The Occurrence of Lymphoma in Patients with Long-standing Hyperthyroidism

By John E. Ultmann, George A. Hyman and Burton Calder

In experimental animals, thyroxin administration leads to hyperplasia of lymphoid tissue, and there is suggestive evidence that the presence of thyrotoxicosis increases the incidence of lymphoid tumors and shortens the survival time of the tumor bearing host (cf. references 26-42). In man, hyperthyroidism, particularly Graves' disease, is frequently associated with lymphoid hyperplasia manifested by lymphocytosis, lymph node enlargement, and splenomegaly (cf. references 2-24). The development of a lymphosarcoma in a patient with long-standing Graves' disease was described for the first time in 1956 and was thought to be coincidental.1 Additional clinical evidence to implicate over-activity of the thyroid as a possible etiologic or contributory factor in the development of lymphomas and allied diseases in man has not been reported to date. The present report, which is intended to stimulate interest in this area, is a summary of a case history previously published and of five additional patients observed with long-standing hyperthyroidism in whom a lymphoma was diagnosed at a later date.

Case Reports

Case 1.—A 67-year-old white male was admitted to New York Hospital on June 23, 1950* with the chief complaint of proptosis of both eyes of 4 months' duration. At age 22, the patient first noted exophthalmos, nervousness, sweating, and heat intolerance. The symptoms at that time were attributed to "thyroid trouble," and the patient received various medications, including iodine. With therapy, he improved, but the exophthalmos persisted. During the ensuing 35 years he continued to receive a variety of medications for intermittent exacerbations of symptoms. At age 60, examination by a physician revealed hypertension, bilateral exophthalmos, lateral deviation of the right eye and impaired convergence, enlarged thyroid gland, and deviation of the trachea to the right. No lymphadenopathy, hepatomegaly, or splenomegaly were noted at that time. The basal metabolic rate was recorded as +40 per cent and +35 per cent. The patient received propylthiouracil with improvement and subsequently did well without medication for 6 years. Four months prior to admission, nervousness, heat intolerance, insomnia, frequent bowel movements, weight loss, and recurrence of his eye symptoms were noted. Treatment with ACTH affected only a temporary remission of the ocular signs.

Physical examination on admission revealed normal vital signs except for the blood pressure of 206/102 mm. of Hg. The patient was hyperactive, and his skin was moist. There was marked exophthalmos with restriction of ocular movement bilaterally, bilateral chemosis, and prolapse of the right lower palpebral conjunctiva. The thyroid gland was

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LYMPHOMA IN LONG-STANDING HYPERTHYROIDISM

markedly enlarged and firm. The chest was emphysematous; the lungs clear. The heart was moderately enlarged. Frequent ventricular extra systoles and a grade II apical systolic murmur were heard. The axillary nodes were enlarged and firm. Both liver and spleen were palpable 5 to 6 cm. below their respective costal margins. Slight wasting of the shoulder musculature was noted. Except for a fine tremor of the extended hands, neurologic examination was normal. The clinical impression was that the patient had Graves' disease associated with a malignant lymphoma.

Hemoglobin determination (Sahli) and red cell count on admission were within normal limits. The white blood cell count ranged between 14,000 and 21,000/cu.mm. with approximately 28 per cent lymphocytes. Bone marrow examination was normal. Other laboratory findings prior to any therapy except intravenous ACTH included: bromsulfalein retention, 4.4 per cent after 45 minutes; blood urea nitrogen, 24 mg. per cent; urea clearance diminished to 39 per cent in the first hour and 25 per cent in the second hour; and serum uric acid 2.7 mg. per cent. The basal metabolic rate was +52 per cent; the serum protein-bound iodine, 4.7 µg. per cent (normal 3.5-8.0 µg. per cent); and total serum cholesterol, 139 mg. per cent. A radioactive iodine uptake study done after 1 month of treatment with propylthiouracil was 37.5 per cent. Axillary lymph node biopsy revealed lymphoblastic lymphosarcoma.

Therapy with ACTH was discontinued. The patient was started on hydriodic acid and propylthiouracil and given 1500 r radiotherapy to each orbit. A gradual decrease of the exophthalmos, eversion and chemosis was noted, and the patient was discharged.

The patient's further course was marked by exacerbations of nervousness, heat intolerance, sweating, hypertension, and a recurrence of eye symptomatology. Progressive mental deterioration and a convulsive episode necessitated hospitalization elsewhere. Bilateral retinal degeneration and papilledema were present. A diffusely abnormal electroencephalogram was recorded and the neurologic consultant suggested that the findings were compatible with cortical degeneration secondary to senile arteriosclerosis. Increasing cervical lymphadenopathy and hepatosplenomegaly were again noted. The patient was treated with radiotherapy to the lymph nodes and intravenous nitrogen mustard. The patient was discharged and lost to follow-up.

Case 2.—A 57-year-old white female was admitted to the Francis Delafield Hospital for the first time in December 1959 complaining of weakness, insomnia, and headaches of "many years" duration. The patient had noted occipital and temporal headaches following fatigue or excitement, palpitations, tremors, anxiety, excessive perspiration, abdominal cramps, weakness, insomnia, and dull pain of both thighs intermittently for the previous 30 years. Partial thyroidectomies were performed in 1930, 1932, and 1950 for control of these symptoms. The second operation afforded symptomatic relief for 10 years, and the third for 2 years. Five years prior to admission the patient noticed recurrence of nervousness, insomnia, and progressive exophthalmos. The basal metabolic rate was +21 per cent and +36 per cent; the serum protein-bound iodine, 3.5 µg. per cent; and radioactive iodine uptake, 55 per cent. The patient was treated with 6 mc. ¹³¹I orally and methimazole (Tapazole). Following therapy, the radioactive iodine uptake decreased to 23 per cent. Other significant past illnesses included frequent upper respiratory infections and chronic bronchitis for "many years." Herpes zoster occurred in 1956.

The spleen tip was first felt in March 1959. In July 1959 the liver was reported as being palpable 3 cm. and the spleen 5 cm. below their respective costal margins. In October 1959, at another hospital, a biopsy of an enlarged supraclavicular node revealed "severe reticuloendothelial hyperplasia" and the patient was given a course of intravenous nitrogen mustard.

Physical examination on admission to the Francis Delafield Hospital revealed the blood pressure to be 120/70 mm. of Hg and the pulse 90. A fine tremor of the hands, exophthalmos, lid lag, increased lacrimation, and blepharitis was noted. The tonsils were hypertrophied. No thyroid tissue was palpated, but multiple scars were noted. Cervical, supraclavicular, axillary, and inguinal lymph nodes were palpated bilaterally. Scattered
moist rales were heard at the left base. The liver was palpable 3 cm. and the spleen 6 cm. below their respective costal margins.

The hemoglobin was 11.5 Gm. per cent; red blood cell count, 4.22 million/cu.mm.; white blood cell count, 4,900/cu.mm. with 80 per cent neutrophils, 13 per cent lymphocytes, and 7 per cent monocytes. There were 168,000 platelets/cu.mm. and 3.1 per cent reticulocytes. Other laboratory findings were: total serum protein 5.9 Gm. per cent with markedly reduced serum gamma globulin; radioactive iodine uptake 61 per cent; serum protein-bound iodine 7.8 µg. per cent; total serum cholesterol 136 mg. per cent; negative direct and indirect Coombs tests. The stool guaiacs were negative for occult blood. Chest x-rays revealed hilar lymphadenopathy.

The patient was treated with reserpine with relief of most of her subjective complaints. The adenopathy waxed and waned spontaneously during her subsequent course. Two additional node biopsies revealed “reticuloendotheliosis.” The patient received no therapy for the lymphoma.

In July 1960 the patient was readmitted for evaluation of a dull, constant, epigastric pain which at times was relieved by food intake and at times was precipitated by it. Gastrointestinal and barium enema x-ray examinations were normal, and the complaints were attributed to an anxiety neurosis. Additional laboratory findings of note during the second admission were the uric acid of 6.4 mg. per cent and 1+ proteinuria.

The patient moved to another city where she died in February 1961. At necropsy, Hodgkin’s granuloma involving the mediastinal, peribronchial, mesenteric, retropertioneal, and axillary lymph nodes, the spleen, liver, bone marrow, lungs, kidneys, and pancreas was found. Residual thyroid tissue was free of lymphoma. Terminal clinical and laboratory findings of uremia and chronic cor pulmonale were attributed to infiltration of the kidneys and lungs by the Hodgkin’s granuloma.

Case 3.—A 59-year-old Negro female was admitted to the Francis Delafield Hospital for the first time in June 1960. A histologic diagnosis of lymphosarcoma had been made in 1958 at another hospital.

The patient reported that partial thyroidectomies were performed in 1928 and 1940 and that the procedures had afforded temporary relief of the antecedent symptoms of nervousness and weight loss. From 1948 to 1953, progressive enlargement of the anterior neck, nervousness, tremor, weight loss, excessive perspiration, intolerance to heat, and occasional lower abdominal pain were noted. In 1952 exophthalmos was noted. Determinations of the basal metabolic rate and serum cholesterol levels in 1952 and early 1953 were reported as normal. The persistent aforementioned symptoms led to the discovery of a diffusely enlarged thyroid gland and an elevated basal metabolic rate, and a sub-total thyroidectomy was performed at another hospital in 1954. Histological examination revealed one large and multiple small colloid adenomata.

In September 1958 she was admitted to another hospital for evaluation of peripheral lymphadenopathy. Biopsy of a left supravacular node revealed lymphoblastic lymphosarcoma. (The slides were subsequently reviewed in the Francis Delafield Hospital and thought to represent a lymphocytic lymphosarcoma.) The patient was treated with intravenous nitrogen mustard (0.4 mg/Kg.) in October and (0.2 mg/Kg.) November 1958 with diminution of the peripheral adenopathy. During the months prior to admission to the Francis Delafield Hospital the patient felt poorly and noted recurrence of the peripheral lymphadenopathy.

The vital signs on admission were normal. Large (5 cm.) axillary and inguinal lymph nodes as well as smaller cervical and supraclavicular lymph nodes were palpated. The thyroid was not palpable. A localized grade II apical systolic murmur was heard. Hepatomegaly and splenomegaly were not noted. A fine intention tremor of the hands was noted, and Chvostek’s sign was positive bilaterally. The hemogram on admission was: hemoglobin 9.8 Gm. per cent, red blood cell count, 3.8 million/cu.mm., white blood cell count, 24,050/cu.mm. with 21 per cent neutrophils, 3 per cent eosinophils, 76 per cent lymphocytes, and 2 per cent monocytes. The platelet count was 170,000/cu.mm. The serum calcium was 4.5 mg. per cent, and the erythrocyte sedimentation rate 83 mm./hr.
LYMPHOMA IN LONG-STANDING HYPERTHYROIDISM

The basal metabolic rate was +11 per cent; the serum protein-bound iodine, 6.8 μg. per cent; serum cholesterol, 171 μg. per cent; and radioactive iodine uptake, 41 per cent. Normal tests included those of liver function, serum alkaline phosphatase, serum phosphorus, and urinary Sulkowitch. The bone marrow aspiration revealed extensive infiltration with medium-sized lymphocytes, a finding considered compatible with chronic lymphocytic leukemia or lymphocytic lymphosarcoma.

The hypoparathyroidism was attributed to parathyroid ablation during sub-total thyroidectomy. The serum calcium returned to normal limits after therapy with calcium lactate and vitamin D. The subsequent course during this and another Francis Delafield Hospital admission later in 1960 was marked by recurrent peripheral and mediastinal lymphadenopathy, hepatomegaly, anemia, thrombocytopenia, fever, hyperuricemia (6.7 mg. per cent), hypogammaglobulinemia, and a psychotic episode. The lymphadenopathy responded to both radiotherapy and chlorambucil. The white cell count never exceeded 20,000 leukocytes/cu.mm. Prednisone (30 mg. daily) was administered in an effort to control the anemia and reduce thrombocytopenic purpura. Recurrent fevers were at various times ascribed to the lymphomatous process, chlorambucil-induced "drug fever," and, late in the course, to a staphylococcal infection. The psychotic episode responded to thorazine. The patient died in November 1960 during the second admission, probably due to advancing lymphoma and staphylococcal infections. Permission to perform a post-mortem examination was not obtained.

Case 4.—A 70-year-old white woman was admitted to the Francis Delafield Hospital for the first time in June 1954, complaining of hoarseness of 6 months' duration and an epigastric mass of 3 months' duration.

The patient reported having had occasional "hypertensive" headaches for 20 years prior to admission. The patient had "goiter trouble" characterized by nervousness, sweating, and thyroid enlargement for at least 10 years prior to admission and had received "many pills," including iodine. The patient reported episodes of pleurisy, pneumonia, sinusitis, and repeated episodes of colds and bronchitis during the previous decade. The patient had complained of dyspnea, orthopnea, and pretibial edema and was digitalized during the previous summer, with relief of symptoms.

The patient appeared nervous and orthopneic to the examining physician. The vital signs were normal except for a blood pressure of 180/65 mm. of Hg. Lid lag was present, and fundoscopic examination revealed some arteriolar narrowing. The thyroid was 2+ enlarged, firm, and without nodularity. No bruit was heard. (Subsequent x-rays revealed substernal extension of the gland with displacement of the trachea to the left.) The left heart border was percussed between the mid-clavicular and anterior axillary lines in the 5th intercostal space, and a localized apical grade I systolic murmur was heard. An abdominal mass 11 by 9 cm. in diameter extended from the umbilicus to the left costal margin. There were no peripheral nodes palpated. Examination of the extremities revealed a fine hand tremor and 2+ pretibial pitting edema.

Laboratory data included: a normal hemogram; basal metabolic rate, +33 per cent; radioactive iodine uptake, 57 per cent; total serum cholesterol, 152 mg. per cent; serum uric acid, 6.1 mg. per cent; and 1+ proteinuria. Indirect laryngoscopy revealed polyps of the right false cord, which, when examined histologically, were found to be cysts of Trichinella spiralis.

The patient was fully digitalized with disappearance of the pretibial edema. An exploratory laparotomy was performed, and large retroperitoneal lymph nodes were found. Biopsy revealed a lymphocytic lymphosarcoma. After therapy with methimazole (Tapazole), the basal metabolic rate decreased to +15 per cent, and the subjective findings associated with thyrotoxicosis disappeared. The patient received 3050 r to the abdomen with regression of the mass and diminution of the gastrointestinal complaints.

The patient had seven subsequent admissions between November 1954 and June 1960. She was treated with propylthiouracil, phenobarbital, and a series of courses of 131I (total dose—21 mc. over the 6-year period). The ranges of the laboratory values during the subsequent course were: basal metabolic rate, +7 per cent to +15 per cent; radioactive
iodine uptake, 81.7 to 36.1 per cent; tri-iodothyronine suppression test (0.000075 Cm. for 8 days) failed to decrease the radioactive iodine uptake below 52.8 per cent; and total serum cholesterol, 191 to 232 mg. per cent. The blood pressure ranged from 170 to 240 mm. of Hg systolic and 80 to 160 mm. of Hg diastolic.

The lymphoma was in remission until August 1958, when the preauricular, axillary, and supraclavicular lymph nodes enlarged. These responded to radiotherapy. The further course was marked by mediastinal lymphadenopathy with recurrent chylos pleural effusion. This was treated with repeated thoracenteses and radiotherapy. Retrograde pyelography revealed obstruction at the left ureteropelvic junction with probable accompanying hydronephrosis. This area and the progressively enlarging left upper quadrant abdominal mass were treated with radiotherapy. Towards the end of the clinical course, the appearance of hypogammaglobulinemia and hyperuricemia (10.9 mg. per cent) was noted, and an episode of herpes zoster occurred. She developed anemia and recurrent infections.

The patient expired in June 1960 of respiratory and cardiac failure. Postmortem examination revealed an adenoma of the right lobe of the thyroid gland and atrophy of the left lobe of the thyroid gland. Lymphocytic lymphosarcoma involved the pancreas, left kidney, and retroperitoneal lymph nodes, but did not involve the thyroid. Other significant findings were acute, focal myocarditis (with no demonstrable cysts of Trichinella spiralis), moderate left ventricular hypertrophy, polynyma emphysema and edema, and hypoplasia of the bone marrow.

Case 5.—A 54-year-old white female was admitted to the Presbyterian Hospital in 1958 with the complaint of weight loss and enlarged spleen of 9 months’ duration.

In March 1934, the patient had been seen at the Presbyterian Hospital complaining of postprandial epigastric distress, nervousness, tremor, and palpitations of “many years’ duration.” Six years prior to admission she had noted enlargement of the neck. The epigastric distress dated back to childhood. Gastrointestinal and gall bladder x-ray studies performed 7 years prior to admission were normal. Physical examination revealed the pulse to be 80/min., the blood pressure 155/90 mm. of Hg, and presence of mild bilateral exophthalmos. The thyroid gland was diffusely enlarged, and a nodule was palpated in the right lobe; no bruit was heard. The remainder of the physical examination was negative, except for a fine tremor of the hands. The basal metabolic rate on admission was +56 per cent. The gastrointestinal x-ray series was again negative. Following preoperative treatment with sodium iodide and luminal, a partial thyroidectomy was performed. Histologic examination revealed “toxic nodular goiter.” A brief improvement in her subjective symptomatology ensued. One month following discharge, the patient again complained of nervousness. Postoperative BMRs of +15 per cent and —5 per cent were reported 4 months later, and, 1 year following her surgery, a basal metabolic rate of +21 per cent was recorded.

Between April 1934 and October 1958 the patient was seen infrequently in the Presbyterian Hospital outpatient department. The complaints, which were usually extreme nervousness, indigestion, and vomiting, remained unexplained after the neurologic examination and repeated gastrointestinal series. No attempt was made during these visits to evaluate the thyroid status. The patient reported an episode of herpes zoster in 1951.

In October 1958 the patient presented to the Presbyterian Hospital with a complaint of a recent 10 pound weight loss and reported that in January 1958 a physician had noted an enlarged spleen. Upon physical examination she was noted to have gross tremors of the hand, head, and neck suggestive of Parkinson’s disease. The pulse was 80/min. and the blood pressure 140/40 mm. of Hg. A grade II systolic murmur was heard over the aortic area and at Erb’s point. Basilar moist rales were heard bilaterally. The thyroid was not enlarged or nodular, and no bruit was heard. The smooth liver was palpated 3 cm., and the tender, smooth spleen 10 cm. below their respective costal margins. Minimal generalized lymphadenopathy and mild pedal edema were noted. Neurologic examination was negative except for the gross tremors.

The laboratory data included: hemoglobin, 9.5 Gm. per cent; red blood cell count, 3.1
LYMPHOMA IN LONG-STANDING HYPERTHYROIDISM

287

million/cu.mm.; white blood cell count, 313,000/cu:mm. with 5 per cent neutrophils, 90 per cent lymphocytes, 4 per cent monocytes, and 1 per cent basophils. A Wintrobe erythrocyte sedimentation rate of 9 mm/hr., serum uric acid of 4.6 mg. per cent, blood urea nitrogen of 20 mg. per cent, 1+ proteinuria, and marked hypogammaglobulinemia were also recorded. The diagnosis of chronic lymphocytic leukemia was thus established.

Since 1958 the patient has had a number of chlorambucil-induced remissions of the chronic lymphocytic leukemia. Thrombocytopenia forced discontinuance of the chlorambucil, which in turn resulted in prompt exacerbation of the leukemia. The patient was last seen in the Hematology Clinic at Presbyterian Hospital in December 1961, at which time the hemogram showed: hemoglobin, 6.8 Gm. per cent; and white blood cell count, 160,000/cu.mm. with 3 per cent neutrophils, 96 per cent lymphocytes, and 1 per cent lymphoblasts. The diagnosis of chronic lymphocytic leukemia was thus established.

Case 6.—A 54-year-old white housewife was admitted for the first time to the Presbyterian Hospital in September 1958 with progressive weakness, palpitations, and precordial pain on exertion, of 1 week's duration.

In 1928, at age 20 years, the patient had noted the onset of weakness, weight loss, nervousness, and palpitations. For a few months early in the course, the patient received an oral iodine preparation. For the next 7 years, the patient received no therapy. During this period her symptoms persisted. In 1935, at age 27 years, the patient underwent a thyroidectomy, and a 6 cm. nodule in the left thyroid lobe was removed. The pathologic diagnosis was "toxic adenoma of thyroid, degenerative." For the next 17 years, the patient remained asymptomatic with no signs or symptoms referable to hyperthyroidism.

In 1952 the patient noted painless, left cervical node enlargement. Biopsy of the node revealed a giant follicular lymphosarcoma. Complete regression of the nodes was achieved with local radiotherapy. The patient was then well for 6 years, until 2 months prior to admission to Presbyterian Hospital in September 1958, when she noted intermittent ankle edema, progressive weakness, palpitation, and precordial pain on exertion.

Examination revealed pallor, tachycardia of 108, temperature of 100.2 F., and a localized grade II apical systolic murmur. There was generalized lymph node enlargement; the spleen extended 8 cm. below the left costal margin; the liver was barely palpable; and minimal pedal edema was present. The thyroid was not palpable through the healed thyroidectomy scar.

Hemoglobin was 7.1 Gm. per cent; red blood cell count was 2.0 million/cu.mm. with 21 per cent reticulocytes; the white blood cell count was 2200/cu.mm. with 70 per cent neutrophils, 22 per cent lymphocytes, 8 per cent monocytes; and 1 nucleated red blood cell per 100 white blood cells was seen. The platelet count was 195,000/cu.mm. Additional laboratory findings included: total serum bilirubin, 1.4 mg. per cent; serum uric acid, 6.3 mg. per cent; direct Coombs test, positive. The chest x-ray revealed normal pulmonary parenchyma and left ventricular enlargement. The following studies were normal: urinalysis, stool guaiacs, 2-hour postprandial blood sugar, cold agglutinin titer, radioactive iodine uptake, electrocardiogram, and serum protein electrophoretic pattern.

The patient was considered to have a Coombs positive hemolytic anemia and hypersplenism secondary to a lymphosarcoma. She responded rapidly to prednisone therapy, 30 to 40 mg. daily, with a reticulocytosis of 30 per cent and return of the white cell count, temperature, pulse, and nodes to normal. When the hemoglobin and red cell count reached a plateau of 9.0 Gm. per cent and 2.6 million/cu.mm., respectively, and the splenomegaly stabilized with the spleen palpable at 2 to 3 cm. below the left costal margin, radiotherapy of 250 r in air over 4 days was given to a 15 x 15 cm. splenic port. By November 1958, the spleen was no longer palpable, and the hemoglobin had risen to 12.2 Gm. per cent with 1.4 per cent reticulocytes and a white blood cell count of 4350/cu.mm. The serum bilirubin was 0.5 mg. per cent and the direct Coombs test negative.

During the past 3½ years, the patient has been asymptomatic on maintenance glucocorticoid therapy, which at present consists of prednisone, 2.5 mg. twice daily. Except for 1 cm. left supravacular lymph node, the physical examination has been negative. In May 1962, the hemoglobin was 12.2 Gm. per cent; red blood cell count, 4 million/cu.mm.;
Table 1.—Data Summarizing Duration, Clinical, and Laboratory Findings as Well as Therapy of Hyperthyroidism in Patients Subsequently Developing Lymphoma

<table>
<thead>
<tr>
<th>Case No. and Sex</th>
<th>Age at Onset of Lymphoma</th>
<th>Age at Onset of Hyperthyroidism</th>
<th>Years of Active Hyperthyroidism</th>
<th>Clinical Findings Associated with Hyperthyroidism</th>
<th>Laboratory Findings during Active Hyperthyroidism</th>
<th>Therapy of Hyperthyroidism</th>
<th>Pathologic Findings Related to Thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Male</td>
<td>67</td>
<td>22</td>
<td>45</td>
<td>goiter, nervousness, excessive perspiration, heat intolerance, exophthalmos, proptosis, tracheal deviation</td>
<td>BMR +35, +40</td>
<td>iodides, propylthiouracil</td>
<td></td>
</tr>
<tr>
<td>2. Female</td>
<td>57</td>
<td>25</td>
<td>32</td>
<td>goiter, nervousness, weight loss, excessive perspiration, tremors, exophthalmos, lid lag</td>
<td>BMR +21, +36, PBI 3.5 to 7.8 μg.% RaI 55 to 61%</td>
<td>partial thyroidectomy in 1930, 1932, and 1950 radioactive iodine, methimazole</td>
<td></td>
</tr>
<tr>
<td>3. Female</td>
<td>54</td>
<td>19</td>
<td>27</td>
<td>goiter, nervousness, weight loss, tremor, excessive perspiration, heat intolerance, exophthalmos</td>
<td>BMR “elevated”</td>
<td>partial thyroidectomy in 1928, 1940, and 1992</td>
<td>Multiple colloid adenoma</td>
</tr>
<tr>
<td>4. Female</td>
<td>70</td>
<td>59</td>
<td>over 10</td>
<td>goiter, nervousness, lid lag, hand tremor, substernal thyroid</td>
<td>RaI 57 to 82% T3 suppression: positive†</td>
<td>iodides, methimazole, propylthiouracil, radioactive iodine</td>
<td>Adenoma</td>
</tr>
<tr>
<td>5. Female</td>
<td>54</td>
<td>23</td>
<td>over 7</td>
<td>goiter, nervousness, tremor, exophthalmos</td>
<td>BMR +56</td>
<td>partial thyroidectomy in 1934</td>
<td>Toxic adenoma</td>
</tr>
<tr>
<td>6. Female</td>
<td>44</td>
<td>20</td>
<td>7</td>
<td>goiter, nervousness, weight loss, palpitations</td>
<td>—</td>
<td>iodiode, partial thyroidectomy in 1935</td>
<td>Toxic adenoma degenerative</td>
</tr>
</tbody>
</table>

* ¹I₁₃¹ 6 mc. 5 years prior to appearance of lymphoma.
† Tri-iodothyronine suppression test (0.000075 Gm. for 8 days) failed to decrease the RaI below 52.8 per cent.
‡ ¹I₁₃¹ administration begun after appearance of lymphoma.
white blood cell count, 3,500/cu.mm. with a normal differential; platelet count, 130,000/cu.mm.; and reticulocyte count, 2.0 per cent. The serum bilirubin was 0.6 mg./per cent and direct Coombs test negative. One attempt to eliminate the glucocorticoid was unsuccessful when the suppressed hemolytic activity became apparent again.

RESULTS

Table 1 summarizes the duration, clinical and laboratory findings, as well as therapy of the hyperthyroidism in the six patients reported in detail above. The manifestations of hyperthyroidism appeared at an early age (19–25 years) in five patients and at age 59 in one. Uncontrolled hyperthyroidism was intermittently present over a period of 7 to 45 years. The hyperthyroidism was active at the time the lymphoma was diagnosed in two patients (cases 2 and 4), partially controlled in one patient (case 1), and it appeared to have been controlled in the other three patients for 8, 17, and 24 years (cases 3, 6, and 5, respectively). In all cases, the history and clinical findings suggested typical hyperthyroidism. Exophthalmos, lid lag, or both were present in all patients, except case 6. Laboratory studies supporting the diagnosis of hyperthyroidism were available in cases 1 to 5. The basal metabolic rate was elevated in cases 1, 2, 3, and 5 during active phases of the hyperthyroidism before the appearance of the lymphoma. In case 4, the elevated basal metabolic rate obtained in the presence of the lymphoma cannot be taken as evidence of hyperthyroidism. Studies with radioactive iodine uptake confirmed the presence of hyperthyroidism in cases 2 and 4. Responses to iodides, antithyroid medicaments, partial thyroidectomy, or radioactive iodine were typical, but not permanently effective in four patients (cases 1–4). In case 6, partial thyroidectomy completely relieved the hyperthyroidism, whereas in case 5 it is not possible to ascertain whether the partial thyroidectomy was immediately fully effective.

When the patients were examined, lymph node enlargement, hepatosplenomegaly, or both suggested the possibility of a lymphoma. The histologic classification of the material obtained at biopsy or postmortem examination is shown in table 2. This table also indicates the sites of involvement, complications, laboratory findings, and therapy in these patients. All patients were anemic at some time in the course of their disease and one patient (case 6) had severe Coombs positive hemolytic anemia. Three patients had leukocytosis and three an absolute lymphocytosis. Four of the five patients (cases 2, 3, 4, and 5), whose serum protein electrophoretic patterns were examined, had hypogammaglobulinemia, and in one (case 4) severe infections recurred. These same four patients gave a history or showed clinical evidence of herpes zoster infection. Hyperuricemia was noted in four patients (cases 2, 3, 4, and 6) but did not cause any complications. The patients received radiation therapy to their local disease and alkylating agents for systemic symptoms. In case 1, ACTH was given in the hope of alleviating the severe proptosis believed to be due to hyperthyroidism as well as lymphosarcoma infiltrates. Two patients (cases 3 and 6) received glucocorticoids to control symptomatic hemolytic anemia. Three of the patients have died (cases 2–4), and postmortem examinations in two (cases 2 and 4) confirmed the diagnosis of
Table 2.—Histologic Classification, Extent, Complications, Laboratory Data, and Therapy of Lymphoma Developing in Patients after Long-standing Hyperthyroidism

<table>
<thead>
<tr>
<th>Case</th>
<th>Histologic Classification of Lymphoma</th>
<th>Extent</th>
<th>Complications</th>
<th>Lowest Hemoglobin Level Gm.%</th>
<th>White Blood Cell Count/cu.mm.</th>
<th>Lymphocytes %</th>
<th>Level of Gamma Globulin</th>
<th>Serum Uric Acid mg.%</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lymphoblastic lymphosarcoma</td>
<td>lymph nodes, liver, spleen</td>
<td>—</td>
<td>10.0</td>
<td>21,200</td>
<td>28</td>
<td>—</td>
<td>2.7</td>
<td>x-ray to nodes and spleen, ACTH, HN₂</td>
</tr>
<tr>
<td>2.</td>
<td>Hodgkin's granuloma</td>
<td>lymph nodes, liver, spleen</td>
<td>herpes zoster</td>
<td>11.5</td>
<td>4,900</td>
<td>13</td>
<td>reduced</td>
<td>6.4</td>
<td>HN₂</td>
</tr>
<tr>
<td>3.</td>
<td>Lymphocytic lymphosarcoma</td>
<td>lymph nodes, liver</td>
<td>herpes zoster</td>
<td>9.8</td>
<td>24,050</td>
<td>76</td>
<td>reduced</td>
<td>4.4-6.7</td>
<td>HN₂, x-ray, chlorambucil, prednisone</td>
</tr>
<tr>
<td>4.</td>
<td>Lymphocytic lymphosarcoma</td>
<td>lymph nodes, chylous effusions</td>
<td>herpes zoster recurrent infections</td>
<td>10.3</td>
<td>4,900</td>
<td>17</td>
<td>reduced</td>
<td>6.1-10.9</td>
<td>x-ray</td>
</tr>
<tr>
<td>5.</td>
<td>Chronic lymphocytic leukemia</td>
<td>lymph nodes, liver, spleen</td>
<td>herpes zoster</td>
<td>9.5</td>
<td>313,300</td>
<td>90</td>
<td>reduced</td>
<td>4.6</td>
<td>chlorambucil</td>
</tr>
<tr>
<td>6.</td>
<td>Giant follicular lymphoma</td>
<td>lymph nodes</td>
<td>Coombs positive, hemolytic anemia</td>
<td>7.1</td>
<td>2,200</td>
<td>22</td>
<td>normal</td>
<td>6.3</td>
<td>x-ray, prednisone</td>
</tr>
</tbody>
</table>
lymphoma. One patient was lost to follow-up (case 1). Cases 5 and 6 are living with their lymphoma in partial remission on chlorambucil and prednisone, respectively; both are euthyroid.

**Discussion**

The presentation of six patients with long-standing hyperthyroidism followed by the development of a lymphoma does not constitute proof of causal relationship. The possibility, however, appears of interest and merits discussion.

The presence of splenomegaly and enlarged lymph nodes was first noted by Askanazy in some of his patients with Graves' disease. This phenomenon was described by others in the next few years. Baldridge and Peterson found that 30 per cent of a series of patients with exophthalmic goiter had splenic enlargement, and at necropsy four of these patients showed lymphoid hyperplasia of the spleen and other lymphoid tissues. Boyd and Sloan noted frequent thymic enlargement in exophthalmic goiter. Grégoire described hyperplasia of thymus and lymphoid tissue in Graves' disease.

Kocher was the first to describe in detail the blood picture in Graves' disease, noting leukopenia, neutropenia, and relative and absolute lymphocytosis. The maximum change in lymphocyte count came at the height of the disease. Following thyroidectomy, the blood picture in the majority of cases returned to normal. These pre- and postoperative changes were substantiated by a number of other observers. Biström thought that they were proportional to the degree of thyrotoxicosis. Gotti confirmed this but Plummer was unable to make this correlation. Jackson found no significant preoperative changes in the blood picture of thyrotoxic patients, but noted a fall in lymphocytes following thyroidectomy. Kocher and Sharpe and Bisgard remarked upon the similarity between the relative lymphocytosis of patients with Graves' and that of aleukemic lymphatic leukemia, and Warthin coined the term “Graves' constitution” to suggest the tendency to lymphoid hyperplasia in hyperthyroidism. These observations were emphasized by Rawson and Goldzieher.

Several hypotheses were formulated to explain the lymphocytosis and lymphoid hyperplasia as increased sympathetic stimulation with release of splenic lymphocytes, release of lymphocytes from the lymphocytic infiltration of the thyroid, and relative deficiency of adrenal steroid. Cameron and Carmichael found that thyroxin-fed rats showed an increase in lymphatic tissue. Houssay recorded hyperplasia of the thymus under similar conditions. Marder and Shrewsbury et al. noted the same changes in lymphoid tissues of mice following administration of thyroxin. Ernström and Gyllensten, Feldman and Dougherty have confirmed these findings. Latta and Benner, however, found that thyroxin-fed rats showed an increased percentage of neutrophils and a decreased percentage of lymphocytes in the peripheral blood.

The interrelationships between thyroxin, the adrenal cortical hormones, ACTH, and the sex hormones have been experimentally explored by Marine.
Daughaday, Shrewsbury, and their co-workers who felt that the blood changes and lymphoid hyperplasia noted in hyperthyroidism are due to partial suppression of the function of the adrenals and gonads. Others believed that hyperthyroidism acts indirectly upon the adrenal cortex by decreasing ACTH secretions. More recent work in animals and man employing isotope technics indicates that although there is an increased rate of adrenal glucocorticoid secretion in thyrotoxicosis, this is accompanied by an increased rate of cortisol plasma disappearance resulting in relative glucocorticoid deficiency.

Much work has been done upon experimental animals with artificially induced states of hypothyroidism. Houssay, Reinhardt et al., and Marine et al. reported that thyroidectomy resulted in early involution of the thymus. White and Dougherty, Chiodi, and Crafts have observed involution of lymphoid tissue and a relative decrease in blood lymphocytes in thyroidectomized rats.

In summary, the investigations cited indicate that hyperthyroidism in man is associated with lymphocytosis and enlargement of lymphoid organs. In animals, administration of thyroxin leads to similar changes, whereas decrease of thyroid function decreases the lymphoid tissue mass.

There is conflicting evidence regarding the role of thyroid function in the incidence and course of tumors in animals. Gillman et al. reported that thiourea feeding in rats markedly decreased the incidence of trypan blue-induced reticulosarcoma of the liver. Morris et al. found that induction of a hypothyroid state increased the mean survival times in rats and AKR mice bearing transplanted lymphoid leukemia. These beneficial effects of the hypothyroid state were vitiated when the animals were given thyroxin. Thyro-parathyroidectomized rats showed a 33 per cent regression of inoculated spindle cell sarcoma and Abbott et al. reported a decrease in incidence of takes of implanted sarcomas in radio-thyroidectomized rats. Other investigators have reported failure of thyroidectomy to decrease the incidence or slow the course of tumors. Kaplan et al. have reported that chronic thyroid stimulation had no influence on radiation-induced lymphoid tumors in C37 black mice. Nagareda and Kaplan, however, reported that induction of hypothyroidism significantly inhibited thymic implant tumor development in female C37 black mice and that when thyroid activity was restored by thyroid graft, lymphoma incidence returned to the level of euthyroid animals. Sloviter noted no effects of hypothyroid function upon rate of tumor growth or survival time in mice bearing a fibrosarcoma. Similarly, Bischoff and Maxwell noted no changes in tumor growth or survival in thyro-parathyroidectomized rats bearing R10 sarcoma or carcinosarcoma.

Grad reported that AKR mice rendered hyperthyroid by thyroxin had a lower incidence of spontaneous leukemia than did mice rendered hypothyroid by thiouracil. He ascribed this to weight loss in the hyperthyroid group. However, AKR mice made hyperthyroid with thyroxin and fed supplements of vitamins and liver had a higher incidence of spontaneous lymphatic leukemia than mice rendered hypothyroid by thiouracil and an
iodine-deficient diet. Grad ascribed these findings entirely to the fact that the vitamin-protected hyperthyroid mice were heavier than the hypothyroid animals. Grad found that hyperthyroidism did not alter the survival time of AKR mice with a transplanted lymphatic leukemia. Recently, Grinberg et al.\textsuperscript{53} reported that mice bearing an autonomous TSH-producing tumor had a marked hyperplasia of all lymphoid tissue and developed a reticulum cell sarcoma.

These experimental studies suggest that thyroxin-induced hyperthyroidism leads to lymphoid hyperplasia and possibly to increased lymphoid tumor incidence. Grinberg and co-workers suggest that thyroid stimulating hormone (TSH) may play an important role on lymphoid stimulation, possibly unrelated to thyroxin production.

Reports regarding the relationship in man of thyroid activity to malignancy in general and lymphoma in particular are sparse. Neither old\textsuperscript{54} nor recent\textsuperscript{55,56} textbooks dealing with thyroid disease allude to any connection between these two disease entities. A survey of the records of two large hospitals in New York\textsuperscript{1} and personal recollections of two thyroid specialists\textsuperscript{57,58} fail to reveal cases of concurrent hyperthyroidism and lymphoma. In all these instances, however, the majority of patients received adequate and prompt treatment for their hyperthyroidism and cannot be compared with the patients herein reported who suffered for 7 to 45 years with active hyperthyroidism. Werner and Quimby\textsuperscript{59} estimated the incidence of leukemia as 1 in 13,000 patients per year in a group of patients treated with radioactive iodine for hyperthyroidism. This was felt not to be significantly greater than the incidence of leukemia in the general population. Recently, Pochin\textsuperscript{\textsuperscript{6}} confirmed these estimates. Werner et al.\textsuperscript{61} re-examined their data and concluded that although there was no increase in the incidence of leukemia, there were significantly fewer chronic cases and significantly more acute cases of leukemia than expected. Particularly noteworthy, of course, is the fact that patients included in the Werner and Quimby and the Pochin surveys were all treated in large medical centers by presumably adequate doses of radioactive iodine which controlled their disease. One of our patients (case 2) received radioactive iodine (6 mc.) 5 years prior to the discovery of the lymphoma; another patient (case 4) received radioactive iodine only after the diagnosis of lymphoma had been established. There is no evidence to implicate iodides, propylthiouracil, or methimazole as carcinogens.\textsuperscript{62}

In the report in 1956 of a patient with long-standing hyperthyroidism who subsequently developed lymphoblastic lymphosarcoma\textsuperscript{1} (case 1 in present study), the concurrence was thought to be coincidental. Three other cases have since been published, reporting concurrent hyperthyroidism and lymphoma, chronic lymphatic leukemia, or giant follicular lymphoblastoma. Solomon and Rubenfelt\textsuperscript{63} reported two patients, one with chronic lymphatic leukemia, and another with giant follicular lymphoma, whose lymphoma developed 31 and 40 months following therapy with radioactive iodine\textsuperscript{131}. They thought the occurrence of lymphoma was not related to the \textsuperscript{131}I. The possible connection between the hyperthyroidism and the lymphoma was not considered. These
two patients are unlike the ones reported in the present study in that their hyperthyroid state was not prolonged (probably less than 1 year) and their response to therapy was adequate. The third patient was reported by Goldberg as "an unusual lymphomatous disease associated with intracytoplasmic crystals in lymphoplasmocytoid cells." Of particular interest in connection with the present report is the patient's history of severe hyperthyroidism with myopathy and generalized lymphadenopathy for 6 to 7 years preceding the diagnosis of lymphoma.

The present study consists of three patients with Graves' disease and three with toxic nodular goiter. Both types of hyperthyroidism have been included in our study because the evidence from the laboratory investigations cited has not excluded the possibility that TSH may be responsible for lymphoid hyperplasia through a mechanism independent of excess thyroxin production.

Three patients in the present series were euthyroid at the time the lymphoma was diagnosed although they previously were hyperthyroid. They are included in this report because it is not known how long the hyperthyroidism must be present or if it must be present continuously.

The present report, although not proving that hyperthyroidism is an etiologic factor in the development of the lymphoma, suggests that the association may not be coincidental.

**SUMMARY**

1) Six patients have been presented who, subsequent to long-standing hyperthyroidism, developed a lymphoma (one lymphoblastic lymphosarcoma, one Hodgkin's disease, one giant follicular lymphoma, and three lymphocytic lymphosarcoma or leukemia).

2) Experimental evidence suggests that hyperthyroidism stimulates and hypothyroidism inhibits lymphoid structures, and hyperthyroidism promotes tumor growth in animals. The mechanism of this action is not clear.

3) Three additional cases of hyperthyroidism followed by the development of a lymphoma were found in the literature.

4) It is suggested that prolonged hyperthyroidism may be a contributory factor in the development of lymphomas or allied disorders in man.

**SUMMARIO IN INTERLINGUA**

1. Es presentate le casos de sex patientes le quales, post longe antecedentes de hyperthyroidismo, disveloppava un lymphoma, i.e. lymphosarcoma lymphoblastic in un caso, morbo de Hodgkin in un, lymphoma folliculari gigante in un, e lymphocytic lymphosarcoma o leucemia in tres.

2. Il existe constatationes experimental que suggere que hyperthyroidismo resulta in un stimulation e hypothyroidismo in un inhibition de structuras lymphoidic, e que hyperthyroidismo promove le crescentia de tumores in animales. Le mechanismo de iste action non es clar.

3. Tres casos additional de hyperthyroidismo sequite per le disveloppamento de un lymphoma esseva trovate in le litteratura.

4. Es formulate le these que prolongate hyperthyroidismo es possibilemente...
LYMPHOMA IN LONG-STANDING HYPERTHYROIDISM

un factor contributori in le disvelopamento de lymphomas o disordines affin in le homine.

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The Occurrence of Lymphoma in Patients with Long-standing Hyperthyroidism

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