The Development of Hodgkin’s Disease and Lymphoma during Anticonvulsant Therapy

By GEORGE A. HYMAN AND SHELDON C. SOMMERS

During the period from 1958 to 1964, 85 cases of so-called pseudolymphoma following anticonvulsant therapy have been reported indicating that this entity is not rare. However, the unexpected occurrence of true malignant lymphoma in 6 patients on anticonvulsant therapy (3 with Hodgkin’s disease and 3 with lymphosarcoma) within a 4-year period in one medical center has prompted this report. This finding may indicate that patients with lymphoma and Hodgkin’s disease superimposed on a seizure disorder actually may outnumber those in whom a pseudolymphomatous adenopathy is provoked by antiseizure therapy. In addition, this association suggests that anticonvulsant therapy may have been an inducing factor in the neoplastic transformation.

The pertinent case histories, clinicopathologic findings and therapeutic management in 6 patients, all recently seen at Presbyterian Hospital and Francis Delafield Hospital in New York City, will be summarized briefly to explore the problem of the development of lymphoma and Hodgkin’s disease during therapy with anticonvulsant drugs. In addition, such an analysis may yield guidelines for the future management of similar patients. Details are presented in Table 1.

REPORT OF CASES

Case 1

A 24-year-old white woman was first admitted in 1958 to the Neurological Institute, New York City, for treatment of severe psychomotor seizures which started in 1950 following an injury to the left temple. Since October 1950 she had been treated with Dilantin, 0.5 Gm./day. In October 1952 phenobarbital, 30 mg., and Mysoline, 250 mg., 3 times daily were added; in 1961, Celontin was also added. In October 1961 a right scalene lymph node biopsy revealed Hodgkin’s disease (Figs. 1 and 2). The blood counts and general physical examination were entirely normal. From May 16 to June 13, 1962, she was given 3000 r tumor dose to the right hilar area using the Betatron, with complete disappearance of the shadow seen by x-ray.

In 1963 and 1964, because of pain in the distribution of the left sciatic nerve, she...
required radiotherapy to the left hemipelvis and to the area of emergence of the 2nd and 3rd left lumbar nerve roots. X-rays, including myelogram and lymphangiogram, were negative. When last seen on February 24, 1965, she continued to have deep left groin and left-sided pain. The Dilantin was discontinued in 1962 and she is receiving Mysoline, 250 mg., phenobarbital, 30 mg., benzedrine, 5 mg., and Thorazine, 25 mg., 3 times daily.

**Case 2**

A Negro girl at the age of 10 years first had psychomotor epilepsy with a grand mal seizure 1 year later. In June 1953 she was started on Dilantin, 0.3 Gm. daily, to which phenobarbital, 30 mg. daily, was added. On June 17, 1954, Dilantin was increased to 400 mg. daily and continued through 1958, at which time it was increased to 500 mg. In 1957, phenobarbital was increased to 30 mg. 4 times daily.

On February 15, 1965, at age 23, when 5 months pregnant, she presented at Presbyterian Hospital in New York City with a right cervical adenopathy of 3 months’ duration. The chest x-ray was negative. There was fever up to 100 F. Hemoglobin was 10 Gm. per cent, white count, 6500 with a normal differential, ESR, 36. A biopsy of the right cervical lymph nodes on March 2, 1965 disclosed Hodgkin’s disease (Figs. 3 and 4). The lymph nodes enlarged rapidly to 6 x 8 cm. in size and cobalt-60 teletherapy was instituted on March 16, 1965, to the cervical nodes with good effect. She has been maintained on Dilantin to the present.

**Case 3**

In May 1964 this 23-year-old white housewife and mother of a 3-month-old child was seen at Francis Delafeld Hospital because of decreased appetite, weight loss of 15 pounds, peripheral lymphadenopathy, and night sweats with onset in November 1963. She had been receiving Dilantin, 0.3 Gm. daily, since July 1962 for petit mal with good effect. A right cervical lymph node biopsy in December 1963 was interpreted as Hodgkin’s disease (Figs. 5 and 6). She had received 20 mg. of nitrogen mustard (0.4 mg./Kg.) on December 15, 1963, at an outside hospital and 8 mg. of Leukeran a day, intermittently, until May 13, 1964, with a transient weight gain and return of a general feeling of well-being. A course of peripheral supervoltage radiotherapy was given at Francis Delafeld Hospital. On July 31, 1964, splenic enlargement was noted. The hemoglobin level progressively declined from 10.6 to 7.9 Gm. with a reticulocyte count of 0.5 per cent, white cell count of 6500 with a normal differential, platelets of 314,000, ESR of 1 17 (Westergren), and a 2+ positive direct Combs test. Mesantoin, 0.1 Gm. 3 times daily, was introduced in September 1964 to replace the Dilantin. This was completely effective, but there was progressive anemia, weight loss, fever, and further painful enlargement of the spleen to 6 cm. below the left costal margin. When a course of Velban, started in October 1964, was unsuccessful, she was admitted to Francis Delafeld Hospital for the first time on December 2, 1964. Phenobarbital was substituted for Mesantoin, successfully. Intravenous pyelography demonstrated involvement of the left retroperitoneal lymph nodes and she was given radiotherapy to this area and then to the spleen, with relief of pain. During the succeeding 8 months there has been a rise in hemoglobin level to 13.0 Gm. per cent, a 15-pound weight gain, and cessation of symptoms.

**Case 4**

A 63-year-old white man had always been healthy, with semiannual normal physical examinations and normal blood counts. through 1961. On October 15, 1962, because of his first generalized seizure, he was admitted to the Neurological Institute in New York City, at which time no etiology could be determined. Dilantin therapy was started, 0.3 Gm. daily through March 11, 1964, when it was reduced to 0.2 Gm. daily. On February 7, 1964, the splenic tip was palpable for the first time. The physical examination was otherwise negative and there was a normal complete blood count. On May 5, 1964, the first
Table 1.—**Anticonvulsant Therapy Followed by Lymphoma. Summary of Data (6 Patients) 1965**

<table>
<thead>
<tr>
<th>Case and Sex</th>
<th>Race and Present Age</th>
<th>Age at Onset and Type of Epilepsy</th>
<th>Age at Onset of Lymphoma and Type and Site of Biopsy Diagnosis</th>
<th>Anticonvulsant Therapy prior to and after Diagnosis of Lymphoma</th>
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<td>Dilantin to 1962</td>
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<td>Phenobarbital—1952</td>
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<td></td>
<td>+ Mysoline—1954</td>
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<td></td>
<td>+ Celontin—1961</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Dilantin to present</td>
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<td></td>
<td>Measontoin Sept.—Dec. 1964</td>
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<td>Phenobarbital† since Dec. 1964</td>
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<td>Phenobarbital† from Jan. 1965</td>
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<td>Dilantin 1941 (7) to 1948</td>
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<td></td>
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<td></td>
<td></td>
<td>Mebaral—1951-1956</td>
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<td></td>
<td>Sept. 1962</td>
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</table>

*No change in lymphoma after withdrawal of Dilantin.
†Adequate control of seizures.

An abnormal leukocyte count was obtained, a total of 8250 with 63 per cent mature lymphocytes and 35 per cent polymorphs.

On July 21, 1964, an asymptomatic left inguinal lymph node was palpated. This was biopsied on August 7, 1964; the diagnosis was lymphocytic lymphosarcoma (Figs. 7 and 8). The chest x-ray was negative. The only other abnormality found was a small homogeneous electrophoretic spike in the serum gamma globulin. Leukeran therapy was introduced in August 1964 but was ineffective. On December 21, 1964, the hemoglobin had fallen to 8.4 Gm. per cent with a further enlargement of the spleen to 16 cm. below the costal margin. A trial of prednisone, 30 mg. daily, was given without improvement.

In January 1965 he received two transfusions and splenic radiotherapy to a total of 550 r.
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Table 1.—Continued

<table>
<thead>
<tr>
<th>Abnormalities at Time of Diagnosis of Lymphoma</th>
<th>Therapy of Lymphoma</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PX</td>
<td>Hematologic</td>
<td>X-ray</td>
<td>Agents</td>
</tr>
<tr>
<td>Negative</td>
<td>None</td>
<td>R. hilar node</td>
<td>X-ray RX to: (1) chest (1962) (2) L. iliac area (1962-1964)</td>
</tr>
<tr>
<td>Negative</td>
<td>None</td>
<td>Chest x-ray negative</td>
<td>X-ray RX to peritoneal area</td>
</tr>
<tr>
<td>L. thyroid and LLQ mass</td>
<td>None</td>
<td>L. thyroid mass</td>
<td>X-ray RX to thyroid</td>
</tr>
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The prednisone was canceled. By April 1965 the spleen had decreased by two-thirds, the hemoglobin had risen to 11 Gm. per cent, the platelet count to 50,000 from 20,000, and the white count had returned to normal. Dilantin therapy was stopped and phenobarbital started. 150 mg. daily. on January 30, 1965, without a subsequent recurrence of the seizures until June 1965, when he was readmitted to the Neurological Institute in semistupor. Work-up disclosed a large mass cortical lesion, presumably due to lymphosarcoma. The patient was started on radotheraphy to the brain with Decadron as supportive therapy, but he died 10 days later in coma. Autopsy permission was refused.

Case 5
A 68-year-old white man was first admitted to Francis Delafield Hospital in May 1956 because of a 30-pound weight loss in 8 months, intermittent fever, and weakness for 2
Fig. 1—Coarse scarring with foci of atypical and anaplastic multinucleated reticulum cells are indicative of Hodgkin’s disease, nodular sclerosing type. Case 1, X 200. All slides stained with hematoxylin and eosin.

Fig. 2.—Typical Reed-Sternberg cells of Hodgkin’s disease were present. Case 1, X 500.

Fig. 3.—Discrete foci of necrosis and fibrosis were found, surrounded by a mixture of lymphoid cells, including Reed-Sternberg cells. Case 2, X 200.

Fig. 4.—Reed-Sternberg cells were identified characteristic of Hodgkin’s disease, granuloma type. Case 2, X 500.
Fig. 5.—A granulomatous type of reaction with many Reed-Sternberg cells and less necrosis or fibrosis suggests an earlier stage of Hodgkin's disease. Case 3, X 100.

Fig. 6.—Mixed lymphoid cells, including typical Reed-Sternberg cells, were evident as well as some eosinophilic leukocytes. Case 3, X 500.

Fig. 7.—The lymph node capsule was infiltrated by lymphoid cells, the peripheral sinusoids were obliterated and the follicular pattern of the cortex was replaced by a monotonous cellular lymphosarcomatous growth. Case 4, X 100.

Fig. 8.—Cells infiltrating the capsule and sinusoids were immature and appeared to represent predominantly immature lymphocytes. Case 4, X 600.
months. He was found to have pneumonia and hypogammaglobulinemia, with a history of grand mal seizures following a head injury in 1935. In 1938 he had been started on phenobarbital, 45 mg. twice daily, to which Dilantin, 0.1 Gm. twice daily, was added when it became available. In 1948, due to “intoxication” by this treatment, it was stopped until 1951. At that time, because of increased seizures, Dilantin and phenobarbital were resumed and Mecobaral, 0.1 Gm. nightly, was added. His seizures had been moderately well controlled.

On January 17, 1957, a biopsy of the scalene lymph node was diagnosed as lymphocytic lymphosarcoma. This had been suspected clinically, although the physical examination, chest x-ray, and complete blood counts were normal. On review, some pathologists regarded the nodes as probably a Dilantin-type atypical hyperplasia (Fig. 9).

From 1957 to 1960, the patient had multiple episodes of furunculosis and skin abscesses. On July 16, 1959, a further biopsy showed definite lymphosarcoma (Fig. 10). In 1960, because of lymph node pressure in the perineum, he received local radiotherapy. In October 1960 the cervical and axillary lymph nodes first became enlarged, followed by all the other peripheral nodes. The blood count remained normal except for hemoglobin of 11.2 Gm. per cent. Continuing seizures did not permit the withdrawal of Dilantin and phenobarbital. Because of progressive mental deterioration, believed due to cerebral arteriosclerosis, he was transferred to a nursing home where he died in July 1961. No autopsy was performed.

**Case 6**

(This patient was a new case presenting in December 1965 after the preparation of the original paper.) A 65-year-old man developed grand mal seizures in 1954 thought to be due to arteriosclerotic cerebrovascular disease. He was started on Dilantin (0.3 Gm./day) and...
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phenobarbital (45 mg./day) on September 24, 1962. In August 1965 he presented with low back pain and was found to have a mass in the left lower quadrant and left thyroid region. Rapid enlargement of the abdominal mass led to a laparotomy on December 9, 1965, and the biopsy of a retroperitoneal node revealed reticulum cell sarcoma. The patient has responded to a course of radiotherapy.

PATHOLOGIC FINDINGS

The lymph node architecture was completely obliterated in the biopsies from the first 3 cases and was partially obliterated in the other 2. Case 1 had matted lymph nodes with a loss of the capsular boundaries, multiple fibrous and hyaline nodules (Fig. 1). This is so-called nodular sclerosing Hodgkin's disease.3

The other 2 instances of Hodgkin's disease were of the granulomatous type, with foci of edema, necrosis, and infiltrates of histiocytes and plasma cells. All 3 had typical binucleate Reed-Sternberg cells, as well as anaplastic mononuclear and multinucleated cells (Figs. 2, 4 and 6). Eosinophils were present in Case 3. In Case 2, there was less fibrosis (Fig. 3) and the alterations appeared relatively early. Case 3 had a rather nodular, granulomatous appearance (Fig. 5).

Case 4 had unusually large lymph nodes with a nodular architecture and infiltrations penetrating the capsule into the perinodal fat (Figs. 7 and 8). The predominant cells were lymphocytes, consistent with lymphocytic lymphosarcoma. Some aspects resembled the so-called polymorphous-cell sarcoma of Symmers.14

Case 5 had two biopsies. In the first biopsy, several lymph nodes (less than 5 mm. in diameter) were removed. Their capsules were intact, the cortex and medulla were poorly demarcated, and the nodes had a solid appearance. On higher power examination, there were close-packed immature lymphocytes and occasional reticulum cells, some with atypical nuclei and prominent nucleoli (Fig. 9). A definite diagnosis of lymphoma was difficult to make and the appearance was more consistent with atypical hyperplasia secondary to Dilantin. Other observers had considered this to be a lymphocytic lymphosarcoma. The second biopsy 30 months later yielded several abnormally large, matted lymph nodes. Microscopically uniform lymphoblastic cells typical of lymphosarcoma had replaced the normal structures and infiltrated the capsules. Similar cells were infiltrating the walls of veins (Fig. 10).

DISCUSSION

The entity of pseudolymphoma following Dilantin and other anticonvulsive therapy was given emphasis following the articles of Saltzstein, Ackerman, and co-workers.10,11 It is worthwhile to define this entity and compare it to true lymphoma—that is, lymphosarcoma and Hodgkin's disease. Pseudolymphoma may be defined as a localized enlargement of lymph nodes that simulates malignant lymphoma clinically and grossly, but which lacks the necessary histologic diagnostic criteria. Obliteration of architectural features, invasion of the peripheral node capsule and blood vessel walls, and clearly recognizable malignant neoplastic cells are generally not observed with pseudolymphoma. Lymphocytic and lymphoblastic lymphosarcoma present a “monotonous” pattern, whereas Hodgkin's disease is characterized microscopically by necrosis, fibrosis, and Reed-Sternberg cells. Typical Reed-Sternberg cells are binucleate or multinucleated with large, pale, overlapping notched or reniform nuclei that contain prominent nucleoli. We include in the term “malignant lymphoma” the following entities: (1) giant follicle lymphoma, (2) stem cell lymphoma, (3) lymphosarcoma, (4) reticulum cell sarcoma, and (5) Hodgkin's disease.
Pseudolymphoma may appear grossly indistinguishable from genuine lymphoma but it fails to meet the histologic criteria. The nodal architecture may be distorted but it is not destroyed, and no architectural or cytologic attributes of malignant neoplasia are clearly identified. Pseudolymphoma is not a specific histologic entity. As a histopathologic diagnostic term it refers to those lymph nodes in which the extent and degree of atypical hyperplasia present either simulate or may be confused with malignant lymphoma. Cytologically there are bizarre reticulum cells, lymphoblasts and unclassifiable lymphoid cells in abundance, but they are not sufficiently anaplastic to be recognizable as lymphoma cells. Early papers emphasized the presence of mononuclear or binucleate cells that simulated, but lacked, the essential features of Reed-Sternberg cells. Thus, lymphosarcoma, lymphocytoma, or giant follicle lymphoma may often be imitated by pseudolymphoma. It should not be considered merely a synonym of so-called atypical Hodgkin's disease.

The clinical picture of pseudolymphoma consists of lymphadenopathy, fever and a morbilliform rash; joint pain and swelling occur often. The spleen and liver may be enlarged, and eosinophilia may occur. There is a short, latent period of days to a few weeks after administration of the offending drug and rapid improvement in the same period of time after withdrawal of the agent. Repeat administration of the drug precipitates the syndrome again.

Admittedly, malignant lymphoma is more difficult to diagnose pathologically than many other neoplasms. Therefore, a history of anticonvulsant administration may help to forestall erroneous diagnosis of cancer. Even the positive history of the administration of anticonvulsant drugs is not definitive, since in the first series of 32 pseudolymphoma cases at least one patient subsequently developed malignant lymphoma.

The present report describes 6 patients with typical Hodgkin's disease or other types of malignant lymphoma who had been receiving therapy with anticonvulsants. The anticonvulsants used were Dilantin, used in all 6 patients, plus phenobarbital used in 3 of the patients, Mysoline and Celontin used in 1 patient, and Mebaral used in 1 patient (see Table 1). Pathologically all the biopsies were typical of malignant lymphoma. The only exception was Case 5, since the first specimen obtained was interpreted as pseudolymphoma by some pathologists and as lymphocytic lymphosarcoma by others. All subsequent biopsies were clearly lymphomatous. This situation exemplifies the difficult differential diagnosis of an atypical lymph node hyperplasia from early lymphoma. The knowledge of anticonvulsant therapy in such an individual may sometimes sway opinion toward pseudolymphoma.

Whether the atypical hyperplasia of lymph nodes sometimes observed during anticonvulsant drug therapy is a precancerous state, and whether Dilantin and related agents sometimes act as carcinogens cannot be answered from the present information. In almost all the previously reported cases when the initial biopsy showed pseudolymphoma, this diagnosis persisted throughout the

*Drugs implicated to date include Dilantin (diphenylhydantoin), Mysoline (primidone), Tridione (trimethadione), Mesantoin, Methoin, Milontin (phonsuximide), and Peganone.
course. In 5 of the present 6 cases the diagnosis of lymphoma was made initially on the first biopsy and remained the diagnosis thereafter. In addition, there is no evidence from animal studies to show that anticonvulsant agents are carcinogenic. However, it is entirely possible that the anticonvulsant drugs are carcinogenic in certain sensitive individuals or act as the inciting factor for lymphoma in these persons. The fact that 6 patients on anticonvulsant therapy were found to have lymphoma in one medical center, in a short period of time, led to a review of the incidence of the diagnosis of atypical lymph node hyperplasia during a 5-year period in this medical center. The diagnosis was only made 8 times in the period in nearly 200 lymph node biopsies. It was found that there were fewer positive biopsies of atypical lymph node hyperplasia (pseudolymphoma) than of true lymphoma in patients receiving anticonvulsant agents. Thus, it appears that lymphoma may occur as often in association with anticonvulsant therapy as pseudolymphoma, again suggesting (1) a relationship between administration of anticonvulsant drugs and lymphoma, and (2) the possibility that anticonvulsant drugs may be carcinogenic in certain susceptible hosts rather than simply allergenic. These possibilities must be borne in mind in persons receiving Dilantin or other anticonvulsants. It is hoped this paper will stimulate other clinical and research reports on this subject.

The management of patients with lymphoma or lymphomatous disorders during the course of anticonvulsant therapy is more complex than in lymphoma developing de novo, because of the constant concern that the pathologist may be in error, and the desire to avoid cancer drug therapy for pseudolymphoma, a benign condition. However, if a carefully studied lymph node biopsy in conjunction with the clinical findings and course indicates a true lymphoma, appropriate therapy for this disorder should be administered without delay. In the uncommon instance when a clear diagnosis is not possible, a trial with the substitution of another agent such as phenobarbital for the original anticonvulsant drug is warranted. Should this fail to yield clinical improvement, such as subsidence of fever and involution of the lymphadenopathy within several weeks, a repeat biopsy is indicated. This may yield proof of lymphoma. The patient should then receive therapy for lymphoma, preferably with radiotherapy, based on the experience in this group of 6 patients. It is worthy of note, even in this small series, that the response to all of the other agents (nitrogen mustard, Leukeran, Velban, and prednisone) was poor, suggesting that chemotherapy is inferior to radiotherapy in this group of patients.

An unnecessary delay in biopsy may allow a true lymphoma that is early and radiation-responsive to progress to an advanced and poorly responsive stage in the interim. Recent reports of supervoltage technics employed in lymphoma, treated at an early stage, were associated with the highest 5-year arrest rate. One cannot anticipate what the response might have been if there had been a delay in treatment, but in the group of patients in this paper early radiotherapy was effective.

In almost all instances, management should include replacement rather than
HYMAN AND SOMMERS withdrawal of the anticonvulsant in use. Although elimination of the offending agent may lead to a rapid subsidence of a nonneoplastic adenopathy, it has not led to a remission of the lymphomatous process (once established) in the patients being presented. Withdrawal of these antiseizure agents may be harmful to the patient's neurologic status, since actual brain damage may result in patients with seizures who are deprived of anticonvulsant therapy. A general withdrawal of these agents is also unnecessary, as indicated by our cases K. Z., J. A. and A. G. (see Table 1), who had completely satisfactory control of seizures following the substitution of phenobarbital for Dilantin, a result also reported in the literature. Occasionally the original anticonvulsant may have to be continued if the other agents fail to control the seizures.

SUMMARY

1. Six patients in whom Hodgkin's disease or lymphosarcoma developed during the use of anticonvulsant agents (Dilantin, phenobarbital, Mysoline, Celontin) are reported.
2. The differential diagnosis from pseudolymphoma, the course of these malignant lymphomas, and their therapeutic management are discussed.
3. Based upon information presently available, it could not be determined whether the atypical hyperplasia sometimes observed during anticonvulsant drug therapy is precancerous, or whether these agents may be carcinogenic in certain sensitive individuals.
4. Patients with a seizure disorder who develop lymphoma require standard therapy for both conditions. The anticonvulsant drugs had no evident adverse effect on the course of the lymphoma, although substitution of another agent seems warranted, if possible, for the offending drug.

SUMMARIO IN INTERLINGUA

1. Es reportate le casos de 6 patientes in qui morbo de Hodgkin o lymphosarcoma se disveloppava durante le uso de pharmacos anticonvulsive (Dilantina, phenobarbital, Mysolina, Celontina).
2. Es commentate le diagnose differential relative a pseudolymphoma, le curso de iste maligne lymphomas, e lor manipulation therapeutic.
3. A base del informationes currentemente disponibile, il non esseva possibile determinar si le hyperplasia atypic que es occasionalmente observate durante chimotherapia anticonvulsive es de character precancerose o si iste agentes es carcinogene in certe susceptibile subjectos.
4. Patientes con un disordine convulsive qui disveloppa lymphoma require le therapia standard pro le un e le altere condition. Le pharmacos anticonvulsive habeva nulle evidente effecto adverse super le curso del lymphoma, sed le substitution de un altere agente pare justificabile in tanto que possibile in loco del pharmaco incriminate.

ADDENDUM*

A 30-year-old white male was examined in January 1966 with complaints of fatigue, nervousness, night sweats, anorexia, and a 25-pound weight loss. Since May 1965 he had

*Case summary kindly supplied by Dr. Herman A. Freckman of Cincinnati, Ohio.
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noted a cough and progressive swelling in the right cervical left axillary and, eventually, left supraclavicular regions. The patient had been receiving Dilantin, 0.1 Cm. 4 times daily, since November 1959 for the control of grand mal seizures following a head injury in August 1959. In addition to the lymphadenopathy described above, a mediastinal mass was seen on chest x-ray. A left cervical node biopsy reviewed by the authors revealed the architecture to be obliterated by lymphocytes, bizarre reticulum cells and occasional plasma cells. A few foci appear fibrotic. Necrosis is not evident. Cells identifiable as Reed-Sternberg cells are noted in abundance. The section was interpreted as Hodgkin's disease. At present the patient is receiving combined Velban and Leukeran therapy with apparent benefit, and has been continued on Dilantin.

REFERENCES

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