Lymphoid Hyperplasia and Neoplasia Associated with a Mouse Pituitary Thyrotropic Tumor*

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SUMMARY

A transplanted autonomous responsive thyrotropic pituitary tumor, designated L24a, developed in an intact LAF1 female mouse 13 months after inoculation of the L24 tumor. The latter is an autonomous thyroid-stimulating mouse pituitary tumor initiated by radiothyroidectomy and serially carried intramuscularly in the LAF1 strain. Subsequent transplants of subline L24a were accompanied by hyperplasia and neoplasia of the reticuloendothelial system and by evidence of somatotropic hyperactivity. The greatest lymphoid-stimulatory effect appeared in radiothyroidectomized mice bearing the L24a tumor. Somatotropic effect was more apparent when the thyroid was intact. The control mice did not develop tissue lymphocytosis during this experiment. The factors which may have contributed to lymphoid stimulation were considered to be a high blood level of TSH, absence of the thyroid gland, the effects of I-131 on lymph nodes and thymus, and possible adrenal gland hypoactivity. Growth hormone and ovarian hyperactivity may also have played a role. Thyrotropin is perhaps of greatest significance.

In the course of hormonal studies with mouse pituitary thyrotropic tumors (24), lymphoid hyperplasia and a variety of lymphomas were observed in mice bearing one line of tumor. Some of the hosts also exhibited somatic gigantism and generalized organ enlargement. This report deals with the circumstances under which the reticuloendothelial system appeared to be affected by the transplanted tumors.

Thyrotropic pituitary tumors were first produced in mice by Gorbman (13) in 1949. Subsequent studies by Furth and his associates led to the development and isolation of a variety of hormonally active pituitary tumors (7, 8, 11). Although it is not established that only one cell type exists in individual growths, transplantable tumor strains have evolved displaying predominantly thyrotropic, adrenotropic, gonadotropic, or mammotrophic activity. The tumors are autonomous or dependent upon ablation of the target organ and show varying degrees of responsiveness to the corresponding hormone.

Somatotropic activity accompanies a variety of pituitary tumors. It has been noted in the complex tumor strains appearing with ionizing radiation (10) and associated with predominantly mammotrophic pituitary tumors in mouse (12) and rat (9). Growth-promoting effects, which Furth and associates attributed to thyroid gland stimulation, have also appeared in intact mice bearing some autonomous strains of thyrotropic tumor (11).

There has been an extensive body of literature recounting the influence of hormones on lymphoid tissues in animals (3). Experiments were conducted by endocrine organ ablation or hormone injection. However, no association of lymphoid hyperplasia and neoplasia with thyrotropic pituitary tumors has been described. Under certain circumstances Furth observed that pituitary tumors may be accompanied by splenomegaly with predominant myelopoiesis. In addition, two mice bearing splenic implants of thyrotropic tumors developed lymphomas at this site (6).
The present observation of lymphoid hyperplasia and neoplasia associated with a thyrotropic tumor gains interest from the early recognition of tissue lymphocytosis in Graves' disease emphasized by Marine (18).

**MATERIALS AND METHODS**

**Tumors.**—Three strains of mouse thyrotropic pituitary tumors have provided the data. They were originally made available by Dr. Jacob Furth and maintained by animal passage since 1958. Tumor 4183 was found to be dependent, and strain L23 grew autonomously and did not respond to thyroid hormone. Strain L24 has been intermediate and is characterized as autonomous, responsive. Cell implants from the responsive tumors survived prolonged suppression of growth with thyroid hormone (24).

Our interest lies mainly in a subline of L24 designated as L24a, which developed in an intact mouse approximately 13 months after such suppression. After this prolonged dormant period in an animal with thyroid secretion, the cells able to proliferate formed a tumor which was regularly accompanied by lymphoid hyperplasia or neoplasia. The mice bearing this tumor also showed a growth-stimulating effect, and large amounts of TSH were present in the blood serum of intact animals. At the time of these observations, the L24a tumor had been carried through two passages.

**Animals.**—All experiments were conducted with LAFj female mice obtained from Jackson Memorial Laboratory, Bar Harbor, Maine. At the time of tumor inoculation the mice were 4–6 weeks old. They were maintained with tap water and Hemlock Farm stock mouse diet.

**Grafting technic.**—Prior to radiothyroidectomy mice were given distilled water and Remington low iodine diet from Nutritional Biochemicals, Inc., containing 0.45 mg. per cent iodized salt, for at least 10 days. Thyroid ablation was then accomplished by the intraperitoneal injection of 50 μc. I131, and tumors were grafted after a 10-day interval. All animals were fed a stock diet throughout the period of tumor development.

Transplantation of tumors was accomplished with a fine, sterile mince in Eagle's solution injected intramuscularly into the right thigh through a #19 gauge needle.

**Thyrotropic hormone assay.**—The blood serum was tested for thyrotropic hormone (TSH) activity by the method of McKenzie (20), with the modification of double the amount of desiccated thyroid in the diet. Radioactivity in the test mice was measured in samples obtained at 2 and 9 hours after inoculation of experimental serum.

**Autopsy technic.**—Terminal body weights and measurements were recorded. The mice were sacrificed within 7–11 months. All organs were removed and dissected free of investing tissue before being weighed on a precision torsion balance. Special attention was paid to the thyroid site in radiothyroidectomized animals for evidence of regeneration of the gland. The pituitary glands were shelled from the sella turcica for weighing. Mice dying spontaneously were discarded, since autolysis precluded histologic study.

**Histologic technic.**—Thin slices of all organs were fixed in Zenker solution, obtained from the Auto-technicon Corporation, for 4–24 hours, depending on the size of the sample. The endocrine organs were wrapped in lens paper for processing. Washing was limited to three changes of water by decanting, and ethyl alcohol provided dehydration. An autotechnicon was used prior to embedding in paraffin.

The routine stain was hematoxylin-eosin. The Schiff reaction after periodic acid, Sudan IV fat stain, Masson trichrome stain or Wilder reticulum stain were applied to tumors, lymphoid tissues, and pituitary glands when of interest.

**Protocol of the experiment.**—The subline L24a tumor had been carried through two passages, with ten female mice used for the first graft, seven without thyroid glands and three normal. The second passage included twenty normal and twenty thyroid-ablated female mice. The other strains, 4183, L24, and L23 were being carried in vivo in the required manner at the same time.

The mice were organized into three groups. Those surviving for histologic study included:

- **Group A:** Three mice radiothyroidectomized and grafted with the original transplanted L24 tumor.
- **Group B:** Six mice radiothyroidectomized and grafted with the strain L24a tumor. When tumors were mature, three animals were sacrificed and studied. The remainder (Group B3) were fed thyroid hormone in the proportion of 0.12 gm/100 gm stock diet, given ad libitum, to observe the effect of suppression of TSH secretion on lymphoid development.
- **Group C:** Subline L24a tumor implanted in twelve intact mice. Some animals failed to develop tumors (Group C1), and served as a means of demonstrating that leukemia or lymphosarcoma from a previous host had not been inadvertently added to the tumor inoculum. They also provided controls for measurements, weights, and circulating hormone level in the absence of tumor.
Reversal of the tumor effects were attempted by excision of the growths in three mice of this group, two weeks prior to being sacrificed (Group C₂).

The pattern of growth and organ changes in radiothyroidectomized mice bearing the dependent tumor 4183 was studied as a control of the effects of radiation. The autonomous L23 tumor served as another thyrotropic control tumor since growth was maintained with thyroid gland intact. Reappeared, and a lesser degree of lymphoid hyperplasia was observed.

The second passage of L24a tumor is represented in the groups planned to demonstrate some of the relationships of significance.

Table 1 presents the data from tumor L24 and the second passage of subline L24a. The weights of mice and organs at the time of autopsy are given in detail with the results of terminal blood assay.

### Table 1

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group A (S) Thyroidect., tumor L24</th>
<th>Group B (6) Thyroidect., tumor L24a</th>
<th>Group C (18) Tumor L24a, intact mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B No thyroid</td>
<td>B₁ Thyroid fed last 8 months</td>
<td>C With tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C₁ No tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C2 Tumor excised 2 weeks</td>
</tr>
<tr>
<td>Body wt. (gm.)</td>
<td>28 ± 3</td>
<td>34 ± 4</td>
<td>46 ± 2</td>
</tr>
<tr>
<td>Length head (cm.)</td>
<td>3 ± 2</td>
<td>3 ± 0</td>
<td>3 ± 10</td>
</tr>
<tr>
<td>Length body (cm.)</td>
<td>10 ± 0</td>
<td>10 ± 0</td>
<td>11.7 ± 0.05</td>
</tr>
<tr>
<td>Spleen (mg.)</td>
<td>190 ± 97</td>
<td>692 ± 404</td>
<td>1005 ± 450</td>
</tr>
<tr>
<td>Thymus (mg.)</td>
<td>36 ± 2</td>
<td>40 ± 14</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>Liver (mg.)</td>
<td>1750 ± 242</td>
<td>1600 ± 510</td>
<td>4500 ± 65</td>
</tr>
<tr>
<td>Kidneys (mg.)</td>
<td>384 ± 30</td>
<td>392 ± 16</td>
<td>1017 ± 369</td>
</tr>
<tr>
<td>Lungs (mg.)</td>
<td>157 ± 14</td>
<td>101 ± 29</td>
<td>300 ± 58</td>
</tr>
<tr>
<td>Subm. gl. (mg.)</td>
<td>113 ± 4</td>
<td>105 ± 0</td>
<td>392 ± 43</td>
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<tr>
<td>Adrenals (mg.)</td>
<td>8 ± 1</td>
<td>9 ± 2</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Ovaries (mg.)</td>
<td>12 ± 1</td>
<td>15 ± 2</td>
<td>27 ± 4</td>
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<tr>
<td>Uterus (mg.)</td>
<td>125 ± 0</td>
<td>55 ± 5</td>
<td>35 ± 5</td>
</tr>
<tr>
<td>Thyroid (mg.)</td>
<td>4.2 ± 0.06</td>
<td>11 ± 1</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>Pituitary (mg.)</td>
<td>116 ± 2</td>
<td>116 ± 10</td>
<td>116 ± 10</td>
</tr>
<tr>
<td>Pancreas (mg.)</td>
<td>450 ± 50</td>
<td>392 ± 56</td>
<td>450 ± 50</td>
</tr>
<tr>
<td>Blood TSH units:</td>
<td>409 ± 103</td>
<td>420 ± 61</td>
<td>392 ± 43</td>
</tr>
<tr>
<td>2 hr.</td>
<td>586 ± 73</td>
<td>725 ± 107</td>
<td>392 ± 43</td>
</tr>
<tr>
<td>9 hr.</td>
<td>409 ± 103</td>
<td>420 ± 61</td>
<td>392 ± 43</td>
</tr>
</tbody>
</table>

*Age of tumors: A, B, C, C₁, 6 months; B₁, 8 months; C₂, 61 months.

**RESULTS**

In the first passage of the subline L24a tumor into ten mice, seven had been radiothyroidectomized and were sacrificed 4 months after tumor implantation. A large, retroperitoneal reticulum-cell sarcoma (Fig. 1) was found in one, a lymphosarcoma in another (Fig. 2), and two mice had large, cystic lymphosarcomas (Fig. 3) in the cervical regions. The remaining three mice did not have tumors but showed greatly enlarged spleens due to lymphoid-reticulum cell hyperplasia and numerous large lymphoid collections in lungs, liver, and kidneys. Histologic details are presented below. In the three mice with intact thyroid glands, no reticuloendothelial tumors appeared. Group A.—L24 tumor in radiothyroidectomized mice. There was no evidence of undue organ enlargement with the exception of the pituitary gland which regularly becomes hyperplastic when the thyroid gland is ablated. There was very high circulating TSH with a 2- and 9-hour response in the test mice.

Group B.—Subline L24a tumor in radiothyroidectomized mice. Organ weights were within expected limits with the exception of the lymphoid tissues. The spleen sizes varied greatly but were generally enlarged. Lymph nodes were not weighed because of the impossibility of dissecting all lymphoid collections. Large, partly cystic, lymphocytic tumors measuring 1–1.5 cm. in diameter appeared in the neck, and lymphoid hyperplasia was in evidence throughout the organized nodes and intraorgan lymphoid nodules. The histologic

Presented in part at the Annual Scientific Meeting of the American Association for Cancer Research, Atlantic City, 1962 (17).
character of the reticuloendothelial system is presented below. Blood TSH levels were greatly enhanced, especially at the 9-hour period in the test animal.

B1: When thyroid was fed to three mice of this group a somatotropic effect emerged, and the lymphoid hyperplasia regressed. The latter was reflected in the lowered spleen weight and absence of lymphoid tumors, although a lesser degree of tissue lymphocytosis remained. The increased weight of many internal organs supported the view that growth hormone-like activity was enhanced, although this was not reflected in body measurements and never reached the magnitude of organ size observed when the thyroid gland was active throughout the experiment. TSH blood levels were restored to normal by thyroid feeding.

Group C.—Subline L24a tumor in mice with intact thyroid gland. When tumors grew, the hosts became gigantic, with proportionate enlargement of head, body, and tail shown by body weight and measurements and by skeletal x-ray films (Fig. 4). The livers were approximately 3 times the normal size, owing to hyperplasia, as well as hypertrophy. Lymphoid enlargement was entirely due to benign proliferations and was less in evidence than that appearing in thyroidectomized mice. Intact thyroid glands were enlarged, commensurate with organ hypertrophy in general. Blood TSH remained at a low level.

C1: The intact mice in this group in which inoculated tumors failed to proliferate were entirely normal in all respects. There was no evidence of somatotropic effect. Leukemia, lymphoma, or lymphocytosis did not appear.

C2: When L24a tumors were removed from intact mice showing gigantism, there was partial reversal of the somatotropic effect and less lymphoid prominence. Since the number is small and the animals were sacrificed 2 weeks after surgical extirpation, the finding is not regarded as conclusive. The general level of secondary effects was still higher than that of mice bearing other thyrotropic tumors.

Histologic findings, lymphomas.—Growth of the tumors was characterized as neoplasms rather than hyperplasia when they were not confined to an organ site and showed complete lack of lymph node architectural features. Our classification of tumors agrees with that described by Dunn (4). Reticulum-cell sarcomas were composed mainly of cells 2-4 times the size of a lymphocyte, with variegated irregular, round, or curved nuclei (Fig. 5). Mitoses occurred irregularly, and necrosis was a prominent feature. Multinucleation was rare.

Lymphosarcomas presented a more uniform small cell collection without pattern. Mitoses were less numerous. When the tumors occurred in the neck, there was a tendency to become cystic, although necrosis was not a feature of the margin of cavities and they usually contained clear fluid (Fig. 6). The significance of the cavitation is not known. It has been noted previously in some cervical lymph nodes in older mice (4).

Lymphoid- reticul ar hyperplasias.—Since it is not possible to quantitate the lymphoid tissue in any organ, the designation of amount of hyperplasia as 1-4+ must remain subjective. The greatly enlarged spleens accompanying L24a tumor in thyroid-ablated mice established the 4+ category of lymphoid and reticulum-cell increase. The red pulp was almost entirely replaced by cells of this system, and myelopoiesis was obscured (Fig. 7). There was a striking diminution in the splenic lymphoid structure (1-2+) when thyroid was fed to mice in this group and thyrotropic blood levels were lowered.

When L24a tumor grew in intact mice which became gigantic, splenomegaly was less pronounced (2-3+), and both hematopoiesis and lymphoreticular hyperplasia were in evidence. The spleens did not appear significantly different histologically when the tumors had been excised 2 weeks prior to autopsy, although they were reduced in size.

Lymph node enlargement was not always generalized, and there were variable amounts of lymphoid nodules in organs. Masses composed equally of mature lymphocytes and of blast forms and reticulum cells were most pronounced in the neck and mediastinum in intact mice, as well as in those receiving 111I. As they encroached upon the trachea, lymphocytes formed solid aggregates invading the wall to the epithelial lining (Fig. 8). Retroperitoneal and axillary nodes were often several times enlarged. The architecture was obscured by crowding of cells but not obliterated, and the capsule remained intact with minimal infiltration of contiguous tissue.

Lymph nodular hyperplasia in internal organs was essentially confined to lungs, liver, and kidneys, appearing as circumscribed aggregates with mitoses and interpreted as local proliferation rather than infiltrates. In the lungs, peribronchial collars of lymphocytes, lymphoblasts, and reticulum cells dotted the sections (Fig. 9). In the kidneys, scattered nodules were found in cortex, medulla, and in peripelvic tissues (Fig. 10). Epithelial structures were not destroyed by lymphoid hyperplasias. In the liver, portal and periporal areas were almost exclusively the site of lymphoid aggregation (Fig. 11).

The size of the thymus did not parallel lymph
node enlargement. It remained distinct from the mediastinal lymphoid structures except in the mouse, where a mediastinal lymphosarcoma obliterated organ identity. The thymus showed its greatest proliferation in Group Chaving tumor growth in gigantic mice with circulating thyroxine. In these animals cortical medullary demarcations had disappeared, and cortical cells prevailed throughout, with occasional mitotic figures. This effect was still in evidence 2 weeks after tumors had been extirpated.

The bone marrow showed relatively little change in any of the groups. There was active hematopoiesis of myeloid and erythroid series, and only rarely was a lymphoid nodule encountered.

Somatotropic effects.—These were apparent histologically, as well as in gross weight and measurement of the intact animals of Group C bearing L24a tumor. The increment was still apparent, although lessened after excision of the tumors.

Liver cells were enlarged by 2-3 times the control size and were commonly multinucleate. Nuclei were large and vesicular with stainable glycogen. From one to four mitoses were recognized per high power field. The cytoplasm was greatly increased and was more basophilic and solid without fat vacuoles. Coarse basophilic granules indicated active protein synthesis, and there was abundant glycogen. These changes appeared throughout the lobule, which was structurally unaltered (Fig. 12).

In the kidneys, all parts of the nephron appeared enlarged, but individual cell increment was recognized with greater difficulty. Smooth muscle fibers appeared thickened where encountered in sections of all organs.

Endocrine organs.—The ovaries showed scattered nodules of lutein cells in all mice, with numerous ripening follicles. In Group C, having somatotropic enhancement, the enlarged ovaries were dominated by closely packed corpora lutea (Fig. 13). This was also true to a lesser degree in the mice bearing L24a tumor, which were fed desiccated thyroid for 2 months. These findings are in accord with those associated with other autonomous thyrotropic tumors (6), but there may also be a relationship to somatotropic activity. Adrenal gland increase in size and weight also paralleled growth-stimulating effects. Medullary tissue came to occupy half the diameter of the gland and cells were 2-3 times enlarged. The intermediate or reticular cortical zone was proportionately increased in width and size of cells, which often appeared partially vacuolated and had some pyknotic nuclei (Fig. 14). The thyroid glands in mice bearing L24a tumor had uniform follicles of average size, filled with deeply stained colloid and lined by epithelial cells approximately half again as high as in the control mice. Lymphoid follicles were not observed. Since the greatest hyperplasia of lymphoid tissues occurred in thyroidectomized mice, it was not possible to establish whether this organ would share in the general increase in tissue lymphocytes.

The pituitary glands varied according to the presence or absence of the thyroid. When thyroidectomy had been accomplished, the enlarged pituitaries were chiefly occupied by swollen, pale degranulated chromophobe cells which failed to give the periodic acid-Schiff (P.A.S.) reaction characteristic of thyrotrrophs (Fig. 15). The glands of animals bearing L24a tumor with intact thyroid did not differ significantly from those without tumors. Deeply stained basophils were prominent. No adenomas appeared.

The parathyroid glands were not regularly studied.

Accessory sex organs.—There was evidence of muscle hypertrophy in thickened walls of the uterus in mice with ovaries which contained numerous corpora lutea. The mammary ducts and acini were not hypertrophied in association with the L24 or L24a tumors under any circumstances.

Thyrotropic tumors.—The L24 tumor and its subline L24a differed only mildly in histologic appearance. At the time of autopsy in the above studies the tumors were, in general, well preserved, with the most extensive scattered areas of necrosis appearing in the new line having greater autonomy. The tumors were composed of relatively uniform rounded cells, usually arranged in compact fashion or in cords (Fig. 16). Uncommonly, there was ring formation without accumulated secretion. Reticulum was delicate, and fibrosis was never a feature. The tumors were highly vascular, and necrosis was accompanied by excessive hemorrhage.

The L24a tumor growing in intact mice did differ somewhat in cell type but not sufficiently to permit recognition from histologic appearance alone. A general feature was enlargement of tumor cells as compared with those not associated with gigantism (Fig. 17). The cytoplasm tended to be more eosinophilic with hematoxylin-eosin stain, but acidophilic granules were not recognized. The cells were also P.A.S.-negative or only faintly stained.

Other thyrotropic tumor lines being carried concurrently.—The dependent 4183 tumor, growing in radiothyroidectomized hosts, was not accompanied by lymphoid prominence or gigantism, indicating that radiation of this magnitude alone did not play a role in either phenomenon.

The autonomous L23 tumor was being carried...
in intact mice. These animals also failed to show somatotropic effect, and the reticuloendothelial system was not hyperplastic. The findings in this regard remain an uncommon event associated uniquely with the subline L24a of this report. The functional capacity of the L24a tumor cell or cells responsible for these body changes is thus a matter of speculation.

DISCUSSION

The possibility that contaminant lymphoma-producing virus or leukemic cells caused the changes described was considered. The L24a tumor appeared in a mouse over a year old, when leukemia is more prevalent. However, leukemia or lymphosarcoma never appeared in animals grafted unsuccessfully with this pituitary tumor, although the inoculum would be expected to carry hypothetical virus or cells. Subcutaneous or intramuscular injection of mouse lymphoma cells ordinarily results in a local tumor, as well as disseminated disease, but in these experiments lymphoma did not appear at the site of tumor graft. Another factor pointing against viral contamination is the lesser degree of tissue lymphocytosis when developing tumors had been excised.

Radiation has also been recognized as lymphomagenic for many years (9). However, radiation alone was not responsible for induction of lymphomas in the present studies, since stimulation appeared in intact mice, as well as in those receiving 50 μc of I131. This amount of isotope has been given to LAFi mice bearing another thyrotropic tumor (4183) without the appearance of similar lymphoid enlargement.

The thyrotropic tumor subline could have augmented a genetic tendency to develop lymphomas. LAFi mice are known to have a low spontaneous occurrence of leukemia, almost never in the first year of life. Our experiments were conducted on mice younger than the age at which leukemia is usually manifest, and the tumors were of variegated pattern. It is probable that hormonal imbalance provided by the L24a thyrotropic tumor at least contributed to the pathogenesis of lymphoid proliferations.

Our attention is accordingly directed to the possible role of three hormones, thyroxine, somatotropin, and thyrotropin.

The activity of the thyroid gland cannot be evoked as an etiologic factor in the development of lymphomas in these experiments. In all instances lymphoid hyperplasia was most striking in the absence of the thyroid gland, and sarcomas appeared only in thyroidectomized mice.

Previous investigators believed that hyperthyroidism influenced the reticuloendothelial system either directly or indirectly. Marine postulated that the lymphoid hyperplasia in Graves' disease was due to low adrenal and gonadal function with thyrotoxicosis. Hypersecretion of thyroid tissue alone was thought to be insufficient (18, 19). Boyd found hyperthyroidism the only human disease other than leukemia in which true hyperplasia of thymic lymphoid tissue developed independent of body weight (1). Adrenocortical or gonadal hormones were thought to exert only modulating influence. Proliferation of lymphocytes is not initiated by their absence.

The influence of thyroxine has been more specifically studied in animal experimentation. Ernström and Gyllensten described the cytologic effect of thyroxine administration in the guinea pig. By histochemical means they demonstrated an acceleration of maturation of plasma cells and increase in differentiation of reticular cells to lymphocytes (5). Cells they regarded as transitional forms became plasma cells.

Since in our experiments lymphoid neoplasms appeared only in thyroidectomized mice bearing a tumor with high thyrotropic activity, this hormone emerges as an agent possibly responsible for lymphocytic stimulation either alone or with other factors. The effect of purified TSH in rats is suggestive but not comparable to the response to a thyrotropic tumor observed in these experiments. Grégoire reported increase in lymphoid tissues of animals which lost weight during thyrotropin therapy. The response of adrenalectomized rats to this regimen was even more pronounced. A study of the rate of restoration of thymus and lymph nodes, previously depleted by radiotherapy, again revealed that TSH was more effective in adrenalectomized, gonadectomized rats (14–16).

Thyrotropin may act directly on lymphocytes and related cells under certain circumstances. Rawson and associates found that tissue culture explants of thymus and lymph nodes inactivated TSH to which they were exposed to a degree comparable to the activity of thyroid explants. This response led them to believe that the cells of thymus and lymph nodes were also target organs for TSH (22). In further support of this concept, Sonenberg found absorption of S35-labeled TSH by thymus and lymph nodes second only to that of the thyroid gland (23). In our observations, other thyrotropic tumors such as L24, from which L24a emerged, did not display comparable lymphocytic stimulating activity, indicating that TSH may have been most effective augmented by other factors.

The effect of growth hormone on mouse and rat
tissues has been extensively studied within the limits imposed by the use of preparations derived from heterologous pituitary glands. One interesting but puzzling demonstration of lymphoid stimulation by growth hormone appears in the work of Moon and associates (21). Lung lymphosarcomas developed in six of fifteen rats given pituitary growth hormone while the control animals remained free. All the experimental rats showed hyperplasia of peribronchial lymphoid tissue. No other organ, including the lymph nodes, shared in the lymphoid hyperplasia. Although it is possible that somatotropic hormone played a subordinate role in the lymphoid hyperplasia of peribronchial lymphoid tissue, all the experimental rats showed reduced, essentially reproducing the biologic situation reported by Grégoire (15). Lung lymphosarcomas may have been responsible for lymphoma development. Since these mice were athyroid, adrenal gland function was probably maintained at a reduced level of TSH, may have been responsible for lymphoma development. Since these mice were athyroid, adrenal gland function was probably reduced, essentially reproducing the biologic situation in rats reported by Grégoire (15).

Maintenance of the reticuloendothelial system is clearly a balance among many factors. In the present experiments lymphocyte stimulation might be expected to dominate as a result of a high level of circulating TSH, radiation effect on lymphoid tissues near the thyroid gland, absence of thyroid hormone with adrenal gland hyapectivity, and possible growth hormone activity with concomitant ovarian follicle hyperplasia. The leading role may perhaps be assigned to thyrotropin, but associated factors have undoubtedly increased the effectiveness of this hormone.

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The authors are indebted to Miss Joan Tierney for thyrotropin assay and to the Photography Departments of Frances Delafield Hospital, New York, and Roswell Park Memorial Institute, Buffalo, for gross and microscopic photographs. The roentgenogram was taken by the Radiology Department of Presbyterian Hospital, New York City.

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Fig. 1.—Retroperitoneal reticulum-cell sarcoma. Smaller tumors appear in the upper mediastinum and left axilla. The spleen has a tenfold enlargement.

Fig. 2.—Lymphosarcoma in the right cervical area. The left cervical and axillary lymph nodes contained smaller growths of the small cell type.

Fig. 3.—Cystic lymphosarcomas in cervical lymph nodes. Axillary node tumors were solid.

Fig. 4.—Roentgenogram of mice inoculated in thigh muscle with L24a tumor. C shows somatotropic effect when the tumor grew in an intact host. C1 is a control mouse in which the tumor failed to grow. B had been radiothyroidectomized, and L24a tumor grew progressively.

Fig. 5.—Reticulum-cell sarcoma in retroperitoneal area. X400.

Fig. 6.—Lymphosarcoma of cervical lymph nodes. X400.

Fig. 7.—Lymphocytic, lymphoblastic, and reticulum-cell replacement of red pulp of the spleen. Malpighian lymphoid follicles remained distinct and appear in part at the lower border. X200.

Fig. 8.—Infiltration of tracheal wall by reticulo-endothelial cells. The lumen appears at upper left corner. The arrow designates cartilage remaining intact. X200.
Fig. 9.—Lymphoid hyperplasia in the lungs. The largest aggregates surround bronchi. X200.

Fig. 10.—Peripelvic lymphoid hyperplasia in the kidney. X200.

Fig. 11.—Lymphoid hyperplasia in the liver of Group B thyroidectomized mouse bearing L24a tumor. There is no diffuse infiltration. The liver cells are of normal size. X200.

Fig. 12.—Liver of Group C intact mouse bearing L24a tumor. Hypertrophy and hyperplasia of liver cells is apparent. Lymphoid aggregates are minimal. X200.
Fig. 13.—Lutein-cell hyperplasia in the ovary of Group C intact mouse with L24a tumor. ×200.

Fig. 14.—Adrenal gland medullary hypertrophy and hyperplasia in Group C intact mouse with L24a tumor. The intermediate zone shows excessive vacuolization and pyknosis. ×400.

Fig. 15.—Hypertrophied chromophobic cells in pituitary of Group B thyroidectomized mouse bearing L24a tumor. ×400.

Fig. 16.—L24a tumor in Group B thyroidectomized mouse. ×400.

Fig. 17.—L24a tumor in Group C intact mouse, which had become gigantic. ×400.
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