# LYMPHADENOPATHY INDUCED BY ANTICONVULSANT DRUGS AND MIMICKING CLINICALLY AND PATHOLOGICALLY MALIGNANT LYMPHOMAS

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SINCE THE introduction of the various hydantoin derivatives and analogues into the therapy of convulsive disorders,[49] scattered reports have appeared in the literature of a peculiar lymphadenopathy directly related to this therapy. These reactions closely mimic various malignant lymphomas, both clinically and pathologically, and a diagnosis of lymphoma might be made by the unwary physician. It is for this reason that this report is being published. Most of the anticonvulsant drugs have been implicated in this reaction, with methoin (Mesantoin) being most frequently implicated. The lymphadenopathy may occur in conjunction with the more widely known reactions to these drugs, such as leukopenia, fever, and skin rashes, or it may appear in the absence of these other reactions. Only a few of the previous case reports included any histological description of the lymph nodes. In the past 5 years, 7 individuals whose clinical courses resembled those previously described have been admitted to either Barnes Hospital or St. Louis Children's Hospital, St. Louis, Mo., and biopsies of appropriate tissues have been performed. These patients form the basis of this report.

## REVIEW OF THE LITERATURE

In the late 1920's and early 1930's, when Nirvanol (5-ethyl-5-phenylhydantoin) was used in the treatment of Sydenham's chorea, lymphadenopathy was a frequent accompaniment of the intentionally induced drug reaction that was the goal of the therapy.[38, 50, 52, 53, 58, 59, 61, 63] However, no reports of the histology of the enlarged nodes are available, and no serious consequences of the adenopathy itself are reported. Because of the severity of the reactions, the serious side effects, and the availability of other means of treating Sydenham's chorea, Nirvanol has never been an approved drug.[16]

In 1940 Coope and Burrows[16] reported on a patient (Table 1, case 1) who developed a severe macular eruption 1 week after the start of diphenylhydantoin (Epanutin) therapy. This was accompanied by pyrexia and palpable nodes in the posterior triangle of the neck. Evidently the symptoms disappeared with cessation of therapy, as the authors stated that there was a recurrence when an attempt was made to resume treatment. The report of Harrison et al.,[34] in 1946, of the first fatality following Mesantoin therapy stated that the patient had slight cervical lymphadenopathy. This patient (Table 1, case 2) was receiving diphenylhydantoin (Dilantin), trimethadione (Tridione), and Mesantoin, and she died of aplastic anemia. At autopsy, the lymph nodes had small germinal centers and showed extramedullary hematopoiesis.

Gaustad, in 1947,[27] described cervical nodes that were slightly enlarged and tender in a 27-year-old man (Table 1, case 3) who had been receiving Hydantal (3-methyl-3, 5-phenylethylhydantoin) for 25 days. The adenopathy was associated with a morbilliform-to-macular rash, fever, leukopenia, and malaise. At about the same time, a preliminary report of 2 patients with cervical adenopathy in the absence of blood dyscrasias appeared.[41] These cases were evidently later incorporated into the report of Bercel et al.[7] Since then several other cases have been reported, and they are summarized in Table 1.

In 1948 3 reports appeared with gross and/or microscopic descriptions of the involved nodes. Van Wyk and Hoffman[64] described the case of a 71-year-old man (Table 1, case 10) who had been receiving Dilantin for about 5 months. He entered the hospital with stomatitis and exfoliative dermatitis. Enlarged left cervical and inguinal nodes were noted on

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TABLE 1

CLINICAL AND PATHOLOGICAL SUMMARY OF REPORTED CASES OF ANTICONVULSANT-INDUCED LYMPHADENOPATHY

| Case no. | Ref. no. Yr. of ref. | Age Race Sex | Drug Durat. admin. | Nodes involved | Other symptoms | Pathological findings | Follow-up |
|---|---|---|---|---|---|---|---|
| 1 | 16<br>1940 | ...<br>... | Epanutin<br>1 wk. | Cerv. | Fever, rash | ... | Recur. when attempt was made to resume treat. |
| 2 | 34<br>1946 | 16<br>...<br>F | Dilantin,<br>Tridione,<br>Mesantoin<br>... | Cerv.<br>(slt.) | Aplast. anemia, 1% eosin. | Autop.; germi. cent. small, extramed. hematopoiesis | Died |
| 3 | 27<br>1947 | 27<br>...<br>M | Hydantal<br>3 wk. | Cerv.<br>(tend.) | Fever, rash, leukopenia | ... | Cleared with cessat. treat. |
| 4<br>5<br>6<br>7<br>8 | 41<br>1947<br>7<br>1950<br>31<br>1947<br>17<br>1949<br>1<br>1948 | ... | Mesantoin<br>... | Cerv.<br>(1"size goose egg") | 2 with leukopenia | ... | 2 with leukopenia recov. when drug discont.; other 3 "reces. & redup. respect. on withdrawal & readmin. ther." |
| 9 | 10<br>1948 | 11<br>...<br>F | Tridione<br>... | Cerv.,<br>inguin.,<br>axil. | Rash, agranulocyt. | Autop.; mesenteric nodes & Peyer's patches hyperplast. (no microscop.) | Died |
| 10 | 64<br>1948 | 71<br>N<br>M | Dilantin<br>5 mo. | Cerv.,<br>inguin. | Anemia, exfol. dermat. | Biop.; destruct. architect., endothel. prolif., infiltrat. eosin. | Died; autop.; periarter. nodosa involv. liver, spleen, kidneys, skin, bone marrow |
| 11 | 29<br>1948 | 6½<br>W<br>M | Dilantin,<br>Tridione<br>... | Few slt. enlarged<br>Clin. | Granulocytopenia | Autop.; nodes slt. enlarged grossly, unremark. microscop. | Died |
| 12 | 35<br>1948 | 17<br>...<br>F | Mesantoin<br>1st mo. | Gen. | Fever, pharyngitis | ... | Cleared with cessat. ther., did not recur with resumpt. ther. |
| 13 | 28<br>1948 | 11<br>W<br>F | Tridione,<br>diphenylene 2 yr. | Cerv.<br>(slt.) | Fever, pancytopenia | Autop.; (no mention nodes) | Died |
| 14<br>15<br>16 | 21<br>1948<br>22<br>1949 | ... | Mesantoin<br>4-8 wk. | Gen.<br>(most prom. cerv.) | Rash, fever, 15% eosin. | ... | Cleared in 1-2 wk. after cessat. ther. |
| 17 | 48<br>1949 | ... | Mesantoin<br>2 wk. | Not specif. | Fever | Biop.; "indistinguish. from Hodgkin's dis." | Recovered on withdrawal drug; fever, rash & adenop. on taking drug again; recovered again on withdrawal |
| 18 | 42<br>1949 | 69<br>...<br>M | Tridione<br>6-7 wk. | Cerv.,<br>submax.,<br>axil. | Rash, icterus, 26% eosin., hepatosplenomeg. | ... | Cleared in 5 wk. on cessat. drug |
| 19 | 4<br>1949 | 29<br>...<br>F | Mesantoin<br>6 days | Gen.<br>(espec. cerv.) | Chills, fever, rash, leukopenia, hepatosplenomeg. | ... | Cleared in 2 wk. on cessat. drug |
| 20 | 8<br>1950 | 30<br>W<br>M | Mesantoin<br>1 wk. | Not specif. | Rash, fever, pharyngitis | ... | Dose reduced briefly & then reinstated with exacerbat. toxic manifest.; after 1 mo., grad. increas. doses without toxicity |
| | | | Thyphenyltoin (in add. to Mesantoin)<br>3 mo. | Cerv. | Fever, pharyngitis, pancytopenia | ... | Recovered with cessat. drug |
| 21 | 47<br>1950 | ... | Mesantoin<br>... | Cerv. | Rash, pharyngitis, tonsillitis | ... | "Therapeutic test reproduced path. picture" |
| 22 | 14<br>1950 | 29<br>N<br>M | Dilantin<br>17 days | Cerv.<br>axil.,<br>inguin.<br>(tend.) | Rash, fever, icterus, 6%-20% eosin., hepatomeg. | Biop.; "chronic inflam." | Cleared with cessat. drug; trial dose 5 wk. later caused rash & eosin.; cleared on cessat. ther. |

TABLE 1 (*Continued*)

CLINICAL AND PATHOLOGICAL SUMMARY OF REPORTED CASES OF ANTICONVULSANT-INDUCED LYMPHADENOPATHY

| Case no. | Ref. no. Yr. of ref. | Age Race Sex | Drug Durat. admin. | Nodes involved | Other symptoms | Pathological findings | Follow-up |
|---|---|---|---|---|---|---|---|
| 23 | 56<br>1950 | 13<br>...<br>M | Mesantoin<br>3 mo. | Gen. | Splenomeg., rash, pancytopenia | ... | Died |
| 24<br>25<br>26 | 26<br>1950* | ...<br>... | Mesantoin<br>... | Not specif. | "Sev. react.", fever, pharyngitis, pancytopenia | ... | Cleared with cessat. ther. |
| 27 | 37<br>1951 | ...<br>...<br>M | Methoin<br>4 mo. | Cerv. | Rash, malaise, lymphocyt., fatigue | ... | Returned to norm. after drug stopped |
| 28 | 15<br>1951 | 21<br>...<br>M | Mesantoin<br>3 wk. | Cerv. (sev.) | Rash, 6% eosin., pharyngitis | Biop.; destruct. architect., retic. cell hyperplas., mitoses, necrosis, phagocyt., eosin. | Resolved with smaller doses; recurred in 17 days, disappear. rapid. when pt. shifted to Luminal |
| 29 | 15<br>1951 | 47<br>...<br>M | Mesantoin<br>3 tab.<br>only | Gen. | Rash, fever, bronchitis | Biop.; similar to case 28 with less necrosis, retic. cell hyperplas., mitoses, phagocyt., eosin. | Resolved with cessat. ther.; reappear. when drug restart. |
| 30 | 36<br>1951 | 29<br>W<br>F | Mesantoin<br>... | Inguin. | Skin pigmenta., 3% eosin. | ... | ... |
| 31<br>to<br>44 | 45<br>1952 | ...† | Mesantoin<br>4 mo.<br>or less | Not specif. | Fever, rash over all nodes, hypertrichosis, skin pigmentat., blood dyscrasias in some nodes | ... | ... |
| 45 | 51<br>1952 | 36<br>...<br>F | Mesantoin<br>20 days | Cerv., submax., mediast. | Fever, myalgia | ... | Regressed slowly on cessat. drug |
| 46 | 51<br>1952 | 56<br>...<br>M | Mesantoin<br>5 wk. | Cerv., then gen. | Fever, urticaria, 11% eosin. | Biop.; architect. altered, retic. hyperplas., many plasma cells, necrosis | Disappear. in 1 mo. when drug stopped |
| 47 | 51<br>1952 | 31<br>...<br>F | Mesantoin<br>1 mo. | Cerv., inguin. | Rash, slt. hepatomeg. | Biop.; alterat. struct., retic. cell hyperplas., eosin., degen. | Sympt. regressed on stopping drug |
| 48 | 51<br>1952 | 46<br>...<br>M | Mesantoin<br>3 mo. | Cerv., axil., inguin. | Prev. hist. skin erupt., grippelike symp., bronchitis, fever, hepatomeg. | Biop.; norm. follic. pattern with pleomorp. react., no necrosis, hyperplas. lymphoid & retic. elements & endothel. | Persist. fever, renal fail., diarrhea, death; drug evident. contin. to death |
| 49 | 62<br>1953 | 11<br>W<br>M | Dilantin<br>2 wk. | Cerv. (slt.) | Fever, rash, 6% eosin. | ... | Recovered rapidly on cessat. ther. |
| 50 | 46<br>1954 | 5<br>...<br>M | Dilantin & phenylacetylurea<br>1 mo. | All palp. nodes, mediast. (X ray) | Fever, rash, 2% eosin. | Biop.; retic. cell hyperplas. replac. follicles, sclerosis at hilum | Recovered with cessat. ther., nodes recur. with resumpt. & disappear. again with cessat. ther. |
| 51<br>to<br>56 | 19<br>1954 | ... | Mesantoin<br>... | Not specif. | Rash, fever, blood alterat., hepatosplenomeg. | ... | ... |

*The report by Garvin and Gibbs[28] included 18 patients who received hydantoin therapy and in whom node involvement was "usual." Other symptoms included rash, fever and pharyngitis; these regressed in 4 to 7 days when therapy was stopped.

†Six of these 14 patients were children, and 8 were adults.

TABLE 1 (*Concluded*)

CLINICAL AND PATHOLOGICAL SUMMARY OF REPORTED CASES OF ANTICONVULSANT-INDUCED LYMPHADENOPATHY

| | Ref. no. | Age | Drug | | | | |
|---|---|---|---|---|---|---|---|
| 57 to 72 | | ... | ... | 14 pt., inguin. & submax. in 2 pt. | | | |
| 73 | | | | | Fever, rash, icterus, hepatomeg., 35% eosin. | | |
| 74 | 43 1957 | 25 ... F | Mesantoin 18 mo. | Cerv., axil. | Clin. diag. dissem. lup. erythem. | ... | |
| 75 | 43 1957 | 18 ... F | Mesantoin 1 mo. | Cerv., axil., | Fever, rash, 7% eosin., pos. lup. erythem. test | | |
| | Case 1 Pres. ser. | 11½ W M | 6 wk. | adenop., mesenteric nodes enlarged at op. | "Acute abdomen" | Append.; tum. retic. cells with num. mitotic figs., eosin., foci necrosis & phagocyt. | Recovered rapidly; well 5 yr. postop. |
| 77 | Case 2 Pres. ser. | 6 W M | Mesantoin 1 wk. | Cerv., inguin., axil. | Rash, conjunct., 3%-9% eosin. | Biop.; retic. cell & lymphoid hyperplas., architect. preserved, few eosin. & small foci necrosis | Recovery with cessat. Mesantoin ther.; seiz. being control. by Gemonil |
| | | | | inguin. gen. | Plasmocyt. 10%, abnorm. ser. prot. (no diag. mult. myel.) | Biop.; 1st, some efface. norm. architec., hyperplas. retic. elements, few plasma cells & eosin.; 2d, replace. most norm. architect., retic. cell hyperplas., mitoses, few areas necrosis, eosin. Biop.; 1st, much obliterat. normal architect., retic. cell hyperplas., mitoses, nuclear debris, eosin.; 2d, sim. to 1st with more eosin. Biop.; hyperplas. lymphoid elements with slt. incr. in retic. cells | Nodes disappear. with cessat. Mesantoin; reappear. & disappear. with resumpt. & cessat. Mesantoin; still has plasmocyt., & abnorm. ser. prot. |
| | Case 6 Pres. ser.‡ | 7 W M | Peganone 5 wk. | Cerv., axil., | splenomeg., 4%-15% | Biop.; compl. obliterat. norm. architect.; infiltrat. lymphocytes, retic. & plasma cells, eosin.; necrosis & | Nodes returned to norm. within days cessat. ther. |
| | Case 7 Pres. ser. | 45 N F | Dilantin 2 wk. | Gen. | Rash, fever, malaise, 5% eosin., icterus, chem. evid. liver damage | destruct. nodal architect. with infiltrat. pleomorp. retic. cells, plasma cells, eosin. | Recovered rapidly with cessat. ther. |

‡This case has been reported previously.[57]

admission. An inguinal node was biopsied, and the histological examination revealed destruction of the normal architecture, endothelial prominence with capillary proliferation, and eosinophilic infiltration. Pigmented macrophages were also found in the node, and the interpretation at the time was a reactive lymphadenitis secondary to the exfoliative dermatitis. At autopsy, 4 days later, the lesions of periarteritis nodosa were found in the liver, spleen, kidneys, skin, and bone marrow.

Gentry and Hill[29] reported the case (Table 1, case 11) of a 6½-year-old boy who died of granulocytopenia, which they attributed to Tridione therapy. He had a few slightly enlarged nodes on admission, and at autopsy the nodes were also described as being slightly enlarged. Microscopically the nodes were "unremarkable." Braithwaite[10] described a similar case (Table 1, case 9), this of an 11-year-old boy who died of agranulocytosis while being treated with Tridione. On admission, the cervical, axillary, and inguinal nodes were enlarged. At autopsy, the mesenteric nodes were also found to be enlarged, and Peyer's patches were described as "hyperplastic." There was no reported microscopic examination of these nodes. A lymph node biopsy, which was microscopically "indistinguishable from those obtained in Hodgkin's disease" was reported by Meller and Resch[48] in 1949. The patient (case 17) had been on Mesantoin for 2 weeks and also had fever. The symptoms abated when the drug was stopped. The patient was given Mesantoin again and developed fever, rash, and adenopathy; again there was recovery when the therapy was stopped.

In 1950 Chaiken et al.[14] reported the case (case 22) of a 29-year-old man who, after being on Dilantin therapy for 17 days, developed malaise, myalgia, a pruritic rash, icterus, and fever. On admission, there were large, tender nodes in the cervical, axillary, and inguinal regions. The liver was also enlarged. The white blood cell count was 8,000, with eosinophils ranging from 6% to 20%. Bone marrow examination revealed an eosinophilia ranging from 28% to 57%. A cervical node was biopsied and disclosed "chronic inflammation." No arterial lesions were described in a simultaneous muscle biopsy. The patient's signs and symptoms cleared with cessation of Dilantin therapy. Five weeks later, a trial dose of the drug was instituted, and the malaise, rash, and eosinophilia reappeared. These again subsided with cessation of therapy.

Several other articles have appeared in the European literature. Chiari[15] reported 2 cases in 1951. The first (case 28) was of a 21-year-old man who had been receiving Mesantoin for 3 weeks when he developed a sore throat, a morbilliform rash, and cervical lymphadenopathy. He had 6% peripheral eosinophilia. A lymph node was biopsied and showed destruction of most of the normal architecture. Reticulum cell hyperplasia with occasional mitotic figures was noted. Areas of necrosis and phagocytosis of cellular and nuclear debris were prominent, and eosinophils were numerous. The patient's therapy was changed to small doses of Mesantoin with resolution of the lymphadenopathy. Seventeen days later, however, the nodes reappeared. They subsequently disappeared rapidly when the medication was again changed to Luminal. Chiari's second case (case 29) was that of a 47-year-old man who had received only 3 tablets of Mesantoin. He developed a rash, bronchitis, and lymphadenopathy. His medication was changed to Luminal with resolution of symptoms. Mesantoin was tried again, and 2 days later the node swelling reappeared. On the following day the node was biopsied. It showed reticulum cell hyperplasia with many mitoses. Cellular degeneration, phagocytosis, and eosinophilic infiltration were noted. Some lymphoid follicular hyperplasia and sparse plasma cells were also present.

Olmer et al.,[51] in 1952, described lymphadenopathy in 4 people (cases 45 to 48) receiving Mesantoin. In 3 of these, nodes were biopsied and showed similar changes. Reticulum cell hyperplasia and plasmocytosis were present in all 3, and necrosis and infiltration with eosinophils were present in 2. Color photomicrographs of the findings were included in the article. Cytological changes similar to all of those previously mentioned were reported by Bodart[9] in 1953. In 1954, Martin et al.[46] described a 5-year-old boy (case 50) who developed a fever and rash 10 days after the initiation of therapy with Dilantin and phenylacetylurea. The drug therapy was stopped, and there was a remission of symptoms. The therapy was restarted, however, 10 days later because of recurrence of the seizures. Four days later the boy again developed fever and rash, this time accompanied by enlargement of all the palpable lymph nodes as well as enlargement of the mediastinal lymph nodes (as demonstrated on roentgenograms). There were only 2% eosinophils in the peripheral blood.

The sternal marrow was normal. An inguinal lymph node was biopsied and showed reticulum cell hyperplasia replacing the follicles and sclerosis at the hilum. There was no mention of eosinophils or necrosis. The child recovered with cessation of the drug therapy.

The most recent report is that of Lindqvist,[48] in 1957, who described 2 cases of disseminated lupus erythematosus after Mesantoin therapy. His second case (Table 1, case 75), was that of an 18-year-old woman who developed fever and cervical lymphadenopathy 1 month after Mesantoin was added to the Epanutin she had been taking. Without any change in therapy, her fever would periodically decrease and increase. After about 6 or 8 weeks, she developed a persistent fever, generalized nontender lymphadenopathy, and a "butterfly" rash that eventually became generalized. Lupus erythematus cells were found in the blood. An axillary lymph node biopsy was performed and showed nonspecific lymphadenitis with an increase of eosinophilic cells. Lindqvist felt that "the histologic picture . . . tallied rather well with that described by [Chiari[15] and Olmer et al.[51]], although the changes were slightly less pronounced." The patient's symptoms, including the lymphadenopathy, responded to adrenocorticotropic hormone therapy.

Several patients included in Table 1 showed only minimal lymphadenopathy. The patient of Harrison et al.[34] (case 2) showed only slight cervical lymphadenopathy, but there was a reduction in the size of the lymph node germinal centers at autopsy, along with extramedullary hematopoiesis. The nodes in the patient reported by Gaustad[27] (case 3) were also only slightly enlarged, but they were tender. The child described by Gentry and Hill[29] (case 11) also had only slightly enlarged nodes, both clinically and at autopsy. In the second case described by Hunter and Jenkins[36] (case 30) there was inguinal lymphadenopathy along with 3% eosinophilia. This is not a significant degree of eosinophilia, and inguinal adenopathy is at best difficult to evaluate. However, no such adenopathy was described in relation to their other 4 patients. Steinberg's[62] patient (case 49) had only slightly enlarged cervical nodes, but he did have 6% eosinophils in the peripheral blood, along with rash and fever, and he recovered rapidly on cessation of therapy.

Both the patient of Gayle et al.[28] (case 13) and Lindqvist's[48] first patient (case 74) showed latent periods much out of proportion to the rest of the patients in this series, and both had only slight cervical lymph node enlargement. The inclusion of these 2 patients in this series might not be justified. DeJong[17] described a case, not included in this series, of jaundice resulting from phenylacetylurea (Phenurone) therapy. A previous diagnosis of infectious mononucleosis had been made, suggesting that there might have been lymphadenopathy. Both the report of Carnicelli and Tedeschi[13] and that of Forster et al.[24] mentioned changes in lymph nodes as results of fatal bone marrow depression, but they did not describe either clinical lymph node swelling or the changes in nodes that others have described in relation to anticonvulsant therapy. Several review articles also mentioned lymphadenopathy related to anticonvulsant therapy, but they did not cite specific examples.[5, 6, 25, 60]

There is only one report of experimental production of lymphadenopathy by anticonvulsants. Kaslaris[39] administered Mesantoin to 4 kittens, 1 of which developed slight lymph node enlargement that on section showed hyperplasia of reticulum cells. Necrosis and mitoses were not present. The nodes in the other 3 kittens were histologically normal. Interestingly, the gingival hyperplasia associated most often with Dilantin but also with the other drugs has been produced in ferrets.[40]

## CASE REPORTS

**Case 1.** In January, 1948, the case of a white boy, 6.5 years old, was diagnosed as that of a behavior problem. He started to have petit mal seizures in June, 1950, and was tried on a variety of drugs, including Tridione, paramethadione (Paradione), phenobarbital, and D-amphetamine (Dexedrine), with only slight improvement. In October, 1952, the Paradione was discontinued. Phensuximide (Milontin) was first given on Oct. 21, 1952, and increased gradually to a maximum dose of 2.7 gm. per day. For 5 days prior to admission, which was on Dec. 12, 1952, he experienced midabdominal pain without nausea or vomiting. On the day of admission, he developed vomiting and diarrhea. On physical examination at the time of admission to St. Louis Children's Hospital (on the service of J. Hollowach), there was tenderness and spasm in both the right upper and right lower quadrants. There was a suggestion of rebound tenderness. No cervical nodes were palpable. Laboratory data showed a hemoglobin level of 13.2 gm. and a white

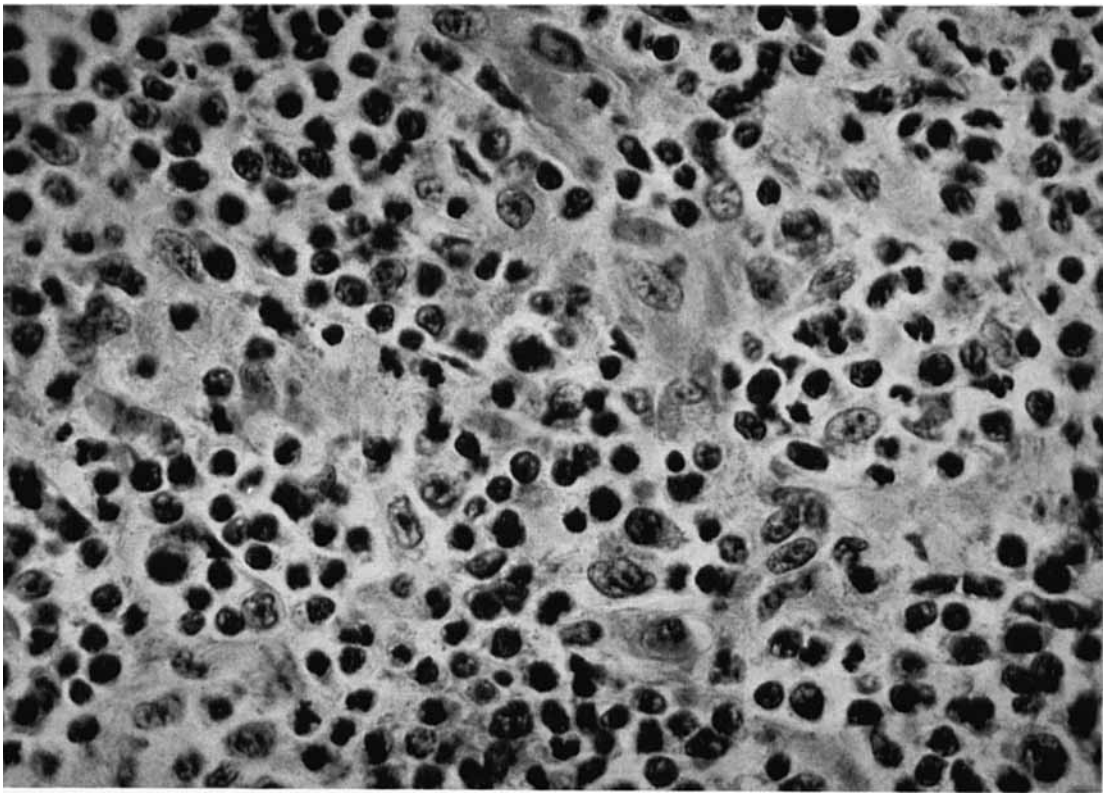


FIG. 1. Case 1. (WU Ill. 58-1100A). Section of the appendiceal mass showing pleomorphic reticulum cells, eosinophils, neutrophils, and nuclear debris. (H. & E. ×750.)

blood cell count of 9,500. Segmented leukocytes represented 91% of the differential count, and eosinophils ranged from 1% to 2%. A preoperative diagnosis of appendicitis was made. He was operated upon (by C. B. Mueller), and several enlarged mesenteric lymph nodes were found. The appendix was intussuscepted into the cecum, and at the base of the appendix a mass of soft, red tissue was noted. The appendix and the mass were removed. Postoperatively the patient recovered rapidly. Grossly, the appendix was congested, but it was not necrotic or perforated. At its base, it was surrounded by a mass of what appeared to be lymphoid tissue, 1 cm. in diameter and 3 ml. in thickness. Microscopically, the architecture of the proximal portion of the appendix was obliterated, and the lumen was occluded by a cellular tumor composed of reticulum cells with numerous mitotic figures (Fig. 1). Eosinophils were prominent in patches and lymphocytes were present, but Reed-Sternberg cells were not seen. Foci of necrosis with phagocytosis were common. The distal portion of the appendix was acutely inflamed. The pathological impression at the time, and on repeated review, was of malignant lymphoma. A subsequent bone marrow study was diagnostically nonspecific.

The Milontin therapy was discontinued when the patient was discharged, and he was maintained in phenobarbital. In October, 1953, because of grand mal seizures, Dilantin was added to the therapeutic regimen. A barium enema and upper gastrointestinal roentgenographic series on Oct. 6, 1954, showed no abnormalities. Acetazolamide (Diamox), in a dose of 250 gm. 4 times a day, was added to the phenobarbital and Dilantin therapy in July of 1956. In March, 1957, an attack interpreted as viral hepatitis, associated with light stools, dark urine (bile and urobilinogen present), jaundice, and minimal splenomegaly, resulted in cessation of the Diamox therapy. He recovered rapidly. A barium enema at that time was entirely normal. When last seen, in November, 1957, 5 years after the operation, he was in good general health. A few small inguinal and cervical nodes were palpable, but the liver was not felt, and only one observer thought he felt the spleen at the left costal margin on unusually deep inspiration. The white blood cell count was 3,700 with a normal differential. At present, he is being maintained on only phenobarbital and Dilantin therapy.

**Case 2.** A white boy, at 16 months of age,

had fallen from a second-story window and suffered a cerebral concussion. He had one clonic convulsion shortly after the fall. He apparently recovered completely, but 6 months later he began having generalized convulsions and petit mal seizures. Dilantin and phenobarbital were started at that time (April, 1949). The child had a history of allergic rhinitis. In January, 1954, he started to have intermittent periods of fever, which continued until his hospital admission. On March 29, 1954, 0.1 gm. per day of Mesantoin was added to his anticonvulsant regimen. One week later, he developed lymphadenopathy, a morbilliform rash, and conjunctivitis. The adenopathy continued until the time of hospital admission. Nine days before admission, his fever recurred, and 7 days before admission, the lymphadenopathy became more marked. He was admitted to St. Louis Children's Hospital (on the service of J. Hollowach) on May 17, 1954.

The only significant physical findings on admission were bilateral cervical lymphadenopathy, consisting of several nontender, nonmatted, freely movable nodes, and smaller inguinal and axillary nodes. The admission laboratory data showed a white blood cell count of 8,200. The differential count included eosinophils ranging from 3% to 9%, a neutrophil count ranging from 31% to 71%, and a lymphocyte count ranging from 39% to 58%. The hemoglobin level was 11.7 gm. A bone marrow study on May 18 was diagnostically nonspecific. On May 20, a cervical lymph node was resected. Four days later, a tonsillectomy and adenoidectomy were performed. Unfortunately, the tissue from the latter operation was not examined histologically. The lymph node measured 8×4×5 ml. and had a pink-yellow color on section. Microscopically, there was slight hyperplasia of both lymphoid and reticulum cells, but the normal architecture with germinal centers was preserved. A few eosinophils, some small foci of necrosis, and a rare mitotic figure were present (Fig. 2). No Reed-Sternberg cells were seen.

The Mesantoin therapy was discontinued while the boy was still in the hospital. His seizures have since been controlled by methbarbital (Gemonil), phenobarbital, and Dilantin. He has remained in good general health. When last seen, in February, 1958, no nodes were palpable.

**Case 3.** A 53-year-old white woman was admitted to Barnes Hospital (on the service of R. Steinkamp) on July 18, 1954, with a chief complaint of painful lumps on her body. She

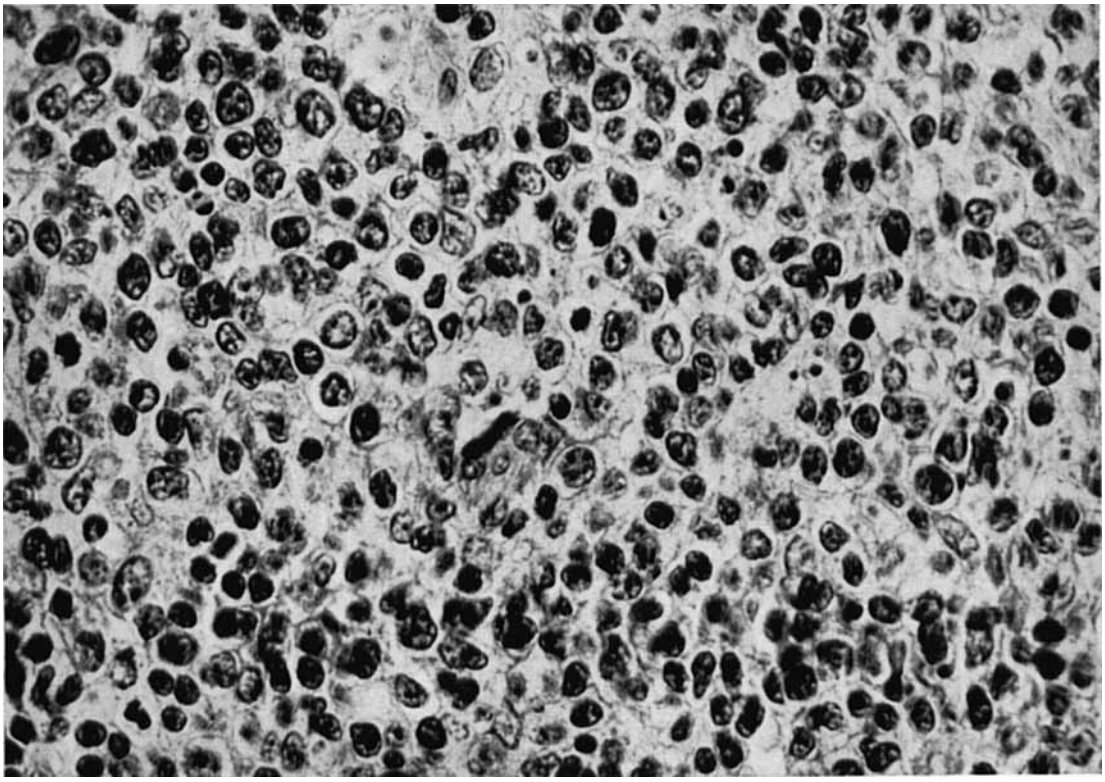


FIG. 2. Case 2. (WU Ill. 58-1101A). Cervical lymph node showing one of the few areas of pleomorphic reticulum cell hyperplasia with nuclear debris. (H. & E. ×750.)

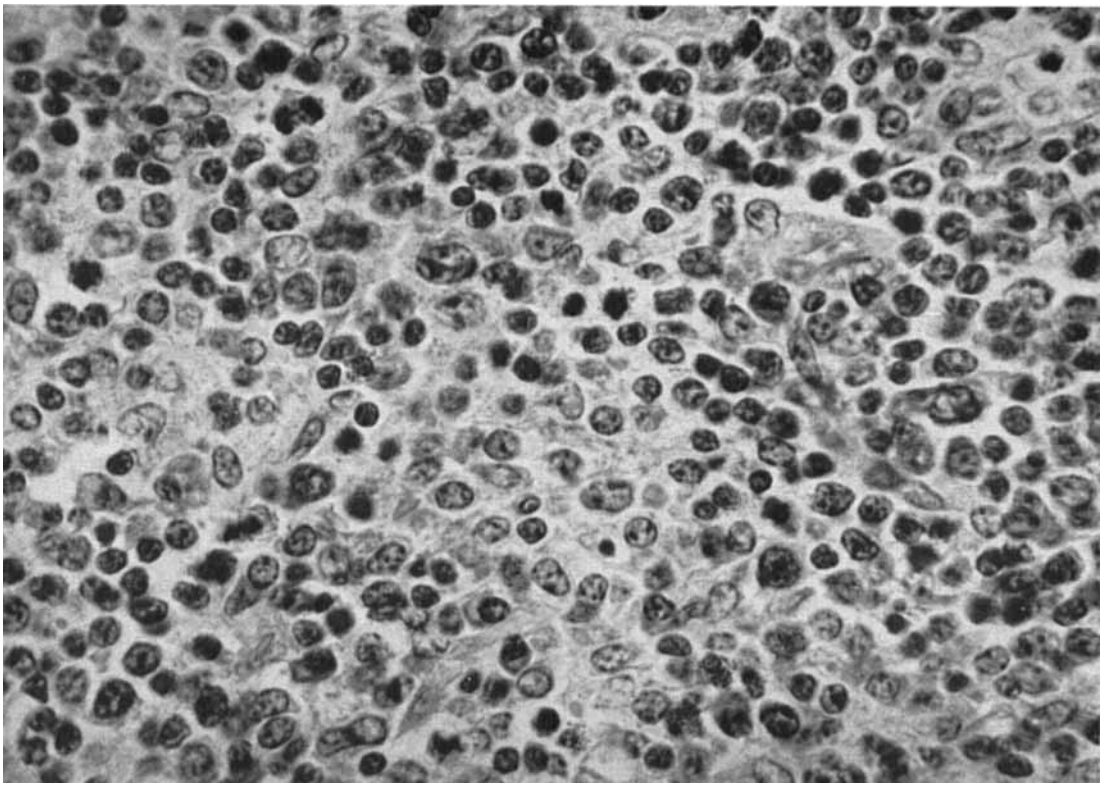


FIG. 3. Case 3. (WU Ill. 58-1102A). Inguinal lymph node showing eosinophils, pleomorphic reticulum cells, lymphocytes, plasma cells, and nuclear debris. (H. & E. ×750.)

had been receiving phenobarbital for 5 years as therapy for mild hypertension. In November, 1953, she had had her first convulsive seizure, and she had had 2 more, in February and March, 1954, respectively. Nicotinic acid therapy was started in March. In early April, an electroencephalogram was interpreted as showing a convulsive disorder, and Dilantin therapy was started. Later in April, approximately 11 weeks before her admission to the hospital, she noted a painful, hard lump under the right mandible. This was not altered by penicillin therapy, and subsequently a similar nodule appeared under the left mandible. On June 1, one of these nodes was removed and showed hyperplasia of the reticulum elements. There was some effacement of the normal architecture, but germinal centers were still seen. Lymphocytes were noted growing out into the capsule. A few plasma cells and eosinophils were seen. In the ensuing 6 weeks, the patient developed tender masses in the right axilla and left inguinal region. She also had other tender areas over her body. There was no fever. On July 12, a bone marrow aspiration was unremarkable except for plasmocytosis of 10%.

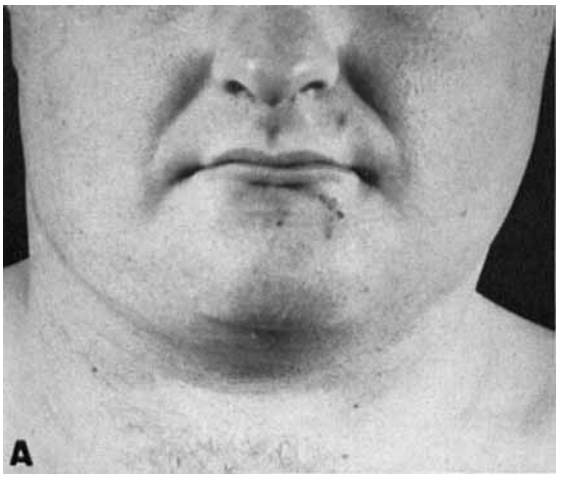
On admission, smooth, slightly tender, enlarged lymph nodes were noted bilaterally in the submandibular regions, in the left cervical and inguinal groups, and in the right axilla. The hemoglobin level was 13.7 gm., and the white blood cell count was 5,900 with only 1% eosinophils. A heterophil antibody titer was negative, and serum protein electrophoresis was interpreted as "abnormal beta-1 globulin." The clinical impression at the time of admission was multiple myeloma (or other lymphoma), but the possibility of a drug reaction was entertained. On July 21, an inguinal node was removed. It showed focal hemorrhage grossly. Microscopically, most of the normal nodal architecture was replaced by a mixed reaction of reticulum cells (often with mitotic figures), plasma cells, eosinophils, and fibroblasts (Fig. 3). Some areas of necrosis were seen, and the capsule did contain lymphocytes. No Reed-Sternberg cells were found. A drug reaction was among the pathological diagnoses considered at the time.

Dilantin was discontinued on July 23, and the patient was maintained on phenobarbital. The lymphadenopathy disappeared. Subsequent to this a trial dose of Dilantin was given, with the reappearance of the nodes. They subsequently disappeared again when the drug was stopped. At present, the patient is alive and well, but she still has the plasmo-

cytosis and abnormal serum proteins. There is no other evidence of multiple myeloma.

**Case 4.** A 26-year-old white male sheet metal worker was admitted to Barnes Hospital (on the ward service) on Sept. 14, 1956, with a chief complaint of "swellings" on his body for 4 months. When he was 2 years old, he had fallen down a flight of stairs. Shortly thereafter he had developed "blanking-out" spells, and eventually a motor component appeared in the seizures. For 6 to 7 years, he had been taking Dilantin. Early in April, 1956, because of the increased frequency of his seizures, Mesantoin (1 tablet twice a day) was given in addition to the Dilantin. Later in April, he had an episode of fever and weakness associated with a macular rash. This was interpreted as tonsillitis or scarlet fever, and he was given some pills that possibly were sulfonamides. Toward the end of the month, he was admitted to the Alton Memorial Hospital, Alton, Ill., and a tonsillectomy was performed.

In May he developed right cervical lymphadenopathy that gradually increased. Five weeks before admission a generalized, pruritic,



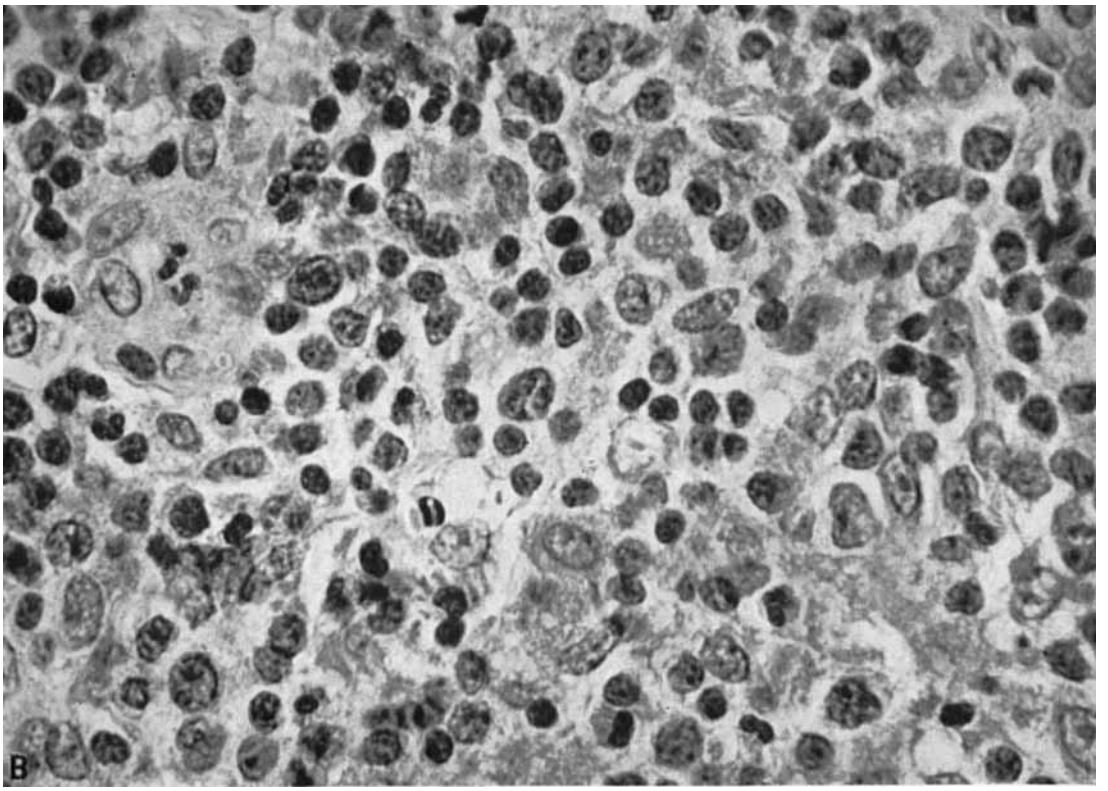




FIG. 4. A, Case 4. (WU Ill. 56-5046). Clinical photograph at the peak of the reaction with the enlarged lymph nodes appearing as generalized cervical swelling. B, Case 4. (WU Ill. 58-1103A). Occipital lymph node containing pleomorphic reticulum cells (with 2 mitotic figures), lymphocytes, and eosinophils. (H. & E. ×750.)

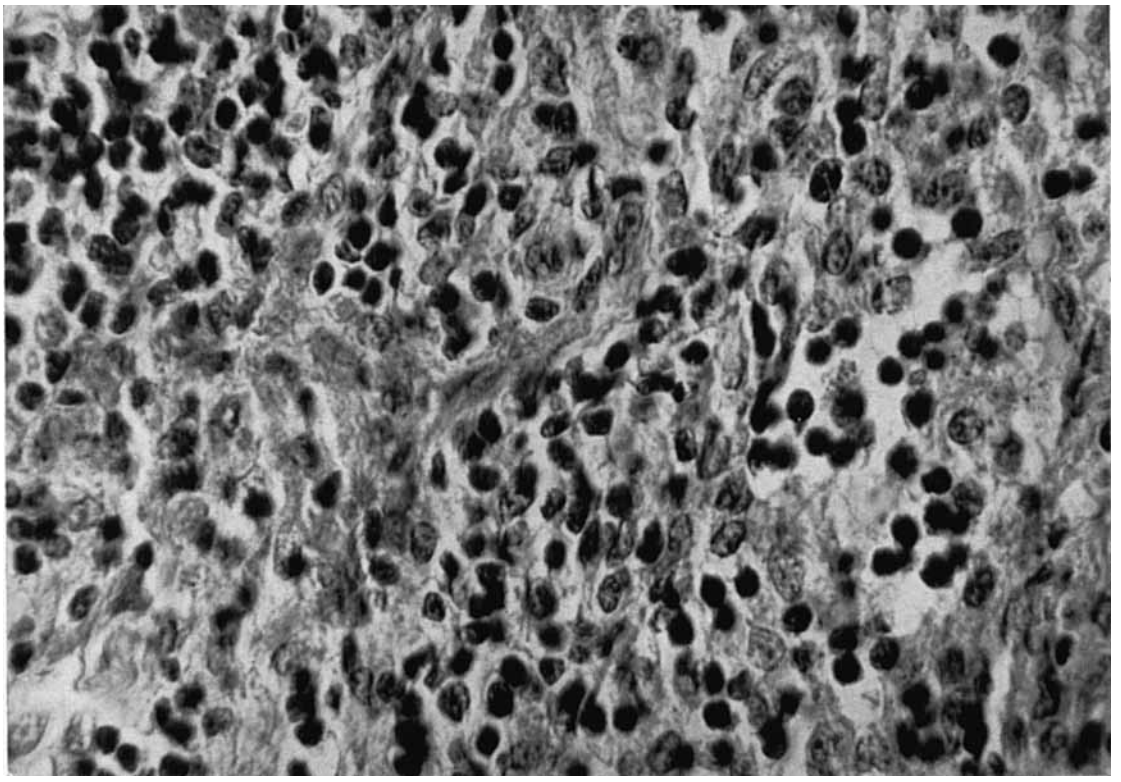


FIG. 5. Case 5. (WU Ill. 58-1104). Cervical lymph node showing hyperplasia of reticulum cells with eosinophils. (H. & E. ×750.)

maculopapular rash appeared, disappeared a few days later, and then reappeared. About 3 or 4 weeks before admission, there was an increase in the size of the nodes, and nodes in other locations (submandibular and inguinal) were visible. He was readmitted to the Alton Memorial Hospital 2 weeks before his admission to Barnes Hospital, and a left inguinal lymph node was resected. Microscopically, the node revealed considerable, but not total, obliteration of the normal architecture. Hyperplasia of the large reticulum cells with several mitotic figures was very prominent. There was a moderate amount of nuclear debris present, but phagocytosis was not marked. A great many eosinophilic leukocytes were seen. No Reed-Sternberg cells could be identified. At the time of the resection, the possibility that this might represent a drug reaction was strongly considered.

On admission to Barnes Hospital, the patient showed a diffuse maculopapular erythematous rash and multiple 1- to 3-cm. firm, nontender nodes over the occiput, in the cervical, submandibular and submental lymph node groups, and in the left axilla and inguinal regions. There was a generalized swelling of the neck (Fig. 4A), and the liver was palpated 5 fingerbreadths below the right costal margin. The initial impression was of Hodgkin's disease. The hemoglobin level was 16.6 gm., and there was leukocytosis of 11,750. The eosinophils ranged from 12% to 25% of the differential count. Mesantoin therapy was discontinued when the patient was admitted to the hospital, but Dilantin therapy was continued.

A left occipital lymph node was resected on Sept. 20, and a bone marrow aspiration was performed the following day. On microscopic examination, this node was similar to the first one, except that even more eosinophils were present (Fig. 4B). The bone marrow was thought to be normal except for an increase in the number of eosinophils. Starting on Sept. 27, bromide therapy was instituted; when therapeutic levels were attained, the Dilantin he had been receiving was discontinued. The patient was followed after his discharge from Barnes Hospital on Oct. 20, 1956, by the clinics of the Washington University School of Medicine. A skin biopsy on Oct. 29 showed some lymphocytes about the vessels in the upper dermis. This was interpreted as nonspecific chronic dermatitis. He was started on primidione (Mysoline) on Nov. 20, 1956, and the phenobarbital dosage was correspondingly reduced. By February, 1957,

there was no palpable lymphadenopathy. Eosinophils represented 1% to 2% of the total white blood cell count.

In late September, 1957, he had some lower abdominal pain, more severe on the left side than on the right. He was seen in the clinic, and a mass of left inguinal nodes as well as an ill defined left lower quadrant abdominal mass was found. No therapy in relation to the masses was undertaken. His symptoms have since slightly abated, but the masses persist. A barium enema on Jan. 20, 1958, was interpreted as showing a left pelvic mass. When seen again at the end of February and in early April, the inguinal mass was restricted to the region of the inguinal biopsy scar. The ill defined, nontender abdominal mass had not increased in size.

**Case 5.** A white boy first began having grand mal seizures at 3 years of age. On several occasions a low blood sugar level was recorded, and at first it was thought that the seizures were attributable to hypoglycemia. Later the child's mother noted that withholding sugar, which previously had aborted the seizures if it were given in the prodromal phase, did not bring on the attacks. Phenobarbital therapy was started in August, 1956, but the patient continued to have seizures. Dilantin therapy was started some time after that (4 capsules per day). Mesantoin therapy (350 mg. per day) was started on Aug. 17, 1957 (at which time the patient was already taking Dilantin and phenobarbital), and the child's seizures decreased in frequency. In early October, 2 months prior to hospital admission, the child developed a generalized petechial rash that disappeared after a "shot" was given to him by his family doctor. He then developed malaise, vague joint pains, anorexia, and constant low grade fever that continued until the time of admission. No seizures occurred during this time, but an episode of diarrhea occurred. This was followed by the "flu," and chlortetracycline (Aureomycin) was given. Six weeks before admission, the child developed right cervical lymphadenopathy. The nodes fluctuated somewhat in size, but during the month prior to the boy's hospital admission they remained almost constantly the same size.

On admission to St. Louis Children's Hospital on Dec. 3, 1957, (on the service of S. Harrison) enlarged nodes were palpated on both sides of the neck. Some of these almost covered the sternomastoid muscle. The nodes were quite firm, and they were separate. A few inguinal nodes were also palpated. The liver was felt 2 cm. below the right costal margin, and the rest of the physical examination was within normal limits. Laboratory data included a hemoglobin level of 13.2 gm., and a white blood cell count of 9,150. The differential included 13% eosinophils and 18% monocytes. A bone marrow aspirate was thought to be normal. Old tuberculin and histoplasmin skin tests were negative. On Dec. 7, a left cervical node was resected. Grossly the node measured 2×1×1 cm., and was gray-white in color. The cut surface was homogeneous. On section, there was hyperplasia of the lymphoid tissue and a slight increase of fibrous connective tissue and reticulum cells (Fig. 5). No necrosis or phagocytosis was seen, and only a few scattered eosinophils were noted.

Since discharge, the lymphadenopathy has completely disappeared. At the present time, the child is in perfect health.

**Case 6.** This case has been reported previously by us.[57] Briefly, it is that of a 7-year-old white boy who had had a convulsive disorder since 3 years of age and also had allergic rhinitis. Three months before admission, he was started on ethotoin (Peganone), and 7 weeks before admission he developed cervical and axillary lymphadenopathy that eventually included nodes "as large as a fist." At the time of admission to St. Louis Children's Hospital (on the service of J. Jaudon), in addition to the large nodes, the liver and spleen were each palpable 1 cm. below the respective costal margins. He had a temperature ranging from 37.4° to 39.2° C. There were eosinophilis ranging from 4% to 15% in the peripheral blood. A bone marrow examination was interpreted as being normal except for a slight increase in eosinophils. One of the nodes was removed on the second hospital day, and the Peganone therapy was discontinued at the same time. Within a matter of days, the enlarged nodes had all but vanished, and they have not since become enlarged again. At the present time, 4 months after the resection, the child is in excellent physical health.

Microscopically, the resected node showed virtually complete obliteration of the normal architecture. It was infiltrated by a pleomorphic reaction including lymphocytes, plasma cells, neutrophils, eosinophils, and reticulum cells (Fig. 6A and B). Many of the latter were large, with pleomorphic nuclei and frequent mitotic figures. No Reed-Sternberg cells were found. There were many areas of necrosis with accompanying phagocytosis of nuclear debris. Some invasion of the capsule by lymphocytic and reticulum elements was seen.

**Case 7.** Approximately 2 or 3 months before admission to Barnes Hospital, a 45-year-old Negro woman began having right-sided head-

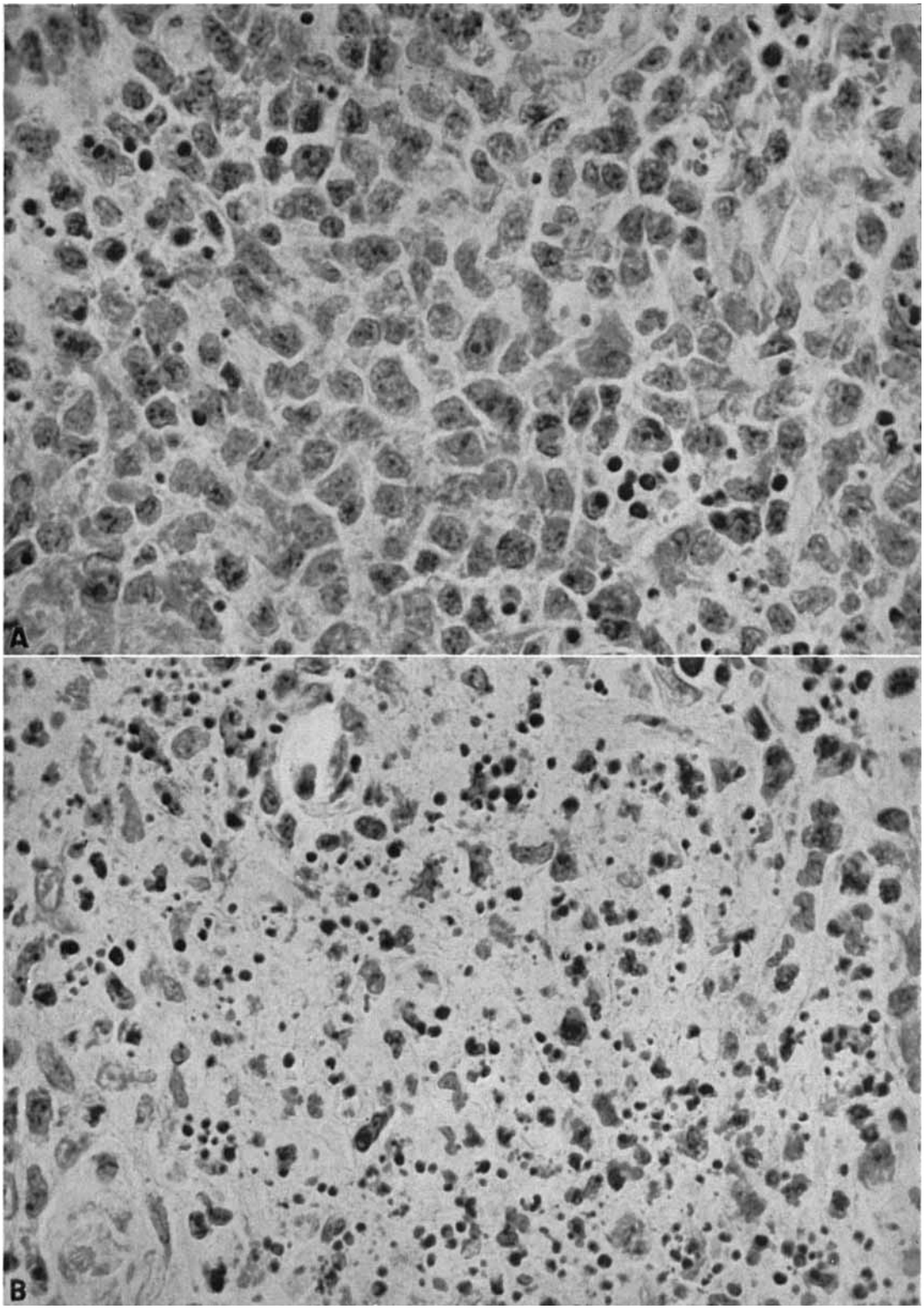



FIG. 6. A, Case 6. (WU Ill. 58-1456A). Pleomorphic, atypical reticulum cells (with a mitotic figure), lymphocytes, and nuclear debris in the cervical lymph node. (H. & E. ×750.) B, Case 6. (WU Ill. 58-1457A). Large focus of necrosis in the cervical lymph node. (H. & E. ×750.)

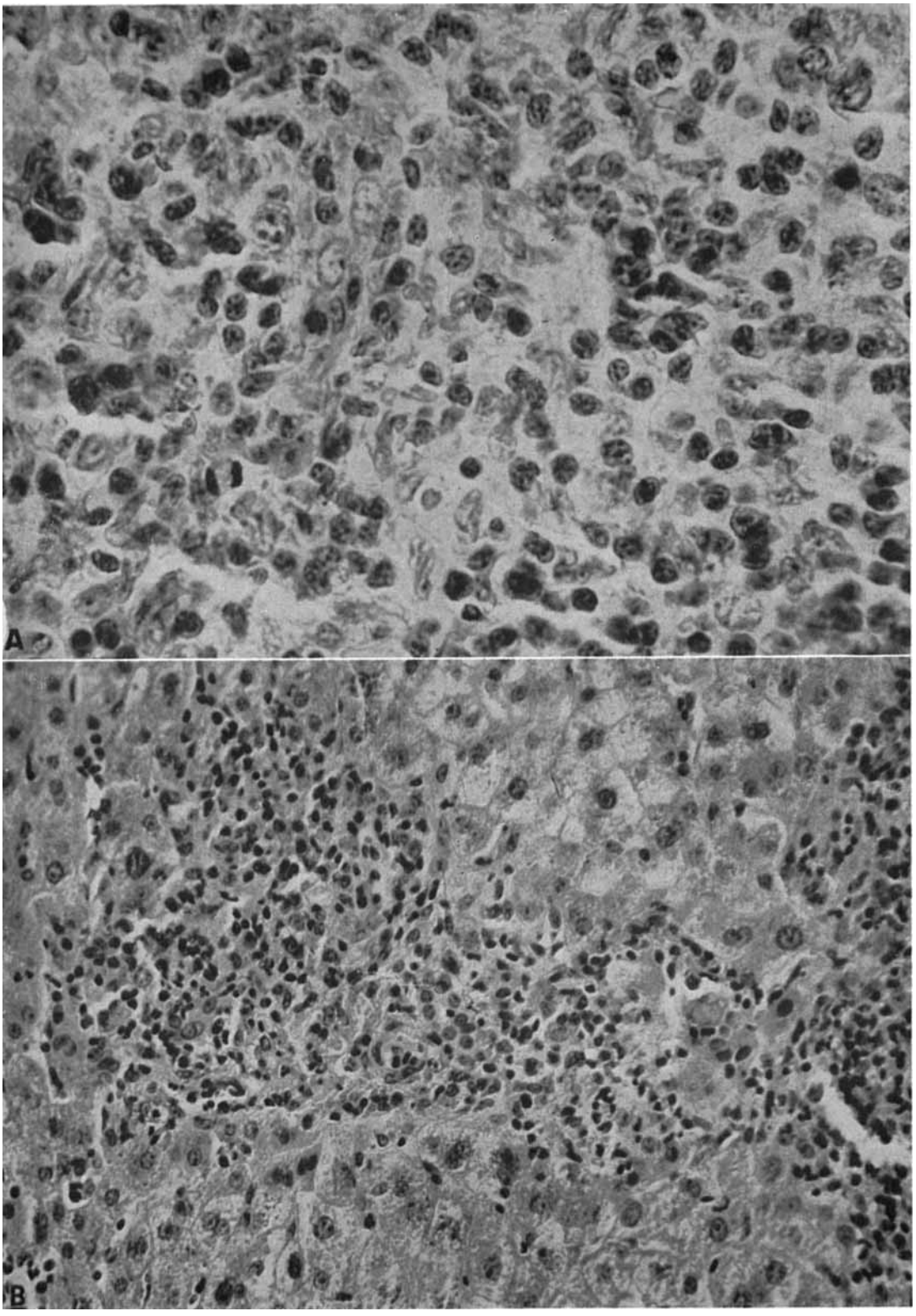



FIG. 7. A, Case 7. (WU Ill. 58-2052A). Cervical lymph node showing infiltration with pleomorphic reticulum cells (with 1 mitotic figure). (H. & E. ×750.) B, Case 7. (WU Ill. 58-2051A). Pericholangiolitic collections of neutrophils, eosinophils, and lymphocytes in liver needle biopsy material. (H. & E. ×370.)

aches that tended to be worse toward the end of the day. The headaches were not accompanied by visual auras, nausea, or vomiting, but symptoms of hot flashes, faintness, numbness, and parasthesias, attributed to the menopause, were aggravated by them. At first, the headaches were relieved by salicylates. She was seen in the Neurology Clinic of the Washington University School of Medicine 5 weeks before her hospital admission. Combining the history of headaches, which were thought to be migraine, and the vague history of previous faintness and numbness, a tentative diagnosis of an idiopathic convulsive disorder was made. Blood studies, urinalyses, and cranial roentgenograms were all normal. An electroencephalogram was interpreted as being "consistent with a convulsive disorder." Therefore, the woman was started on Dilantin therapy (0.1 gm. twice a day) 1 month before admission.

Three weeks before admission, she developed a generalized pruritic maculopapular rash. She was again seen in the clinic, at which time her white blood cell count was 7,000. No differential was performed. The Dilantin therapy was continued. Shortly after this, she developed lymphadenopathy involving all of the palpable nodes. There was a brief episode of transient lessening of symptoms afterwards, but severe fever, chills, malaise, and swelling of her hands and feet began 4 days before her hospital admission and continued until the time of admission.

She was admitted to Barnes Hospital (on the ward service) on March 4, 1958. At that time she had a temperature of 39° C. and a pulse rate of 100. She appeared acutely ill and uncomfortable. Her skin was covered with a maculopapular erythematous eruption that tended to be petechial on her legs. Large, soft, slightly tender nodes were felt in all of the node groups, but those in the left posterior cervical chain and in the axillae were especially enlarged. No abdominal organs were palpated, and no icterus was noted on examination.

The white blood cell count was 8,250, with a differential count that included 5% eosinophils. The hemoglobin level was 11.3 gm., and the hematocrit was 38%. At the time of the latter test, it was noted that the serum was icteric. Therefore, a series of "liver function" tests were performed, and they showed a total serum bilirubin level of 1.5 mg. per 100 cc. (with the direct-acting level being 0.5 mg. per 100 cc.), a serum alkaline phosphatase level of 13.1 Bodansky units, and sulfobromophthalein (Bromsulphalein) retention of 36.2% in 45 minutes. The serum glutamic-oxaloacetic transaminase was 850 units and the glutamic-pyruvic transaminase was 430 units. Serum protein levels, cephalin cholesterol flocculation, and thymol turbidity were within normal limits. A lupus erythematosus test was negative, and the erythrocyte sedimentation rate was 23 mm. per hour.

Because of previous experience with reactions to hydantoin drugs, the patient was considered, at the time of hospital admission, to have such a drug reaction, and the Dilantin therapy was discontinued. Adrenal cortical hormones (prednisone) were employed in her therapy, and her headaches were relieved with salicylates and narcotics. On March 7, removal of 2 left supraclavicular lymph nodes along with skin and skeletal muscle was performed. Grossly the skin and muscle were unremarkable. One of the nodes measured 3 mm. in diameter, and the other 1.5×0.5×0.5 cm. Both were firm in consistency, and the architecture appeared to be preserved. There was some focal hemorrhage in the larger node. Microscopically, both nodes showed areas in which the normal nodal architecture was preserved and areas in which it was destroyed. In the latter areas, there was infiltration of large pleomorphic reticulum cells with frequent mitotic figures, eosinophils, plasma cells, neutrophils, and lymphocytes (Fig. 7A). No necrosis or phagocytosis was seen. The skin sections demonstrated a perivascular infiltration of lymphocytes, macrophages, plasma cells, and eosinophils in the upper dermis. The muscle sections were unremarkable. The nodal changes were interpreted as being those of a hydantoin-induced lymphadenopathy, while the skin changes were thought to represent a drug reaction.

A liver needle biopsy was performed on March 11. Collections of inflammatory cells, especially neutrophils, eosinophils, and lymphocytes, were present about the small cholangioles in the portal spaces and scattered elsewhere throughout the parenchyma (Fig. 7B). A few necrotic hepatic cells and other vacuolated liver cells were noted. Both bile and lipochromatic pigment were seen. No bile plugs or "bile lakes" were found. This picture was thought to be representative of a toxic cholangiolitis not unlike that described in reaction to chlorpromazine hydrochloride.

Clinically, the patient improved rapidly. The adenopathy was virtually gone by the fourth hospital day, and the skin rash cleared up with equal rapidity. By March 19 the serum glutamic-oxaloacetic transaminase had fallen to 69 units, and the serum glutamic-pyruvic transaminase to 100 units. The cephalin cholesterol flocculation was 3+, and the thymol turbidity 8.5 units at this time. The serum alkaline phosphatase was 10.1 Bodansky

units, and the serum bilirubin less than 0.8 mg. per 100 cc. A high axillary lymph node was removed on March 21. This showed only the changes associated with dermatopathic lymphadenopathy. The patient developed an erythematous rash postoperatively that was attributed to the pentobarbital (Nembutal) used as a preoperative medication. This cleared up rapidly when the drug was discontinued and the dosage of prednisone was increased. She was discharged from the hospital on March 30 to be followed in the clinics of the Washington University School of Medicine. Her medication at the present time includes prednisone, antacids, and vitamins.

## DISCUSSION

The usual reactions to the anticonvulsant drugs were well summarized in the book of Goodman and Gilman[32] and that of Alexander.[2] Both books briefly described adenopathy resulting from Dilantin and Nirvanol therapy. The chemical structural similarities of the various hydantoin derivatives is obvious, but, as has been pointed out by Goodman and Gilman[32] and others, the other anticonvulsant drugs also have similar chemical structures. This may give some basis to the similar actions and toxic effects of these drugs. It has been shown that in man and dogs, Mesantoin is demethylated to Nirvanol metabolically.[11, 12]

Our third patient (Table 1, case 78) and the fourth patient (case 48) of Olmer et al.[51] both showed a persistent plasmocytosis in the bone marrow and resected nodes. Neither ever showed conclusive evidence of multiple myeloma, although our patient did have abnormal serum proteins. Another case of the drug reaction mimicking appendicitis, similar to the case of our first patient (case 76), has been reported in relation to Dilantin therapy.[65] This patient was not operated on, but cessation of Dilantin therapy resulted in disappearance of the symptoms. No adenopathy was described in this case.

In reviewing Table 1, it can be seen that a rather characteristic clinical syndrome can be described. The lymphadenopathy most frequently involves the cervical nodes, although it can involve any palpable or visualizable groups of nodes. Perhaps this is because the cervical nodes are examined more closely than are some of the other lymph node groups, but in our fourth (case 79), fifth (case 80), sixth (case 81), and seventh (case 82) patients, the cervical adenopathy was greatly out of proportion in relation to the swelling in other node groups. The nodes are often tender, but they are not invariably so. They vary in size from minimal enlargement to "the size of a goose egg," as in one of the cases 4 to 8, or "as large as a fist," as in case 81. The swelling may begin as soon as 1 week after therapy is started, or it may be delayed for as many as 18 months (case 74) or 2 years (case 13). In only 3 cases (cases 10, 13, and 74) was there a latent period of more than 4 months.

The lymphadenopathy is usually associated with the more common manifestations of drug reactions, such as esoinophilia, fever, blood dyscrasias, and skin disorders. The latter include morbilliform or scarlatiniform rashes, urticaria, exfoliative dermatitis, and abnormal pigmentation. Conjunctivitis has also been reported in association with lymphadenopathy. Splenic or hepatic enlargement occurs frequently. The nodal involvement can occur in the absence of some of the other manifestations of a drug reaction. Only in our first case (case 76) did it occur in the absence of all of the other signs and symptoms of a drug reaction. The lymphadenopathy in itself is not fatal. Those patients who have died succumbed to other reactions, such as agranulocytosis, pancytopenia, or periarteritis nodosa. In the great majority of patients, the lymphadenopathy disappeared, along with the other symptoms, in 1 or 2 weeks after cessation of therapy.

The gross appearance of the removed nodes is certainly nonspecific. They are enlarged, gray, and only moderately firm. Areas of hemorrhage and necrosis are occasionally seen with the naked eye. Histologically, the nodes show varying degrees of effacement of the normal architecture and a rather pleomorphic cellular reaction. Characteristically, there is hyperplasia of the reticulum cells and infiltration with eosinophils. Neutrophils, plasma cells, and young lymphocytes are also seen. Mitotic figures and abnormal reticulum cells may also be quite prominent, as in our first (case 76) and sixth (case 81) cases. Patches of necrosis and nuclear debris, the latter often present in macrophages, is quite a consistent finding.

Diagnostically the problem is, as stated at the beginning of this paper, to differentiate this drug reaction from the reaction seen in the presence of the various malignant lymphomas. The clinical history of the patient is of major importance. The "drug reaction" cause of lymphadenopathy should always be

considered when a patient who has been started on a new anticonvulsant drug in the previous few months develops enlarged nodes. The association of the onset of adenopathy with the onset of fever and skin rash is also helpful diagnostically, but the lymphomas can also produce these reactions. A finding of eosinophilia in the peripheral blood and bone marrow would lend support to the diagnosis of a drug reaction. Leukopenia, agranulocytosis, anemia, or pancytopenia can occur as a result of either lymphomas or drug reactions.

Histologically, in the drug reaction there is not the uniform picture of mature lymphocytes that there is in association with lymphosarcoma or chronic lymphatic leukemia. Reed-Sternberg cells are never seen, and this, along with the fact that the nodes in the drug reaction are usually discrete rather than matted, should be noted as a differentiation from Hodgkin's disease. There is also less fibrosis in the drug reaction. Otherwise, the drug reaction and Hodgkin's disease morphologically resemble each other fairly closely. The distinction between the adenopathy induced by anticonvulsant therapy and that in the acute leukemias and reticulum cell sarcoma may be more difficult. The blood and bone marrow picture is of prime importance in the former. It was only in the follow-up that we were reasonably certain that our first case (case 76) did not involve reticulum cell sarcoma. Even in the sections of this case, however, the small foci of necrosis and infiltration with eosinophils, which are characteristic of the drug reaction, were seen. This is the only case in which significant invasion of surrounding tissue was seen. Slight invasion of the nodal capsule occurred in 2 other cases of ours (cases 78 and 81).

Etiologically, the adenopathy is best considered part of a patient's allergic idiosyncracy in relation to the drugs. The relation of the onset of the nodal swelling to the recent introduction of a new drug into the patient's therapy and the disappearance of the swelling with cessation of therapy is excellent presumptive evidence that the drug causes the reaction. In a few of the cases in this series (cases 1, 4 to 8, 17, 20, 21, 28, 29, and 78), resumption of therapy with the offending drug caused an exacerbation of the adenopathy. The rarity of the reaction makes the postulation of an idiosyncracy tenable. Using the figures cited by Forster,[23] there must be approximately a million epileptics in the United States alone at the present time, and the majority of them must be receiving some medication. The search of the world's literature (Table 1) shows less than a hundred cases of lymphadenopathy resulting from therapy with the hydantoin and hydantoin-like drugs. Most authors consider the rash, fever, and bone marrow depression to be an allergic reaction. Many of the patients had a previous history of allergies. The finding of peripheral blood and bone marrow eosinophilia and infiltration of the nodes by eosinophilic leukocytes lends more evidence to an allergic origin. Similarly, at least 3 of the cases in this series (cases 10, 74, and 75) were associated with either periarteritis nodosa or disseminated lupus erythematosus, both of which are considered by many to be allergic reactions of one type or another.[54] The entire course is similar to that of serum sickness,[44] as was pointed out even in the days of Nirvanol therapy.[58, 61] Lymphadenopathy is an important component of serum sickness.

Histological descriptions of the lymph nodes in serum sickness are rare.[20, 55] Germuth[30] described granulomatous and diffuse inflammatory reactions composed of reticulum cells and epithelioid cells in the mesenteric lymph nodes of rabbits given intravenous bovine serum. His photomicrographs are not too unlike our sections.

The clinical and pathological similarity of the drug-induced lesions to the various malignant lymphomas leads to speculation regarding etiological relationships. Certainly, further clinical studies and animal experiments should be done with this in mind.

## SUMMARY

A clinical and pathological syndrome closely mimicking malignant lymphomas can result from treatment with the various hydantoin and hydantoin-like drugs. This reaction should be seriously considered before any therapy directed at a lymphoma is instituted.

Clinically, the syndrome includes lymphadenopathy, fever, exanthema, eosinophilia, and, less frequently, hepatosplenomegaly. Pathologically, the nodes show obliteration of the normal architecture, hyperplasia of the reticulum cells and other elements, with frequent mitoses, infiltration with eosinophilic leukocytes, focal necroses, and phagocytosis. No Reed-Sternberg cells are present.

Cessation of therapy with the offending drug results in remission of the clinical and pathological findings.

Etiologically, this lymphadenopathic reaction is felt to be the result of an allergic response.

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