Histogenesis of Thymic Lymphoma Induced by a Murine Leukemia Virus (Rich) *

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SUMMARY

Following inoculation of a newly isolated murine leukemia virus (Rich), lymphoma evolved in the thymuses of BALB/c mice. Tumor evolution occurred unilaterally in only one of the two paired thymus glands. Unilateral thymic lymphocyte depletion and unilateral thymic lymphoma in situ preceded the appearance of the unilateral lymphoma. Most cells of one thymus, but no cells of the opposite thymus, evolved into tumor, suggesting that the leukemogenic effect of the virus on the thymic cells was indirect.

The period of tumor evolution and early dissemination was unmarked by apparent illness. In this system the development of anemia and the presence of tumor cells in the peripheral blood stream, lymph nodes, and bone marrow are very late manifestations of the lymphoma.

In a recent study of the pathogenesis of AKR lymphoma the evolution of the tumor was related to the anatomy of the thymuses (12, 13). It was noted that the left and right thymus glands (in mice) are paired bilateral structures and, further, that when lymphoma developed in these mice it almost always evolved in only one thymus. The significance of the tumor's evolving in only one of two paired glands when both are exposed to the same leukemogenic viral influence was discussed.

Quantitative data for the occurrence of unilateral lymphoma in other murine leukemia systems (viral, x-ray, and chemical) are not yet available. Recently, a potent murine leukemia virus was isolated in our laboratory which induces lymphoid leukemia in high incidence after a short latency (7). To determine whether this virus-induced lymphoma also arose in only one thymus, similar to the unilateral evolution of tumor in the AKR mice, the following pathogenesis study was conducted.

MATERIALS AND METHODS

Virus.—The characteristics of the newly isolated murine leukemia virus used in this study have recently been presented (7). The agent consists of 80- to 90-mu particles with double limiting membranes comparable in size and morphology to other murine leukemogenic viruses. Phagelike tailed particles have been observed in electron micrographs of blood concentrates (8). Serial passage in 4- to 6-week-old BALB/c mice yielded a lymphoma incidence of 80–100 per cent with a latency of 50–70 days. The resulting lymphoma is a rapidly proliferating undifferentiated "stem-cell" lymphoid tumor, histologically indistinguishable from the other murine lymphomas (Figs. 17, 19, 20, 26). The early splenic erythroblastic response which occurs after infection with the Friend and Rauscher viruses does not occur in the disease induced by this agent.

Mice.—Inbred weanling BALB/c mice were obtained from the Jackson Memorial Laboratory, Bar Harbor, Maine. The response of these animals to the virus was identical to that of BALB/c mice bred in our own colony from a nucleus kindly supplied by Dr. H. Andervont, of the National Cancer Institute, National Institutes of Health.

Preparation of the virus.—The spleen, lymph nodes, and mediastinal mass from leukemic Swiss mice previously given inoculations of passage virus were harvested, and a 20 per cent homogenate was prepared in normal saline. The homogenate was centrifuged at 4° C. and the cell-free supernatant used as virus stock. It had been established in earlier filtration experiments that the centrifugate prepared under these conditions (750 X g for 30 minutes) was indeed cell-free and was capable of transmitting the disease (7).

Inoculation.—155 female 4- to 6-week-old BALB/c mice were given inoculations intraperitoneally of 0.2 ml. of the virus stock; 51 uninoculated mice from the same lot served as controls.

Protocol.—At regular intervals beginning the day after inoculation (usually 2–3 times weekly) six infected and two control mice selected at random were bled through
the retro-orbital plexus to provide specimens for examination of the peripheral blood. These animals were then sacrificed with ether, weighed, and dissected. All remaining animals were individually inspected 3 times weekly for palpable nodes or other signs of illness. The left thymus, right thymus, axillary nodes, and spleen were weighed on paper tares; touch impressions of the spleen were prepared before fixation with the other vital organs. The tissues were fixed for 12–24 hours in a solution consisting of 750 ml. 90 per cent ethanol, 75 ml. 40 per cent formaldehyde, and 37 ml. glacial acetic acid. The sternum was decalcified by continuous agitation in a solution consisting of equal parts of 50 per cent formic acid and 20 per cent sodium citrate for 48 hours, following which procedure it was processed with the other tissues. After fixation the tissues were dehydrated in graded alcohols and cleared overnight in cedarwood oil. They were then rinsed in xylene and embedded in Paraplast®. Step semi-serial sections were cut at 4 μ and stained with a hematoxylin-eosin preparation supplemented in selected cases with a periodic acid-Schiff stain. Touch impressions of the spleen and smears of the peripheral blood were stained with Wright’s stain.

RESULTS

GENERAL

Following inoculation the infected animals showed no changes until the 20th day. Until this time their general appearance, weight, peripheral blood values, and autopsy findings were identical with those for control mice. From the 20th day until the first sporadic appearance of tumor on day 48 there was a gradual reduction in size and weight of both thymuses, subtle alterations in the histology of the thymuses and spleen, and a tendency toward a reduction in the size of the peripheral lymph nodes. After the 50–55th day, most of the thymuses showed marked alterations in size and histology, and many contained early lymphoma. All animals were individually inspected thrice weekly, but none showed clinical signs of illness such as roughened fur, decreased activity, or weight loss until the lymphoma was very far advanced. Animals in which the tumor was still limited to the thymuses were indistinguishable from control animals by general appearance, behavior, and studies of the peripheral blood. Only after dissemination of tumor cells from the thymuses and subsequent extensive growth in the spleen, liver, and lymph nodes occurred did indications of anemia (pallor of eyes), mediastinal mass (superior vena cava syndrome), weight loss, and lethargy develop. The inguinal lymph nodes became palpable only when the tumor was far advanced and represented a very late manifestation of the disease.

Early post-inoculation changes in the thymuses.—The left and right thymuses of both the control and the infected animals lost weight during the period of observation. Whereas the controls did so gradually (senescent involution or atrophy), those of the virus-inoculated mice did so more rapidly, beginning about the 20th day.

The early histologic changes in the thymuses of the virus-infected mice were distinct and reflected the observed weight loss and moderate reduction in size. Partial loss of stored cortical lymphocytes occurred bilaterally in infected mice. This was evidenced by the decrease in width of the cortices and the decrease in the density of stored cortical lymphocytes. In some instances large numbers of thymic lymphocytes could be observed within the intrathymic venules which open to the systemic circulation.

Those lymphocytes remaining in the thymuses after early bilateral lymphocyte depletion tended to be larger, had increased cytoplasm-nucleus ratios, less dense nuclear basophilic staining, and an increased number of mitoses. These cells resembled the medium and large lymphocytes described by St. Marie and Leblond (10). As the small lymphocytes left the thymuses those organs shrank in size, and the remaining cells tended to draw together. This drawing-together increased the relative concentration of large lymphocytes, many of which showed mitotic activity. The apparent increase in numbers of large lymphocytes with frequent mitoses simulated hyperplasia.

Hassall's corpuscles.—The Hassall's corpuscles and the intrathymic portions of the pharyngo-thymic duct remnants with which they are associated showed histological alterations not observed in the control thymuses. These changes, while difficult to quantitate, occurred between 20 and 50 days and were usually found in both the right and left thymuses in equal degree.

After day 20, the Hassall's bodies were increased in size but fewer in number, and were lined by thin, flattened nonkeratinizing epithelial cells. They were often filled with large numbers of partially autolyzed cells and cell debris (Figs. 1–3). Many contained lymphocytes and lipochrome-containing epithelial cells ("PAS" cells). Many of these large "ripe" corpuscles had ruptured, spilling partially autolyzed debris (Figs. 2, 3). Often such ruptured corpuscles were surrounded by proliferating multinucleated epithelial cells which resembled foreign-body giant cells (Figs. 4, 5). There were very few small Hassall's corpuscles present (one- to five-cell stage) compared with those in the controls, suggesting that new corpuscles were not being formed at the normal rate.

The intrathymic portions of the old pharyngo-thymic duct system, representing the original pharyngeal diverticula from which the two thymuses develop, were lined by ciliated epithelium. In many virus-inoculated animals they were bilaterally distended with unstained fluid and contained large numbers of lymphocytes and lipochrome-laden epithelial cells ("PAS" cells).

LATE PRELEUKEMIC THYMIC CHANGES

From day 50 through day 83, when the last group of mice were sacrificed, four categories of thymic morphology could be distinguished in the 67 virus-inoculated mice sacrificed in this period: (a) moderate bilateral senescent involution (no change from control animals), (b) marked unilateral lymphocyte depletion, (c) early lymphoma in situ, and (d) overt lymphoma.

Group 1: Moderate bilateral senescent lymphocyte depletion (no change from control animals).—The majority of these animals were those killed earlier in this time
period between days 50 and 60 and showed only moderate loss of small cortical lymphocytes and an apparent increase in the number of remaining large hyperplastic-like lymphocytes. Twenty-nine of the 67 virus-inoculated mice killed between days 50 and 85 were classified in this group.

**Group 2: Unilateral lymphocyte depletion.**—Those mice in which one thymus showed more than a 30 per cent weight loss compared with the other thymus, had histologic evidence of unilateral lymphocyte depletion, and no evidence of lymphoma or lymphoma in situ were classified in this group. Eight virus-inoculated mice but no control mice showed this change.

Table 1 lists the weights of the right and left thymuses in these eight mice showing unilateral lymphocyte depletion. In five the left was the smaller organ, whereas in three the right was smaller. The unilateral per cent loss in weight (per cent difference) is listed and may be compared with the values obtained for the two control animals killed on the same day.

Figures 6–9 illustrate the histology of characteristic examples. In Figure 6 the affected right thymus weighed 8 mg. compared with the more normal-sized left thymus, which weighed 17 mg. (Fig. 7). The histologic lymphocyte depletion and contracture of the epithelial reticulum may be observed in the small right thymus (Fig. 8), whereas normal architectural structure is preserved in the larger left thymus (Fig. 9). Hemorrhage into perivascular lymphatic spaces, although a prominent feature in preleukemia AKR thymuses (11–13), was only rarely observed in this study.

**Group 3: Lymphoma in situ.**—To describe those depleted thymuses in which the histologic changes suggested lymphoma but did not yet fulfill all the usual criteria for malignancy, the term “lymphoma in situ” was adopted. We have used this term in the same sense as Kaplan’s term “lymphosarcoma in situ” (5), to suggest a coming-into-being of the tumor cells. Six of the mice killed between days 50 and 83 had unilateral thymic changes classified as lymphoma in situ. In these thymuses the normal architecture was replaced by sheets of large, uniform cells with vesicular, basophilic nuclei which had one or several prominent nucleoli. Mitoses were frequent, and multinucleated giant cells possibly of epithelial origin were common. The histologic appearance of the sheets of large, uniform cells was similar to that seen in lymphoma cells. In these early cases, however, the tumor had not yet expanded the affected thymus, and that organ was still relatively small. Table 2 shows the weights of the pair of thymuses where unilateral lymphoma in situ was diagnosed microscopically. In four cases the left thymus was affected, and in two cases the right thymus was involved. The magnitude of weight loss between the normal large thymus and the small thymus showing lymphoma in situ is similar to the weight loss observed in specimens showing unilateral lymphocyte depletion.

Figures 10–15 compare the differences in histology in a typical specimen between the normal-sized right thymus, weighing 17 mg., and the affected left thymus, showing lymphoma in situ weighing 7 mg. The loss of archi-

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**Table 1**

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<th>Sacrificed on Day:</th>
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Mean per cent difference: 53.1
Standard deviation: ±15.7

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**Table 2**

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Mean per cent difference: 37.7
Standard deviation: 21.8

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tectural form is visible in the left thymus under low power. Figures 12, and 13 compare the cortical lymphocyte density of the normal and affected organ, and in Figures 14 and 15 the cellular changes may be observed. The increase in mitoses, increase in cell size, and loss of architectural markings in the affected organ are visible in Figure 15. In each instance lymphoma in situ was observed only in one of the two thymuses. In five of the six cases the lymphoma in situ was present in the smaller of the two thymuses.

Group 4: Overt lymphoma.—The diagnosis of thymic lymphoma was made only when, in addition to the usual cytologic criteria for “malignancy” (i.e., increased cell size, increased nuclear staining, increased mitoses, and architectural disorganization), the tumor cells had actually proliferated to the extent that the tumor-bearing organ was significantly larger than the normal organ. Thus, this class represents only lymphomas actually proliferating, distinct from the lymphoma in situ changes in Group 3. Cases where dissemination to the other organs occurred (spleen, liver, and peripheral nodes) are described below. Fourteen cases of proliferating lymphoma still limited to the thymuses were obtained from the 67 virus-inoculated mice killed after day 50. In three cases tumor was present in the right thymus only, and in nine cases tumor was present in the left thymus only. In two cases tumor was present in both the left and the right thymus. In these two instances the left thymus was twice the size of the right thymus, suggesting that tumor may have originated in the left organ and recently invaded the right thymus. Twelve of the fourteen cases (85 per cent), therefore, showed unilateral lymphoma.

Figure 18 shows the characteristic grossly visible changes in these mice. One thymus, either right or left, was normal or somewhat small in size, whereas the other thymus was enlarged 3–5 times. Figures 16 and 17 illustrate the unilateral lymphoma present in only one of the two paired thymus glands. In Figure 16, the normal right thymus, while partially depleted (11 mg.), was free of tumor cells and had a normal cortico-medullary structure. Figure 17 illustrates the left thymus of this animal which weighed 53 mg. This thymus was filled and distended by tumor cells which have expanded the existing connective tissue framework. Although the structure grossly resembled a thymus in external configuration, color, location, and consistency, histologically it consisted only of tumor cells.

Leukemic Changes

Tumor was present in organs other than the thymuses only when it was already present in at least one thymus. The thymuses.—In those thymuses in which lymphoma was present, very little of the original structure remained. In most instances while the tumor mass grossly had the configuration of an enormously enlarged thymus, histologically it consisted only of lymphoma cells, blood vessels, and some connective tissue fascia. In the larger, tumor-filled thymuses, tumor cells were present outside the capsule of the affected organ. (In pilot studies, where the left and right thymuses were not separated, direct invasion of tumor across the interthymic connective tissue fascia was observed.)

The size of the tumor-filled thymuses varied greatly. Generalized lymphoma was occasionally noted in mice with normal-sized thymuses. These thymuses, however, histologically were completely replaced with tumor cells. Particularly in the older mice used for passage of the agent, tumor cells disseminated while the tumor-laden thymuses were still small. In these cases, even though the thymuses were filled with tumor they did not enlarge.

Spleen.—Spleenic tumor was present only after at least one thymus was filled with tumor. The earliest recognizable tumor in the spleen was in the lymphoid follicles and not in the red pulp. Tumor cell growth in the spleen produced marked enlargement of that organ. In these enlarged spleens free tumor cells could be identified in the intrasplenic branches of the splenic vein, which opens to the portal vein. Figure 20 illustrates the appearance of the tumor cells in a touch impression of a tumor-infiltrated spleen.

Liver.—Tumor was present in the liver only when extensive tumor was also present in the spleen. In each case where tumor was present in the liver, individual tumor cells were present in the intrasplenic branches of the splenic vein. The tumor cells in the liver were usually located in the connective tissue sheaths about the intrahepatic branches of the portal vein, although numerous small clusters of five to ten tumor cells were scattered in the blood sinusoids.

Lymph nodes.—Tumor cells were present in the peripheral nodes only after extensive tumor was present in the spleen and liver. The cells were located almost exclusively in the sheathing about the blood venules which normally are occupied by lymphocytes and reticular cells. No tumor cells were observed in the peripheral lymphatic sinuses even when the tumor in the perivenule cuffs had greatly enlarged the node. The supracecal (mesenteric) lymph node aggregate was often markedly enlarged.

Peripheral blood.—Those animals with extensive tumor in the thymuses, spleen, liver, and lymph nodes showed alterations in the peripheral blood. The white counts increased from a normal range of 7–10,000 cells per cu.mm. to levels of 50,000 or higher. The majority of these cells were similar to the tumor cells observed histologically in the tissues. The remainder of the circulating white cells were polymorphonuclear leukocytes. Circulating lymphocytes were extremely rare and were never in excess of 3–5 per cent of the differential count. Figure 19 illustrates characteristic tumor (lymphoma) cells in the peripheral blood of an animal with tumor-infiltrated tissues. In the preleukemic period, or at the time when tumor was limited to one thymus, no abnormality of the circulating white cells was observed.

Bone marrow.—The sternal marrow in control animals was visible as a series of dark red oblong dashes, corresponding to the segmentation of the sternum. In animals with generalized lymphoma the red dashes were no longer visible. Histologically, the sternal marrow of all animals except those with generalized lymphoma was normal. Only when tumor was present in the spleen, liver, and lymph nodes was it noted in the sternal marrow. Figures
21 and 22 illustrate a low- and high-power view of a sternal segment from a control mouse. Figures 23 and 24 show a comparable sternal segment from a virus-infected mouse in which tumor change has already occurred in one thymus (Fig. 18). Note that the sternal marrow shows no changes from the control sternum. In Figures 25 and 26 a comparable sternal segment is illustrated from an animal with disseminated lymphoma, showing the replacement of the marrow by tumor cells. In some instances direct penetration of the sternal marrow by tumor cells from the mediastinal mass was present (Fig. 25, arrow).

**DISCUSSION**

Following inoculation with the viral agent used in this study, a disease resulted which was indistinguishable from lymphatic leukemia. The evolution of the leukemia occurred in a regular, sequential process. The first change observed was a unilateral loss of the stored lymphocytes from one thymus. This was followed by a coming-together or contracture of the epithelial cells in that thymus. An evolution of tumor cells then occurred in the small, contracted thymus, while the opposite thymus remained normal. Once formed, the tumor cells gained access to the systemic circulation and selectively localized in the spleen and later in the lymph nodes. Further dissemination to other organs and the accumulation of tumor cells in the blood stream occurred shortly before death. The process, once initiated in one thymus, terminated in a massive dissemination of tumor cells which were found in almost every organ of the body.

The alterations in the thymuses which preceded the appearance of lymphoma in this study suggest a pattern of sequence in the evolution of tumor. This suggested sequence is represented in Chart 1. Such a sequence, although difficult to reconstruct from random sections through the paired thymuses, is more apparent when the two thymuses are separately examined. This pattern of

![Chart 1](chart.png)

**Chart 1.**—Evolution of lymphoma following inoculation with a murine leukemia virus (Rich). Shortly after inoculation the two thymuses lose some lymphocytes (B). In the immediate preleukemic period one thymus loses all remaining lymphocytes and becomes small (C). The epithelial cells of that thymus then lie close to one another and appear to transform to lymphoma cells (D). The lymphoma cells proliferate and enlarge that thymus (E). The opposite, normal thymus is locally invaded by tumor cells (F) which disseminate to the spleen (G) and lymph nodes (H).
unilateral preleukemic lymphocyte depletion and unilateral tumor change was also observed in the evolution of AKR thymic lymphoma, described previously (13).

In this study fourteen specimens were obtained where tumor was still confined to the thymuses. In twelve of these the tumor was present in only one thymus. In the two cases, where tumor was present bilaterally, the difference in size between the two tumor-filled thymuses also suggested a unilateral origin. In addition to the fourteen cases of overt thymic lymphoma, six cases of lymphoma in situ were obtained, all of which were unilateral. Thus, of the twenty cases (thymic lymphoma and lymphoma in situ) eighteen cases (90 per cent) showed a unilateral tumor evolution. The data in the present study agree with those of the previous study in AKR mice, where a unilateral origin of the lymphoma could be demonstrated in 95 per cent of the cases.

The phenomenon of unilateral thymic lymphoma is not limited to the two lymphoma systems (AKR and Rich agent) already reported. In a recent pathogenesis study of the Friend and Rauscher diseases we have distinguished two completely separate host responses: an early splenic reticulum-cell hyperplasia with erythroblastosis and a late thymic lymphoma. In all cases observed the thymic lymphoma in these diseases arose unilaterally, in a manner similar to that in the AKR and Rich lymphoma studies. Data for the incidence of unilateral lymphoma following x-rays or carcinogens in mice are not available from existing pathogenesis studies, because these works have treated the two thymuses as a single organ. Consideration of the data of Arnesen for AKR mice (1), Dunn et al. for Moloney virus lymphoma (3), Kaplan for x-ray-induced lymphoma (4), and Rappaport and Baroni for carcinogen-induced lymphoma (6) suggests that unilateral tumor evolution does indeed occur in those systems. Studies now in progress in our laboratory will specifically determine whether the x-ray and carcinogen-induced lymphomas also evolve unilaterally.

The consistent evolution of lymphoma in only one of the two thymuses in the viral lymphomas studied is of great interest. Since the viral agent is presumably distributed to both thymuses but tumor evolves in only one, it suggests that the leukemogenic effect of the virus on the thymic cells may be indirect. If the viral agent directly affected individual thymic cells, then bilateral tumor change would be expected to occur in a considerable number of mice. Further, if the viral effect were directly on individual thymic cells then one might expect to find small foci of lymphoma in an otherwise normal thymus. This was not observed in these studies. Our histologic observations on the very early unilateral lymphoma-in situ (Figs. 10–15) suggested that the tumor change occurred in many cells of that thymus at the same time. Thus, many cells of one thymus appeared to be changing to tumor, whereas no cells of the other thymus were so affected. This apparent transformation of the cells of one thymus but none of the cells in the opposite thymus suggests that the leukemogenic effect of the virus may be an indirect effect, involving host mechanisms still to be elucidated.

In this study we have illustrated the unilateral loss of lymphocytes from one of the two thymuses in the preleukemic period. The cells remaining in the lymphocyte-depleted organ (epithelial reticulum and some mesenchymal cells) draw together as the organ shrinks in size (Fig. 6). The earliest evidence of tumor change always occurred in the small, depleted thymuses (Fig. 15). Since these cells were morphologically similar to lymphoma cells but could not yet definitely be identified as such, they have been designated "lymphoma in situ." The finding of lymphoma in situ involving large numbers of thymic epithelial cells suggests that the thymic lymphocytes are probably not involved in leukemogenesis. We, like Rappaport and Baroni (6), were unable to find any instance where the large lymphocytes of the subcortical zones seemed to change to tumor cells. Although it is not possible to establish the matter by morphologic means alone, it was our impression that the tumor cells evolved in the small, depleted thymuses from the sheets of epithelial reticulum cells which had drawn together after the lymphocytes had been discharged. Most of the cells remaining after lymphocyte depletion are epithelial cells. The possibility suggests itself, therefore, that the "lymphoma" cells arise directly from the thymic epithelial cells. This possibility was considered by Arnesen (1) and if true would represent the neoplastic analogy to the suggested normal evolution of lymphocytes from epithelial cells in the thymuses, described most recently by Auerbach (2).

The epithelial cells of the thymuses form the Hassall's corpuscles by what has been suggested to be a regular cyclic dynamic mechanism (11). The function of these epithelial structures, which are located only in the thymuses, is not known. On the basis of their morphologic attributes it has been suggested that some type of digestion of cells may regularly occur in the central cavity of the larger corpuscles (11). Alterations in these structures in the preleukemic period in this study consisted of an increased amount of cell debris in the central cavities (Figs. 2, 3) and a decrease in the numbers of newly formed, small, Hassall's bodies. Some of the granulomatous changes associated with the ruptured Hassall's corpuscles were reminiscent of the virus-induced thymic changes described by Rowe and Capps (9).

The size of the tumor-filled thymuses varied widely. In a few cases, even though the thymuses were completely replaced with tumor and dissemination had already occurred, the thymuses were not enlarged in size, and grossly appeared normal. Histologically, however, they were completely replaced by tumor cells. Perhaps the small size of the primary thymic tumor mass reflected a rapid rate of release of tumor cells into the systemic circulation, in a manner analogous to the depletion of normal lymphocytes from the thymuses (11).

ACKNOWLEDGMENTS

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1 R. Siegler and M. A. Rich, Comparative Pathogenesis of Viral Lymphomas. Submitted for publication.
REFERENCES


Fig. 1.—Low-power orientation view of a right thymus 23 days after virus inoculation. Three prominent, enlarged Hassall’s corpuscles (arrows) are present. H. & E. stain, X100.

Fig. 2.—High-power view of one enlarged Hassall’s corpuscle from Figure 1. Note early rupture of the corpuscle (between arrows) and (eosinophilic) cell debris in central cavity. X440.

Fig. 3.—Another enlarged Hassall’s body from Figure 1, showing nuclear fragments, amorphous debris in the central cavity, and early rupture. X440.

Fig. 4.—Foreign-body, giant-cell reaction at site of rupture of a Hassall’s body. Day 23, virus-infected mouse. X440.

Fig. 5.—Another foreign-body giant cell near ruptured Hassall’s corpuscle. X440.
Figs. 6-9.—Unilateral lymphocyte depletion, 63 days post-inoculation.

Fig. 6.—The right thymus is half the size and weight of the left organ. In the right thymus the cortex has been emptied of its stored lymphocytes, and the epithelial reticulum cells remaining have drawn together (contracture). Compare with essentially normal architecture in the left thymus (Fig. 7). H.&E. stain, X40.

Fig. 7.—Left thymus, shows no change from normal controls. X40.

Fig. 8.—High-power view of Figure 6, to illustrate the cytology of the epithelial cells which have drawn together following depletion of lymphocytes. Note the close resemblance to the epithelial cells in Figure 15, which already show many mitoses. X440.

Fig. 9.—High-power view of Figure 7, showing normal numbers of small lymphocytes and an occasional dispersed epithelial cell (arrow). X440.
Figs. 10-15.—Unilateral lymphoma *in situ*, 63 days post-inoculation.

Fig. 10.—Right thymus, weighing 17 mg. is essentially normal. H.&E. stain, ×40.

Fig. 11.—Left thymus, unilaterally depleted of lymphocytes (7 mg.).

Fig. 12.—Medium-power view of right (normal) thymus to show normal cortical storage of lymphocytes. Lymphocyte-free lighter-stained central area is small branch of medulla. ×100.

Fig. 13.—Medium-power view of left thymus, to show loss of cortical lymphocytes. ×100.

Fig. 14.—High-power view of right (normal) thymus to show normal numbers of lymphocytes. The epithelial cells, although not visible in this photograph, are widely scattered as single cells. ×440.

Fig. 15.—High-power view of left thymus to show close approximation of epithelial cells, many of which have enlarged nuclei, increased mitotic activity and cytologic similarity with lymphoma cells (compare with Figure 17). ×440.
Figs. 16-18.—Unilateral lymphoma, 64 days post-inoculation.

Fig. 16.—High-power view of right (normal) thymus to show normal appearance of stored cortical lymphocytes. ×440.

Fig. 17.—High-power view of left thymus to show dense sheets of tumor cells. ×440.

Fig. 18.—Unilateral lymphoma. The enlarged thymus is filled with tumor cells which have expanded the organ. The right thymus (rectangle) is normal in size for the age and has a normal histologic appearance. 82 days post-inoculation. ×5.

Figs. 19, 20.—Disseminated lymphoma.

Fig. 19.—Peripheral blood smear from animal with disseminated lymphoma, to illustrate appearance of tumor cells. Wright’s stain, ×2000.

Fig. 20.—Wet touch impression of tumor-infiltrated spleen. Three large tumor cells with pale-stained nuclei are present (arrows). Note the small, clear vacuole in the nucleus of each tumor cell. Wright’s stain, ×2000.
Figs. 21-26.—Late involvement of bone marrow.

Fig. 21.—Segment of sternal marrow, to show normal venous channels and cellularity. Control mouse. H. & E. stain, X40.

Fig. 22.—High-power view from Figure 21, to show normal cellular composition of control marrow. X440.

Fig. 23.—Sternal segment of animal which had advanced lymphoma in one thymus (see Figure 18). Note no change from control mouse (Figs. 21, 22).

Fig. 24.—High-power view of Figure 23, to show normal cellular composition. X440.

Fig. 25.—Segment of sternum of mouse with disseminated lymphoma. Tumor cells now fill the marrow and also are present in the retrosternal (mediastinal) connective tissue (arrow). X40.

Fig. 26.—High-power view of tumor-replaced marrow from Figure 25. X440.
Histogenesis of Thymic Lymphoma Induced by a Murine Leukemia Virus (Rich)


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