>≥1:4</td>
<td>30/50</td>
<td>60</td>
</tr>
</tbody>
</table>

* Includes mostly newly trapped healthy wild mice.

Other Pathology. A protozoan parasite, coccidium, was found in the kidney sections of mice from Colony 3 about twice as frequently (31%) as in mice from the other colonies (17%). Relatively little chronic inflammation accompanied this infestation. In mice from Colony 3 coccidiosis was noted no more frequently in mice with lymphoma than in mice dying from other causes. A fibromuscular scarring of the wall of pulmonary vessels, probably the residua of a preceding vasculitis and pneumonitis, was found about 20 times more commonly (6%) in necropsied mice from Colony 1 than in necropsied mice from the other colonies (0.3%). Thickened capillary basement membranes (glomeruloscle-
Table 4  
**CF gs antigen and C-type particles in spontaneous tumor-bearing aging wild mice**

Ten % aqueous tumor and spleen extracts from necropsied mice were tested by CF for mouse C-type virus gs antigen using as antisera a 1:20 dilution of pooled sera from Fischer rats bearing Moloney sarcoma virus-induced tumor transplants (13). The same tissues were examined by EM for C-type particles.

<table>
<thead>
<tr>
<th>Colonies</th>
<th>CF</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tumor</td>
<td>Spleen</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>15/25*</td>
<td>22/35</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>1/1</td>
<td>0/1</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>0/4</td>
<td>0/3</td>
</tr>
<tr>
<td>Lung adenoma</td>
<td>2/4</td>
<td>1/6</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>0/5</td>
<td>0/6</td>
</tr>
</tbody>
</table>

* Number positive at titer of 1:2 or greater/number tested.  
b Number positive for C-type particles/number tested.  
NT, not tested.

Discussion

These results show a highly predictable association between the predilection to lymphoma and paralysis in wild mice and the extent of spleen CF gs antigen and C-type particle expression. Mice from Colony 3 (LC) with the highest prevalence and titer of spleen gs antigen had an earlier onset and an approximately 10-fold greater incidence of lymphoma than did mice from Colonies 1 and 2 with lower prevalence and titer of spleen CF gs antigen. When lymphoma did arise in mice from the other colonies (1 and 2), they were fewer in number but were usually also positive for CF gs antigen and C-type particles. Only mice from Colony 3 and the equally gs antigen-positive mice from Colony 4 developed the paralytic disease.

The detection of high-titered (≥1:4) CF gs antigen in spleens of newly trapped wild mice is, thus, an excellent marker to predict susceptibility to lymphoma and paralysis in aging populations of wild mice from specific trapping areas. Crosses between high- and low-leukemia-incidence strains of laboratory mice have also indicated highly significant and predictable associations between CF gs antigen in spleen (15, 19) or infectious virus titer in tail extracts (17) of young mice and lymphomagenesis later in life. The experimental transmission of lymphoma and/or paralysis by several different C-type viral isolates derived from wild mice from Colonies 3 and 4 (6, 21) and the in vivo neutralization of both induced diseases with specific viral antisera (14) established the indigenous C-type RNA virus as the critical determinant for lymphoma and the hind leg paralytic disease in wild mice. In addition, by cross-breeding wild mice from Colony 3 with C57BL/10Sn inbred mice, homozygous for the Fv-1b allele, both gs antigen expression and virus replication have been suppressed and lymphomas and paralysis have been prevented in the progeny. 3

These data leave unanswered the possible role of indigenous C-type virus on nonlymphomatous tumorigenesis in wild mice. By the methods used, the level of virus expression was about the same in mice bearing nonlymphomatous tumors as in non-tumor-bearing mice from the same colony. In laboratory mice, it is clear that production of p30 antigen or complete virus is not required for oncogenic expression and that different portions of the viral genome are subject to independent regulation (16). Thus, the absence of p30 antigen detectable by CF and of C-type particles detectable by EM in most of the carcinomas, sarcomas, and pulmonary adenomas from mice in Colonies 1 and 2 could be explained by the selective activation of viral oncogene(s) without concomitant activation of latent virogenes. Of course, low levels of p30 or complete virus expression might yet be detectable by more sensitive methods of assay, e.g., radioimmunoassay, virus isolation from the primary tumor, or cultured tumor cells. Virus-coded proteins, other than p30, for which assay systems are now being developed, e.g., envelope glycoprotein (gp69/71), could be important determinants in the neoplastic transformation of certain epithelial cells and also in the degeneration of spinal cord motor neurons in LC wild mice. Other host cell genes, as yet largely unspecified, in addition to those known to influence viral leukemogene-

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sis (18), are also undoubtedly involved in determining the target cell for virus expression and also for malignant transformation. It will be important to determine whether or not control of C-type virus expressions by specific immunological or genetic measures will also prevent occurrence of nonlymphomatous tumors in wild mice. Of course, the mammary tumor virus seen by EM in normal lactating breast biopsies of about 60% of wild mice, regardless of trapping area (24), is probably involved in the pathogenesis of spontaneous breast carcinoma in wild mice.

The increased incidence of lymphomatous and epithelial tumors in Colony 3 mice might, of course, be related to an impairment of immune surveillance due to the heavy load of replicating C-type virus in lymphoreticular tissues (2, 20). In view of the considerable exposure of these mice to infectious C-type virus early in life (unpublished observations), some degree of immunological tolerance to this virus would not be surprising. The incidence of glomerulonephritis, which has been considered an index of immunity to autogenous C-type virus in laboratory mice (12), was low (2%) in Colony 3 mice and was increased but still low (5%) in age-matched lymphoma-resistant mice from Colony 1. Glomerulonephritis was of equally low frequency (2%) in mice from all these trapping areas and other lesions, e.g., systemic vasculitis or amyloidosis, suggestive of an immunogenic or autoimmune pathogenesis, were lacking in mice from all trapping areas. It is, of course, possible that immunological techniques might reveal age-related evidence of C-type virus antigen-antibody deposition in the kidneys of Colony 3 and other wild mice as was found in aging AKR mice (22). The higher incidence of coccidiosis in Colony 3 mice was probably not related to a weakened immunological competence because the parasite was confined to the kidneys and was generally associated with minimal chronic inflammation. Moreover, a generalized severe defectiveness in immune responsiveness in Colony 3 mice is not likely since their mortality from causes other than lymphoma, tumors, or paralysis did not exceed that of Colony 1 mice. Nor did the activity of other latent murine viruses such as LCM, polyoma, and cytomegalovirus appear increased in mice from Colony 3. The uniquely increased incidence of lymphoma and carcinoma in Colony 3 mice thus suggests that any immune deficiency in these mice may be quite specific for their indigenous C-type virus and for certain transformed lymphoid and epithelial cells. Studies on the tumor-specific and the viral-specific humoral and cellular immune competence of mice from the 3 colonies are underway.

There is no ready explanation for the unexpected degree of indigenous C-type virus activity found in wild mice from Areas 3 and 4. We have been unable to detect untoward exposure to environmental carcinogens or radioactivity at these sites. Area 3, populated by mice with the highest virus expression, is essentially smog free, whereas Areas 1 and 2, with least virus expression, are located in regions of heavy air pollution. In previous studies of laboratory mice exposed over their lifetime to ambient levels of Los Angeles air pollution, no tumorigenic effect was observed (8). A disturbance of 40 miles separates Areas 3 and 4, which probably rules out horizontal virus spread or migration of mice between these areas. Genetic factors, as yet almost entirely undefined in wild mice, undoubtedly account for these major differences in C-type virus expression and associated host response in different populations of wild mice. The H-2k allele associated with increased lymphomagenesis in laboratory mice (18) was not found in mice from any of these trapping areas (J. Klein, personal communication).

If we are to apply the information gained from this wild mouse model system to the human cancer problem, several major points emerge: (a) familial clusters of leukemia cases should be identified for the specific purpose of obtaining tissues for virus isolation; (b) lymphomas and tumors of hematopoietic origin should be the optimum tissues from which to recover complete C-type virus; (c) virological and seroepidemiological evidence of C-type virus expression should be looked for in unexplained motor neuron diseases such as amyotrophic lateral sclerosis; (d) reagents and techniques need to be developed for detecting covert expression (e.g., gp69/71 without p30 or complete virus) of the C-type viral genome(s) in carcinomas and other nonlymphomatous tumors; (e) more knowledge is needed about how host cell genes regulate C-type virus expression and control autogenous host-immune responsiveness to virus-specific and tumor-specific antigens and how this response can be strengthened by C-type viral vaccines. Our studies on wild mice and, ultimately, humans are aimed in this direction.

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