Spontaneous Regression of Chemically Induced Malignant Lymphoma in Swiss Mice

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SUMMARY

Female NIH general purpose (random-bred Swiss-Webster) mice were given a single i.p. injection of 1-ethyl-1-nitrosourea (1 μmole/g) at 5 weeks of age. In 2 experiments, 246 of 462 and 94 of 152 mice developed thymic or nonthymic malignant lymphoma between 10 and 35 weeks after treatment. Of these 340 cases, 38 underwent spontaneous regression, which was accompanied by rapid weight loss and the development of severe, generally fatal hypoplastic anemia. Another 19 cases showed histological evidence of incipient regression at autopsy. Regression was characterized histologically by cellular depletion and fibrosis of lymphoid tissues and of visceral lymphoma deposits. Lymphomas which subsequently regressed could be transplanted by grafting lymph node cells into neonatal recipients during the florid phase of the disease. In one case, transplantation was attempted once during the florid phase of the disease and a second time after regression had occurred; transplantation was successful the first time but not the second. The cause of the regression/anemia syndrome is unknown; possible explanations are discussed.

INTRODUCTION

Autochthonous lymphomas of the mouse, whether spontaneous or induced by chemicals or other exogenous agents, generally follow a progressive and fatal course and by both histological and biological criteria are among the most highly malignant of murine cancers. We report here what we believe to be the first observation of spontaneous regression of chemically induced lymphocytic cancers in mice.

The progressive course of the great majority of murine lymphomas is characterized by a steady increase in the number of neoplastic cells in both lymphoid and nonlymphoid tissues of diseased mice and consequently by a steady increase in size of lymph nodes, thymus, spleen, liver, and other affected organs. The phenomenon which we term regression is characterized by massive disintegration of neoplastic lymphoid cells in tumor deposits throughout the body, resulting in a steady decrease in both the number of lymphoid cells in these deposits and in the size of the organs in which they occur. Decreasing neoplastic cell populations are replaced by fibrous, often hyalinized, connective tissue, the eosinophilic character of which in tissue sections stained with hematoxylin and eosin contrasts markedly with the basophilic tumor cell deposits observed during the florid phase of the disease. Regression, however, is not in this case synonymous with restoration of health; the malignant lymphoma is superseded by an aplastic anemia of steadily increasing severity, to which affected animals eventually succumb.

The regression phenomenon was detected in certain of 462 GP\(^1\) mice that had received ENU once i.p. and had then originally been divided into 11 groups of 42 animals and subjected to various regimens of treatment with the double-stranded complex of polynucleosinic and polynucleotidic acids/diethylaminoethyl dextran complex in an attempt to modify the oncogenic effects of ENU (Experiment 1). No statistically significant differences in frequency of lymphoma regression were noted among these groups. Regressions were seen in all of them, including a positive control group which received no treatment except the original dose of ENU. Accordingly, all 462 animals are considered as 1 group in this report. In a 2nd experiment, 152 mice were given ENU, but no double-stranded complex of polynucleosinic and polynucleotidic acids/diethylaminoethyl dextran complex, in order to confirm the initial discovery and to provide animals from which lymph nodes could be removed during the florid phase of the disease, i.e., when the mice were overtly leukemic, for both histological diagnosis of malignant lymphoma and for cell transplantation to newborn recipients. In 3 cases, lymphoma was successfully transplanted to newborn mice from the lymph nodes of donors that subsequently developed the regression syndrome. This 2nd series of experiments confirms the neoplastic nature of the lymphoproliferative disorder from which the regression syndrome develops.

MATERIALS AND METHODS

ENU (MW 117) was synthesized by nitrosation of ethylurea (Aldrich Chemical Company, Inc., Milwaukee, Wis.) according to the general procedure for its methyl homolog (1), except that performed ethylurea was substituted for ethylurea generated in situ. Pure ENU was obtained by dissolving the crude product in CH\(_2\)Cl\(_2\), drying over sodium sulfate, and recrystallizing. ENU obtained this way in the form of fine, pale yellow needles (m.p. 103–104°, with decomposition, open capillary, corrected) is stable indefinitely at 4° if protected from moisture. It is dissolved for injection in

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\(^{1}\) The abbreviations used are: GP, general purpose (NIH random-bred line of Swiss-Webster mice); ENU, 1-ethyl-1-nitrosourea.
trioctanoin (Eastman Organic Chemicals, Rochester, N. Y.) to a concentration of 17.6 ng/ml (150 μmoles/ml). Young female GP mice were obtained from the Laboratory Aids Branch, Division of Research Services, NIH, and were housed 6 to a cage and given Purina laboratory diet and tap water ad libitum. They received a single i.p. injection of ENU in trioctanoin at the age of 5 weeks, at a dose of 1 μmole/g of body weight. All treated mice were examined daily for signs of disease but were kept alive as long as possible and either killed when obviously moribund or necropsied when found dead. Diagnoses of reticular cancers were made provisionally on the basis of signs (the labored respiration and cyanosis characteristic of thymic lymphoma and/or the palpable spleen and visibly enlarged lymph nodes which in the absence of labored respiration indicate nonthymic lymphocytic, myeloid, plasma cell, or reticulum cell cancers) and were confirmed by histological examination of Wright-stained smears of the pleural effusion surrounding a mediastinal tumor or from the jugular vein at autopsy and was drawn into heparinized capillary glass tubes.

RESULTS

Experiment 1

After a transient loss in body weight at 1 week after ENU injection, the mice gained weight normally and appeared healthy. Only 2 of the 462 treated mice died before the 1st case of lymphoma appeared. One of the first mice to develop the signs of thymic lymphoma (12 weeks after treatment) lost weight rapidly, became extremely anemic, and finally died 1 week later. At autopsy, all viscera were abnormally pale, there were no signs of hemorrhage, and all lymphoid tissue was involuted and deep yellow. The gross appearance of the viscera did not suggest a diagnosis of lymphoma. Histological examination showed extreme lymphocyte depletion of the spleen and lymphoid tissues (cf. Figs. 3, 4, 11, 16, and 17) and no evidence of lymphoma aggregates in the viscera, but a peculiar perivascular fibrosis was present around the portal tracts of the liver, in the same pattern as a typical lymphoma deposit but practically devoid of lymphoid cells (cf. Figs. 6 and 8). None of these lesions were necrotic. This fibrotic pattern was strikingly similar to that seen in human cases of leukemia or Hodgkin's disease after drug- or radiation-induced remissions (13, 19).

Additional mice with regressing lymphomas, a total of 48 over the next 23 weeks, were easily identified by their extreme pallor, which reflected severe anemia. The normal hematocrit for untreated female GP mice ranges from 52 to 62% packed red cells (an average of 57.9% was seen in 18 mice aged 23 weeks and also in 23 mice aged 64 weeks). Hematocrits for visibly anemic animals were generally below 20 and frequently below 10%. Most, but not all, of these animals had definite physical signs of lymphoma prior to the onset of anemia. In such cases, the signs of lymphoma abated as the severity of the anemia increased. The labored breathing typically caused by a mediastinal tumor became more natural; such animals were later found to have small, lymphocyte-depleted, fibrotic thymic tumors. Inguinal, axillary, and cervical lymph nodes which had been visibly enlarged began to decrease progressively in size after the onset of anemia; lymph nodes regressed in some anemic mice to the point where they could not be felt on palpation, and histological examination at this stage revealed fibrotic, lymphocyte-depleted nodes with no evidence of extracapsular invasion by lymphoma cells. Marked lymphoid depletion was also observed in the spleen, especially in the Malpighian corpuscles, together with depopulation of the characteristic perivascular lymphoma aggregates in the lungs, liver, kidneys, and other viscera. Neoplastic lymphoid cell deposits in all these sites were replaced partially or completely by fibrotic, sparsely cellular connective tissue scars.

These 48 cases of regressing lymphoma/anemia were grouped into 3 categories, according to the extent of lymphoma regression observed histologically in sections of spleen, thymus, 1 or more lymph nodes, and liver. Sternal marrow, lung, kidney, and salivary glands were also examined in many cases. A brief summary of histological findings in representative cases from each of Categories 1 to 3 is presented in Table 1. Typical scars are compared with normal tissues and lymphoma aggregates in Figs. 1 to 4 (thymus), 5 to 8 (liver), 9 to 11 (spleen), and 14 to 17 (lymph nodes). The 3 categories are defined by the following criteria.

Complete Regression. No single low-power field (100X), in any tissue section examined, was compatible with full-blown, florid malignant lymphoma. Fifteen such cases were found (3.2% of mice at risk, 6.1% of malignant lymphomas). Survival times (interval between ENU injection and death) ranged from 13 to 29 weeks (mean, 20.0 weeks; median, 19.0 weeks).

Partial Regression. Some low-power fields in 1 or more tissues were compatible with florid lymphoma, but a substantial proportion of the tissues examined contained fibrous scars in areas where lymphoma deposits would be expected. Fifteen such cases were found (survival time, 14.0 to 26.5 weeks; mean, 20.6; median, 21.0).

Incipient Regression. Most low-power fields were diagnostic for lymphocytic cancers, but at least 2 low-power fields from 1 or more tissue sections showed partial disintegration of lymphoma deposits and signs of fibrous replacement. Eighteen such cases were found (survival time, 17.0 to 31.0 weeks; mean, 22.0; median, 21.0).

All surviving animals were killed 35 weeks after ENU injection, by which time the S-shaped curve for lymphoma induction (percentage of animals at risk dead of lymphoma versus time) had reached its plateau. A total of 198 reticular cancers were diagnosed in which no clinical or histological signs of regression were detected. These were progressive and fatal and included 1 myeloid leukemia, 3 reticulum cell sarcomas, and 194 lymphocytic or stem cell lymphomas of which two-thirds featured a thymic tumor. None of these mice were significantly anemic, despite lymphoma deposits in the bone marrow. The incidence of nonregressing lymphomas was 42.9% of animals at risk. Survival times ranged from 10.0 to 35.5 weeks (mean, 20.9; median, 20.0).

Several features of the histological patterns observed in animals from Categories 1 and 2 deserve emphasis. The extent
of regression observed is not uniform in all tissues of any given mouse. It varies, especially in cases of partial regression (Category 2), from site to site. In a single liver section, one may find portal triads which are heavily infiltrated by typical lymphoma aggregates, others which are surrounded by fibrous scars, and yet others which are surrounded by fibrous scars in which islands of neoplastic lymphocytes persist. The perivascular lesions described in the liver are also seen in other tissues in which lymphoma deposits occur, including the lungs, kidneys, and exocrine glands. Also, the sternal marrow in these mice was often nearly acellular (Fig. 13), and compensatory extramedullary hematopoiesis was never prominent in the liver or elsewhere, despite the profound anemia of many individuals. When myeloid metaplasia was observed, it usually consisted of small foci of extramedullary granulocytopoiesis. The anemia observed in these mice appears therefore predominantly aplastic.

No animals included in the categories described above had any visible hemorrhagic lesions which might have contributed to their anemic condition, although intestinal contents were not examined for occult blood. A hemolytic component may exist, but no erythrocyte survival times have been determined. Severe hemolytic anemia can develop in splenectomized or physiologically compromised mice that harbor a latent infection by Hemobartonella or other hemolytic organisms (17), but we have not been able to transfer the GP mouse anemia to newborn mice by i.p. injection of liver and spleen homogenates from advanced cases, nor have we been able to potentiate a possible latent infection by splenectomy in adult mice that received acemic liver and spleen homogenates when newly born. We conclude that Hemobartonella or related organisms probably play no part in the pathogenesis of this condition.

**Experiment 2**

Although the morphological features of the florid phase of this condition are perfectly consistent with those of lymphocytic cancers, in that the normal structures of lymph nodes, spleen, and thymus are obliterated by masses of large, atypical cells of a single morphological type which also form large, invasive, metastatic deposits in other tissues, there are human conditions in which benign lymphoid hyperplasia very closely mimics the histological features of malignant lymphoma. These include postvaccination lymphadenitis (Ref. 19, pp. 436-437) and reactions to certain anticonvulsant drugs, such as diphenylhydantoin (7, 23). We therefore considered it important to demonstrate that the lymphoproliferative condition which undergoes regression is capable of being transferred by cell graft to other animals and of producing in them a progressive and fatal disease identical in all aspects with malignant lymphoma.

A 2nd group of 152 female GP mice were given 1 μmole/g of trioctanoin i.p. once only at 5 weeks of age, as in the previous study. They received no other injections or treatment of any kind and were housed, fed, and given water as before. Each mouse was examined weekly for signs of lymphoma. Those that developed visibly swollen inguinal nodes, but in which the disease did not appear to be pursuing an especially fulminant course, were lightly anesthetized with ether, and an inguinal lymph node was removed. One-half of the node was fixed in formalin and kept for subsequent embedding for histological examination in the same paraffin block with other tissues and lymph nodes from the same animal, subsequently obtained at autopsy. In this way, identical sectioning and staining of both biopsy (florid phase) and autopsy (regressive phase) tissues was assured. The other
half of the biopsied lymph node was passed gently through a fine mesh screen in Earle's balanced salt solution. A portion of the resulting single-cell suspension was treated with erythrosin, and unstained (viable) cells were counted in a hemocytometer. Depending on the number of cells obtained, between 10^4 and 10^6 cells in 0.05 ml were injected i.p. into neonatal GP mice (less than 24 hr old). One litter of 8 to 14 mice was used for each lymph node donor; these were observed for the development of lymphoma. Neonatal recipients were used because of their immunological immaturity; GP mice are random-bred, and adults rarely accept tissue homografts.

A total of 94 of the 152 ENU-treated mice in this experiment developed reticular cancers. Eleven of these were subjected to inguinal node biopsy from which a histological diagnosis of lymphocytic cancer was made. Transplantation of malignant lymph node cells to 1 or more neonatal recipients was successful in each of these cases. Every mouse that developed signs of cancer following neonatal injection of such cells died with florid, widespread malignant lymphoma in the viscera by the age of 10 weeks. No regressions were seen in transplant recipients, including those that received cells from 3 donors which subsequently developed the regression/anemia syndrome (Table 2). Complete regression was seen in 2 of these donors, and partial regression was seen in 1. The 2 cases of complete regression occurred among the 11 lymph node biopsy subjects; the partial regression occurred in an animal from which cells for grafting were only obtained at autopsy. A viable cell suspension of the same concentration (4 X 10^7 cells/ml) as that used in the biopsy studies was prepared from the spleen and mesenteric lymph node of 1 of the completely regressed donors, and transplantation was again attempted (2 X 10^6 cells/recipient). None of the 13 recipients of this suspension developed lymphoma, in contrast to the 8 neonatal recipients of the same number of biopsied lymph node cells removed from this same animal 7 days previously, all of which died of malignant lymphoma by the age of 66 days (Figs. 14 to 19 and Table 2). We conclude from these studies that the lymphoproliferative condition which precedes the regression/anemia syndrome is definitely neoplastic and that the proportion of neoplastic cells in the lymphoid tissues of these animals decreases as the regression syndrome develops, in accord with the histological observations.

A total of 4 complete and 4 partial regressions were observed in the 152 animals at risk in this experiment or approximately 2.6% in each category. This is not significantly different from the 3.2% of mice at risk observed in each of these categories in Experiment 1. As in Experiment 1, when regression occurred it did so rapidly. The case listed in Table 2 in which the disease passed from florid malignant lymphoma (lymphocytic) to complete regression in 8 days is typical.

**DISCUSSION**

The lymphoma regression/anemia syndrome described here represents a striking exception to the general rule that malignant cancers grow progressively and inexorably, even as the normal tissues of the host waste away. In contrast to the voluminous literature on regression of transplanted tumors, there are very few experimental models of neoplastic disease in which spontaneous regression of established, autochthonous tumors is observed. The best-documented studies of spontaneous regression of chemically induced autochthonous tumors have dealt with cutaneous papillomas in rabbits (22) and in mice (25), where immune processes have been shown to be involved (15), and with mammary adenocarcinoma in rats, which is markedly hormone dependent (11, 12). Malignant lymphoma has not been reported to regress spontaneously in mice; to our knowledge, the only similar observation is that of Rich et al. (20, 21) who found that the erythroblastic phase of Friend virus infection was self-limited when 1 particular strain of virus was inoculated into Swiss or DBA/2 mice. Regression

**Table 2**

<table>
<thead>
<tr>
<th>Donor</th>
<th>Signs</th>
<th>Biopsy (date)</th>
<th>Autopsy (date)</th>
<th>Hematocrit (%)</th>
<th>Source</th>
<th>No. (x 10^6)</th>
<th>Transplanted lymphoma/anemia syndrome</th>
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<tbody>
<tr>
<td>X346</td>
<td>Labored respiration</td>
<td>Lymphoma, partial regression (8/20)</td>
<td>Autopsy (8/20)</td>
<td>2</td>
<td>9/11</td>
<td></td>
<td></td>
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<tr>
<td>X12</td>
<td>Labored respiration (9/3)</td>
<td>Lymphoma (9/17)</td>
<td>Complete regression (9/24)</td>
<td>7 (9/24)</td>
<td>Biopsy (9/17)</td>
<td>2</td>
<td>8/8</td>
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<td></td>
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of this proliferative response to viral infection was not, however, accompanied by the development of hypoplastic anemia. Ischemic fibrosis of the sphenoidal sinus, which resembles the marrow aplasia observed in our mice, has been seen in murine myeloid leukemia (8, 26, 27). It is caused, apparently, by compression of blood vessels which pass through bony foramina, as a result of progressive growth of perivascular cuffs of leukemic cells. This condition produces anemia (hematocrits may fall to 20%) but without regression of visceral leukemic infiltrates, so the resemblance to the condition reported in this paper is marginal.

The lymphoma regression/anemia syndrome was discovered only because animals with obvious physical signs of lymphoma were allowed to live as long as possible in 1 experiment. In previous studies, when ENU-treated GP mice that had developed physical signs of lymphoma were killed immediately, so few cases of this syndrome were seen that it went unrecognized. Of 345 lymphomas diagnosed histologically (all lymphocytic or stem cell in origin except for 2 myeloid leukemias and 9 reticulum cell sarcomas) that developed in 674 female GP mice given 1 μmole/g of ENU in several previous studies in this laboratory, only 4 cases of partial lymphoma regression could be identified with reasonable assurance from a retrospective study of autopsy records and histological sections.

We consider at least 3 alternative explanations for the occurrence of the lymphoma regression/anemia syndrome to be sufficiently plausible to merit investigation. These are the possibilities that the syndrome is caused by: (a) infection; (b) exhaustion of some factor required for survival and growth of hematopoietic stem cells, which might be either nutritive or hormonal in nature; and (c) immune response to an established, autologous cancer, with autoimmune damage to closely related normal tissues, in this case, erythropoietic stem cells. We have not been able to isolate an infectious agent by cultivation either on agar media or in tissue culture or by injection of newborn mice with tissue homogenates, but we do not feel that the hypothesis of infection has been tested carefully enough to be rejected. The nutritional dependence of some lymphomas on exogenous L-asparagine has made L-asparaginase a useful therapeutic agent (4, 14), and certain sublines of Swiss mice are extremely susceptible to protein deficiency anemia, which is aplastic and may cause hematocrits to fall to 20% after only 4 weeks of feeding a low-protein diet; hematocrits as low as 1% may be seen after 6 weeks (2). While our lymphomatous animals had unlimited access to an adequate diet, the fact that they progressively lost weight during the course of their disease demonstrates that a severe derangement of their metabolic balance did occur, and the possible role of nutritive factors in the development of their lymphoma regression and anemia remains to be evaluated. The histological features of this syndrome resemble those of severe, chronic graft versus host reactions (3, 9, 16) and are compatible with an “autoimmune” mechanism for the development of this condition. It may be significant that Swiss mice, the only line of animals in which we have seen lymphoma regression, are very susceptible to immunopathologic tissue damage which accompanies infections by lymphocytic choriomeningitis virus (10, 18) and Plasmodium berghei (24). Also, the histogenetically related reticulum cell sarcomas of SJL/J mice do appear to be at least partially subject to immune control; the latent period for these spontaneous cancers is shortened by treating SJL/J mice with antilymphocyte serum, presumably due to its immunosuppressive effects (5). Furthermore, although the primary, autologous cancers do not regress, their transplants often do, frequently after attaining considerable size, and these tumors are demonstrably antigenic (6).

The hypothetical role of immune processes in either aspect of the lymphoma regression/anemia syndrome could be most convincingly demonstrated by experiments involving passive transfer of immune cells or serum, which can best be performed in syngeneic animals. Efforts are in progress to detect this syndrome in inbred strains of mice and to evaluate the possible roles of immunity and of nutritive, hormonal, and infectious factors in its development.

ACKNOWLEDGMENTS

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REFERENCES

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Figs. 1 to 4. Thymic tumors in ENU-treated female GP mice. H & E.

Fig. 1. Lymphocytic cancer adjacent to heart muscle in a mouse with lymphoma aggregates in the liver, kidney, and sternal marrow, × 26.5. Cortex and medulla of the thymus are replaced by tumor cells.

Fig. 2. Higher magnification of the same section shows the highly cellular structure of this tumor. × 100.

This anemic mouse (L45) had had respiratory difficulties indicative of thymic lymphoma 3 weeks previously. × 26.

Fig. 4. Higher magnification shows fibrous connective tissue comprising the tumor. × 100. Similar tissue replaced most of the white pulp in spleen, nodes, and thymus of this animal and was present in the periportal areas of the liver (“complete regression”).

Figs. 5 to 8. Hepatic tissue in normal and lymphomatous mice and in anemic animals after lymphoma regression. H & E.

Fig. 5. Normal liver. Note absence of connective tissue between the arteries, vein, and bile ducts in portal triads. × 63.

Fig. 6. Periportal and sinusoidal lymphoma infiltrates in liver of mouse with ENU-induced lymphocytic neoplasm. × 63. (Photographed through green filter to enhance contrast.)

Fig. 7. Fibrous connective tissue scar surrounding a portal triad in an anemic mouse (A25) which had had generalized lymphadenopathy and hepatosplenomegaly 25 days earlier. × 63. Nearly all portal triads in the tissue section were similar in appearance. Similar perivascular fibrosis was seen in the salivary glands and kidneys; the thymus, lymph nodes, and splenic white pulp were replaced entirely by morphologically similar tissue (“complete regression”).

Fig. 8. Higher magnification of Fig. 7. × 160.

Figs. 9 to 13. The spleen and sternal marrow in normal and lymphomatous mice and in anemic mice after regression of lymphoma. H & E, × 40.

Fig. 9. Spleen of normal, untreated GP mouse. The lymphoid tissue of the Malpighian corpuscles is clearly demarcated from the surrounding red pulp, and the central arteries are clearly visible.

Fig. 10. Portion of greatly enlarged spleen from mouse with ENU-induced lymphocytic cancer. All normal structures are obliterated by masses of neoplastic lymphocytes.

Fig. 11. Spleen after lymphoma regression (Case F23). The splenic capsule and the centers of the Malpighian corpuscles are fibrotic; only a halo of lymphocytes remains around the periphery of the capsule.

Fig. 12. Normal sternum showing densely cellular marrow.

Fig. 13. Sternal marrow from anemic mouse (Case 152) showing nearly aplastic marrow. The remaining hematopoietic foci are exclusively granulocytic.

This animal was noted to have a fibrotic thymic tumor, periportal fibrosis in the liver, and fibrotic white pulp in the spleen.

Figs. 14 to 19. Lymph nodes from a case (X12) of ENU-induced lymphocytic cancer, before and after regression, and from a transplanted lymphoma. H & E.

Fig. 14. Visibly enlarged inguinal lymph node removed surgically from ENU-treated GP mouse 14 days after onset of respiratory signs of thymic lymphoma. Normal architecture is obliterated. Numerous macrophages give the section a “starry sky” appearance. × 20.

Fig. 15. Higher magnification shows uniform population of large neoplastic lymphocytes, invading capsule (right) but not extending into the surrounding tissue. × 160.

Fig. 16. Pancreatic lymph nodes from same animal, killed 8 days after surgery. The nodes are almost entirely replaced by fibrous connective tissue; only a few subcapsular foci of lymphoid cells remain. × 20. This animal also had a fibrotic spleen and thymic tumor.

Fig. 17. Higher magnification of larger node from Fig. 16. × 160.

Fig. 18. Cervical lymph node removed at autopsy from GP mouse killed at 22 days of age. This animal received 2 × 10⁶ cells i.p. from the lymph node shown in Fig. 14, when less than 24 hr old. "Starry sky” lymphocytic cancer has obliterated normal architecture and invaded extracapsular connective tissue. Massive lymphoma deposits were observed in the liver, spleen, and kidneys and s.c. at the site of injection. × 20.

Fig. 19. Higher magnification shows lymphoma extending from node (left) to extracapsular tissues (right). × 160.
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