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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Cutaneous and immunologic reactions to phenytoin

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Dallas, TX, Rochester, NY, and Davis, CA

Phenytoin (diphenylhydantoin; Dilantin) is a highly effective and widely prescribed anticonvulsant and antiarrhythmic agent. Since 1938 it has been invaluable in the treatment of grand mal and psychomotor epilepsy. Hydantoin derivatives have been used medicinally for more than a half-century. In recent years dermatologists have broadened the indications for phenytoin use to include recessive dystrophic epidermolysis bullosa, linear scleroderma, and pachyonychia congenita. In spite of widespread use and popularity, it is interesting that the frequency of complications relating to drug therapy remains low, relatively speaking. Nevertheless, a broad spectrum of cutaneous and immunologic reactions to phenytoin have been reported. These range from tissue proliferative syndromes (side effects), drug hypersensitivity syndromes (allergic effects), and a possible linkage with lymphoma (idiosyncratic effects). Therapeutic and toxic reactions to this commonly prescribed drug are comprehensively reviewed, analyzed, and summarized in this monograph. (J AM ACAD DERMATOL 1988;18:721-41.)

Phenytoin (diphenylhydantoin; Dilantin) revolutionized the treatment of convulsive disorders in 1938 and remains today a mainstay of therapy.1 Investigation of phenytoin effects has led to enhanced understanding of collagen synthesis and modeling, as well as its utilization in dermatologic therapeutics (for example, treatment of dystrophic epidermolysis bullosa). Cutaneous reactions to phenytoin (Table I) represent only part of a broad spectrum of adverse drug effects (Table II), which include allergic hypersensitivity, immunologic abnormalities, and toxic side effects.

In spite of a cornucopia of case reports and descriptive accounts, the literature lacks a comprehensive critical overview of the phenytoin experience. Our purpose is to summarize known drug effects and underlying mechanisms, clarify confusing terminology, and highlight avenues for further investigation of the cutaneous and immunologic effects of phenytoin.

PHARMACOLOGY2,3

Clinically useful hydantoins include phenytoin, mephenytoin (Mesantoin), and phenylethylhydantoin

Table I. Phenytoin-associated exanthems

<table>
<thead>
<tr>
<th>Acneiform</th>
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<tr>
<td>Exfoliative dermatitis</td>
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<tr>
<td>Erythroderma</td>
</tr>
<tr>
<td>Toxic erythema</td>
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<tr>
<td>Hyper- and hypopigmentation</td>
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<tr>
<td>Maculopapular (morbilliform)</td>
</tr>
<tr>
<td>Pseudolymphoma/lymphoma</td>
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<tr>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Vesiculobullous</td>
</tr>
<tr>
<td>Erythema multiforme minor</td>
</tr>
<tr>
<td>Erythema multiforme major</td>
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</table>

From the University of Rochester School of Medicine, Rochester,**
and the University of California, Davis School of Medicine, Davis,***
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Table II. Phenytoin reactions

I. Predictable (known mechanisms)
   A. Overdose (dose-related toxic side effects)
      1. Central nervous system toxicity
      2. Cardiopulmonary toxicity
   B. Drug interactions (effects present when two or more drugs are given simultaneously but absent if administered alone)
   C. Side effects (undesirable pharmacologic effects present at therapeutic doses)
      1. Collagen synthesis
         a. Gingival hyperplasia
         b. Coarse facial features
         c. Heel pad thickening
      2. Nondermatologic
         a. Hemorrhagic disease of newborn
         b. Osteomalacia
         c. Folate deficiency

II. Unpredictable (genetically determined susceptible population?)
   A. Idiosyncratic drug effects (unusual reactions different from pharmacologic effects—unknown mechanisms)
      1. Acne
      2. Hypertrichosis
      3. Nondermatologic
         a. Peripheral neuropathy
         b. Hepatomegaly/induction of hepatic enzymes
         c. Hyperglycemia
   B. Allergic hypersensitivity (adverse immune response to drug administration)
      1. Phenytoin hypersensitivity syndrome
   C. Immunologic effects
   D. Delayed toxic effects
      1. Teratogenicity (fetal hydantoin syndrome)
      2. Carcinogenicity (pseudolymphoma/lymphoma)

Phenytoin (Nirvanol). The ability of hydantoins to induce hypersensitivity reactions was the basis for their initial therapeutic applications. In the 1920s Sydenham's chorea was treated by administering phenylethylhydantoin until a hypersensitivity reaction (fever, rash, and lymphadenopathy) developed.4 Hypersensitivity reactions have limited the use of mefenytoin, the N-methyl derivative of phenylethylhydantoin, which is demethylated in vivo to phenylethylhydantoin (Fig. 1).

Phenytoin is rapidly absorbed from the adult gastrointestinal tract and is absorbed more slowly when given intramuscularly. Its half-life is approximately 22 hours. It has an intermediate degree of binding to plasma proteins in comparison with other anticonvulsants. Reduced plasma protein binding of phenytoin occurs in neonates, pregnant women, and the elderly. Children require higher doses relative to body weight to achieve steady-state therapeutic plasma concentrations, and drug half-life varies widely depending upon the maturity of organ detoxification systems.

Therapeutic drug levels (10 to 20 μg/ml) are easily maintained in adults. In infants and children the relationship between plasma concentration, daily dose, and hepatic metabolism is more variable, resulting in increased toxicity and failure to achieve therapeutic drug levels.5

In newborn infants, the erratic gastric and intramuscular absorption of phenytoin and its unpredictable plasma half-life make close monitoring of drug levels mandatory. In newborn infants, age-related changes and the concentration-dependence of phenytoin elimination can cause phenytoin levels to decrease when constant doses are given.6

The newborn infant does not predictably absorb
oral phenytoin in any form; phenytoin half-life and elimination rates vary widely. The plasma half-life is prolonged and variable during the first week of life; after the first month plasma half-life shortens considerably and begins to stabilize.

To summarize, concentration-dependent kinetics are more reliable in adults, while frequent blood levels must be obtained in neonates to ensure that therapeutic drug levels have been attained and maintained. Saturation kinetics in neonates tend to stabilize by the third month of life, at which point there is a reliable correlation between the dose of phenytoin administered and resultant plasma levels.

Other factors may influence absorption of phenytoin. Oral phenytoin absorption is impaired when it is given concurrently to patients receiving continuous nasogastric tube feedings. Concomitant use of antacids and sucralfate (which works by binding to proteins, pepsin, and bile salts) may decrease absorption of phenytoin. Use of oral contraceptives increases steady-state plasma phenytoin concentration relative to dose.

Hepatic microsomal mixed-function oxidases transform most phenytoin into inactive hydroxylated metabolites; less than 5% is excreted unchanged in the urine. Pathways for phenytoin metabolism are the same in infants and adults. Phenytoin affects transmembrane sodium and calcium flux and may influence nucleic acid metabolism and protein synthesis. Detailed reviews of pharmacologic effects are available.

### INDICATIONS

Phenytoin is used widely in therapeutics (Table II). Neurologic applications include treatment of epilepsy, trigeminal neuralgia and peripheral neuropathy, and seizure prophylaxis both prior
Table III. Indications for phenytoin

<table>
<thead>
<tr>
<th>FDA approved</th>
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<tbody>
<tr>
<td>Seizures (generalized tonic-clonic, partial</td>
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<tr>
<td>complex)</td>
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<tr>
<td>Status epileptic</td>
</tr>
<tr>
<td>Prevention and treatment of seizures during</td>
</tr>
<tr>
<td>neurosurgery</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Other</td>
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<tr>
<td>Prophylaxis of seizures after head trauma</td>
</tr>
<tr>
<td>Analgesia (trigeminal neuralgia, peripheral</td>
</tr>
<tr>
<td>neuropathy)</td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
</tr>
<tr>
<td>Linear scleroderma</td>
</tr>
<tr>
<td>Pachyonychia congenita</td>
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</tbody>
</table>

FDA: Food and Drug Administration.

to neurosurgical procedures and after head trauma. With present microneurosurgical techniques, the risk of postoperative epilepsy is small and phenytoin prophylaxis criteria are being redefined.19 Phenytoin is used to control cardiac arrhythmias, especially those associated with digitalis toxicity. In dermatology, phenytoin has been used to treat dystrophic epidermolysis bullosa (see “Side Effects”), linear scleroderma,20,21 and pachyonychia congenita.22 Recently phenytoin has been used with good effect in treating rheumatoid arthritis.23

PREDICTABLE REACTIONS

Overdose

Neurologic toxicity associated with phenytoin use is more closely related to actual serum levels than to dosage, as shown below24:

<table>
<thead>
<tr>
<th>Serum level</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20 µg/ml</td>
<td>Normal therapeutic level</td>
</tr>
<tr>
<td>20-40 µg/ml</td>
<td>Nystagmus/ataxia</td>
</tr>
<tr>
<td>&gt;40 µg/ml</td>
<td>Dysarthria/lethargy/mental changes</td>
</tr>
</tbody>
</table>

Central nervous system side effects are usually dose-related and are rare at serum levels of less than 30 µg/ml. Sustained elevated serum levels of phenytoin may cause intellectual deterioration, depression, exacerbation of behavioral disorders, and psychomotor retardation.25,26 Chronic phenytoin administration can be associated with cerebellar degeneration, possibly due in part to hypoxia.27

Cardiopulmonary complications (cardiac and respiratory arrest, hypotension, arrhythmias) have been reported following intravenous loading with phenytoin. They are infrequent28-30 and only rarely fatal.31

Drug interactions

Failure of PUVA (psoralens plus ultraviolet A) therapy has been reported as a consequence of abnormally low serum levels of 8-methoxypsoralen during phenytoin therapy. Normal serum levels of 8-methoxypsoralen were observed after phenytoin was discontinued. The effect is probably due to induction of hepatic enzymes by phenytoin, leading to increased metabolism of psoralens.32

The phenytoin-miconazole interaction is relevant to dermatologists. Miconazole inhibits hepatic cytochrome P-450, decreasing phenytoin metabolism. A phenytoin-controlled epileptic developed neurologic signs of phenytoin intoxication 1 day after initiation of treatment with intravenous miconazole; his phenytoin level was 43 µg/ml after 1 week of therapy. Cimetidine, an imidazole structurally related to miconazole, also inhibits phenytoin metabolism.33

By enhancing hepatic microsomal enzyme activity, phenytoin decreases blood levels of dexamethasone and cortisol34 and inhibits the effectiveness of standard plasma dexamethasone suppression tests.35 Pheynytoin can increase the anticoagulant activity of warfarin by displacing it from protein binding sites.13 Several reviews are available featuring compilations of drug interactions affecting phenytoin levels.2,3,13

Side effects

Collagen synthesis

Pathophysiology. Pheynytoin inhibits collagenase activity in vitro.36 This inhibition is the basis for its utilization in treatment of recessive dystrophic epidermolysis bullosa, a disease in which collagenase activity is increased.37,38 Bauer et al39 linked blistering in recessive dystrophic epidermolysis bullosa to increased collagenase activity and showed that phenytoin inhibited the synthesis and/or secretion of collagenase by fibroblasts. Pheynytoin had no effect on purified human skin
collagenase but inhibited collagenase expression when added to skin explant cultures. Phenytoin produced significant dose-dependent decreased blistering in 12 of 17 patients. It did not inhibit collagenase activity in cultured fibroblasts obtained from clinically unresponsive patients. Other investigators have confirmed the beneficial effect of phenytoin in both recessive dystrophic epidermolysis bullosa and in junctional epidermolysis bullosa, as well as the ability of phenytoin to inhibit collagenase activity.

Alternative mechanisms proposed to explain phenytoin effects on the integument include stimulation of protein and collagen synthesis, enhanced wound healing, stimulation of fibroblast growth with decreased collagenolysis, and interference with prolyl hydroxylation.

**Gingival hyperplasia.** The incidence of phenytoin-induced gingival hyperplasia is variable: 90% in institutionalized epileptics and 40% to 60% in outpatients. Children are most often and more severely afflicted, but there is neither a sexual nor racial predilection. Gingival hyperplasia is somewhat independent of dosage and duration of treatment, usually decreasing markedly within 1 year of stopping the drug (although total resolution may not occur). It does not occur in edentulous gums but can develop in patients wearing dentures.

Phenytoin-enlarged gingivae contain significantly higher amounts of collagen compared to normal and inflamed gingival tissues. The ratio of type I to type III collagen has been found to be different in hyperplastic tissue, with less type I and an elevated amount of type III collagen present. The amount of type V collagen did not differ among normal, inflamed, and phenytoin-enlarged gingivae.

Hassell and others have suggested that a subpopulation of gingival fibroblasts may be genetically programmed for increased protein synthesis and specifically produce increased amounts of collagen. "Permissive" blood levels of phenytoin, genetic susceptibility, and the indigenous bacterial colonization of the mouth provide an environment that induces or selects for these fibroblasts.

Gingival hyperplasia is graded according to clinical severity, from minimal overgrowth (grade 1) to massive enlargement of the gingiva covering 75% or more of the tooth surface (grade 4). In the absence of local irritation, gingival hyperplasia appears as firm, pink, gingival bulges (enlarged interdental papilla), most pronounced in the anterior gingival region (Fig. 2). Histologically, gingival hyperplasia is characterized by acanthosis, elongation of rete ridges, subepithelial fibrosis,

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and an increase in both the number of fibroblasts and the amount of collagen in the gingival connective tissue.*

The only treatment for gingival hyperplasia is withdrawal of phenytoin; dose reduction is not effective.† Gingivectomy can be used as a temporizing measure to retard decay and periodontal disease when discontinuation of phenytoin is not feasible. Recently the CO₂ laser has been used to perform gingoectomy.62 Advantages of the laser include a dry field, noncontact surgery, laser sterilization of the surgical area, more rapid healing, minimal postoperative discomfort, and minimal time spent to perform the procedure.63 A positive-pressure mouthpiece may prevent recurrences of gingival hyperplasia after gingivectomy.64

The effect of a plaque control program on the development of phenytoin-induced gingival overgrowth was studied in 16 epileptic children, 8 to 16 years old, during a 2-year longitudinal study. In spite of this prevention program, gingival enlargement was evident after 1 month and the development of gingival hyperplasia was not prevented.65 In noninstitutionalized epileptics, the degree of gingival hyperplasia correlates with gingivitis, visible plaque index, and duration of phenytoin therapy.

The exaggerated effect of phenytoin on gingival tissue is probably multifactorial—a combination of pharmacologic effects (inhibition of collagenase expression, stimulation of fibroblast growth, and collagen production) compounded by constant trauma, inflammation, and a high cell turnover rate.

Coarse facies. Phenytoin has effects on tissues other than the gingiva. Phenytoin-induced facial changes include enlargement of the lips and nose and thickening of the face and scalp (Fig. 3). In one study, coarse facial features and calvarial thickening were observed in one third of institutionalized seizure patients.66 Coarse facies developed in one sister of each of two pairs of identical twins.67 The affected twin in each pair had coarse facial features, gingival hyperplasia, epilepsy, and a history of anticonvulsant therapy (including phenytoin). The normal twin of each pair had no history of anticonvulsant treatment nor facial abnormalities.

Coarse facies may represent one extreme of a
dose-related, anticonvulsant-induced, tissue proliferative syndrome. Whether facial changes resolve after discontinuation of phenytoin is not known. No histologic studies have been done.

**Heel pad thickening.** Long-term phenytoin therapy is associated with asymptomatic heel pad thickening, the degree of which increases with duration of anticonvulsant treatment. Fifty-eight percent of patients taking phenytoin for more than one decade showed significant thickening of the heel pad, compared to sex- and age-matched controls.68

**Nondermatologic side effects.** Three major nondermatologic side effects of phenytoin therapy are discussed in detail below and include hemorrhagic disease of the newborn,69-71 osteomalacia,72-77 and folate deficiency (with or without megaloblastic anemia).78-85

Phenytoin can increase porphobilinogen excretion, inducing porphyrin attacks in patients with acute intermittent porphyria. Acute attacks are heralded by severe abdominal pain, tachycardia, and hypertension.86

Recent studies have shown that the metabolism of phenytoin is not influenced by thyroid dysfunction.87 Phenytoin and thyroxine compete for binding sites on thyroglobulin, resulting in decreased serum protein-bound iodine in euthyroid patients. The levels of thyroid-stimulating hormone and free thyroid hormone concentrations are usually normal, however, and patients are clinically euthyroid.88 Thyroid size may increase in patients taking phenytoin. This is probably a compensatory mechanism resulting from the low free thyroid hormones in serum that may result from phenytoin-induced increased hepatic degradation of thyroid hormones.89

Phenytoin readily crosses the placenta and may cause profound depletion of vitamin K–dependent clotting factors in the fetus.69-71 A resultant hemorrhagic diathesis may occur within 24 hours of delivery, resulting in intracranial bleeding and death.69 Several factors contribute to hemorrhagic disease of the newborn: the half-life of phenytoin in the fetus is prolonged because of immaturity of fetal enzyme systems, and phenytoin may inhibit transport of vitamin K as well as addition of γ-carboxyglutamic acid to the precursor molecules of clotting factors II, VII, IX, and X. Mothers taking phenytoin and their newborn infants should receive vitamin K supplementation.

Long-term anticonvulsant therapy is associated with an increased incidence of osteopenia, osteomalacia, hypocalcemia, and elevated alkaline phosphatase activity. Skeletal toxicity is thought to result from increased catabolism of vitamin D and its metabolites.72 Anticonvulsant drug-induced osteomalacia shares many features in common with rickets.73,74

Overt bone disease due to anticonvulsants is not common and is probably exacerbated by multiple factors, including nutritional status, sun exposure, and levels of physical activity. It is difficult to separate endogenous drug effects per se (the ability of phenytoin to alter the metabolism of vitamin D and calcium) from exogenous factors when considering the institutionalized epileptic. Exogenous confounding factors include physical inactivity, poor nutrition, and supratherapeutic levels of multiple anticonvulsant medications. A high prevalence of toxic anticonvulsant drug concentrations in institutionalized versus outpatient epileptics was found by Aman et al.89 Comparison of such a population to ambulatory outpatients is problematic.

The frequency and severity of osteomalacia in active juvenile outpatients receiving phenytoin are not known. It is believed that ambulatory, physically active epileptics receiving adequate sun exposure will not develop significant osteomalacia.76,77

Undoubtedly, the patients at highest risk for hypocalcemia and skeletal changes are those who, because of severe epilepsy and mental retardation, require institutionalization. Institutionalized patients taking both phenytoin and phenobarbital had lower serum levels of 25-hydroxycholcalciferol and calcium, higher alkaline phosphatase levels, and lower bone masses than patients on monodrug regimens or age-matched controls.75 The institutionalized patient should receive vitamin D supplementation (4000-6000 IU vitamin D$_2$ daily for 4 months, followed by a maintenance regimen of 1000 IU vitamin D$_2$ daily).74,91 Baseline and follow-up measurements should include serum and
Fig. 4. Phenytoin-associated hypertrichosis.
Fig. 5. Phenytoin hypersensitivity syndrome: erythema multiforme.
Fig. 6. Toxic epidermal necrolysis in an infant.

urinary calcium, serum phosphorus, and alkaline phosphatase.

Altered bone metabolism has been attributed to dose-related stimulation of hepatic microsomal oxidases, accelerated breakdown of vitamins D₂ and D₃ into inactive metabolites, and decreased intestinal absorption of calcium. Resultant hypocalcemia may lead to secondary hyperparathyroidism.⁵⁸,⁵⁹

Epileptics taking phenytoin have lower folate levels and increased folate clearance, compared to controls, and this can cause megaloblastic anemia.⁹² The etiology of this folate deficiency is not entirely clear, but it has been attributed, in part,
to selective malabsorption.\textsuperscript{79-82} Dermatologic manifestations of folate deficiency include cheilitis, glossitis, and mucosal ulceration. Bone marrow studies show megaloblastic changes in all cell lines, decreased deoxyribonucleic acid (DNA) synthesis, and disordered marrow cell division. The anemia is responsive to folate supplementation, but administration of folate has been shown to increase seizure frequency in patients who previously have been stabilized.\textsuperscript{83,85}

Phenytoin has also been associated with a mild, nonprogressive leukopenia. Infection is seldom a problem, and progression to agranulocytosis is rare.\textsuperscript{79}

**UNPREDICTABLE REACTIONS**

**Drug idiosyncrasy**

**Acne.** Phenytoin is widely assumed to increase the frequency and severity of acne (Fig. 3),\textsuperscript{93} but not all investigators agree. When Greenwood et al\textsuperscript{94} compared 242 epileptics taking anticonvulsant medications to 2,176 age- and sex-matched controls, no differences in either prevalence of acne or sebum excretion rates were found. Testosterone levels in men taking phenytoin were normal. Investigational data pertaining to the hormonal effects of phenytoin seem to contradict clinical experience, and further investigation is needed. The apparent increase in the prevalence of acne may be due to abnormalities in keratinization induced by phenytoin rather than hormonal factors alone.

**Hypertrichosis.** Hypertrichosis occurs in about 12\% of children receiving phenytoin, usually within 3 months of initiating therapy.\textsuperscript{25,95} It occurs on extensor surfaces of the extremities and on the trunk and face (Fig. 4). Hypertrichosis persists with continued administration of phenytoin but resolves within 1 year of discontinuing the drug. Whether phenytoin affects the hypothalamic-pituitary axis or adrenal function has not yet been clarified.\textsuperscript{25}

**Nondermatologic idiosyncratic effects.** Phenytoin-induced agranulocytosis is rare and total leukocyte counts decrease to well below 2500/mm\textsuperscript{3}. Infection invariably occurs. Whether phenytoin causes agranulocytosis through peripheral immunologic destruction of granulocytes or through marrow stem cell suppression is unknown. If phenytoin is discontinued and other complications are treated successfully, complete recovery can be expected.\textsuperscript{78}

A predominantly sensory, peripheral neuropathy may develop in up to 30\% of institutionalized epileptics taking phenytoin.\textsuperscript{25,96} In one report, sural nerve biopsy showed loss of large myelinated fibers and segmental demyelination accompanied by axonal shrinkage. The neuropathy improved when phenytoin was discontinued.\textsuperscript{97}

Phenytoin has been shown to inhibit insulin release, causing hyperglycemia and glycosuria.\textsuperscript{98,99} Hepatic enzyme induction, hepatomegaly, and elevated levels of all liver function enzymes may be seen.\textsuperscript{93} Increased serum γ-glutamyl transpeptidase activity occurs in 90\% of patients on long-term phenytoin therapy, most often to moderate levels, but occasionally to high levels; this rise in γ-glutamyl transpeptidase activity is accentuated by regular consumption of alcohol.\textsuperscript{100}

**Allergic hypersensitivity: phenytoin hypersensitivity syndrome**

Cutaneous eruptions occur in up to 19\% of patients receiving phenytoin.\textsuperscript{101} A small percentage of these patients develop a phenytoin hypersensitivity syndrome of variable severity that resolves rapidly once the drug is withdrawn. Multisystem abnormalities may continue to evolve even after discontinuation of phenytoin. The literature on phenytoin hypersensitivity syndrome and pseudolymphoma consists primarily of this subset of persistent reactors, who develop generalized cutaneous eruptions accompanied by multisystem abnormalities.

Several features of the “phenytoin syndrome” suggest that it is a form of allergic hypersensitivity: lack of correlation with known pharmacologic properties (toxicity, side effects); lack of linear relationship to dosage; need for an induction period after initial exposure but not on reexposure; involvement of only a small proportion of the population; mediation by immune mechanisms; and reappearance after challenge.

The incidence of phenytoin hypersensitivity syndrome is not known because of the variability in presentation, the diversity of clinical and lab-
Table IV. Common clinical and laboratory features of phenytoin hypersensitivity syndrome

<table>
<thead>
<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>No sex or age predilection</td>
</tr>
<tr>
<td>Onset within 3 months of initiating phenytoin therapy (within 1 day if previously sensitized)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Rash</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Lymphadenopathy (localized/generalized)</td>
</tr>
<tr>
<td>Conjunctivitis/pharyngitis/strawberry tongue</td>
</tr>
<tr>
<td>Hepatomegaly/hepatitis</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Leukocytosis with eosinophilia</td>
</tr>
<tr>
<td>Defects in cell-mediated humoral immunity</td>
</tr>
<tr>
<td>Lymphocyte transformation caused by exposure to phenytoin in culture</td>
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<tr>
<td>Spontaneous resolution after discontinuation of phenytoin; reappearance with challenge</td>
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oratory abnormalities, the lack of strict diagnostic criteria, and the failure to report all cases. Rapp et al.\(^{101}\) prospectively studied cutaneous reactions in 151 head-injured patients given phenytoin for prophylaxis of posttraumatic seizures. Although exanthems occurred in 19%, florid phenytoin hypersensitivity syndrome developed in only two patients. In another study, 18% of brain tumor patients receiving phenytoin developed cutaneous reactions.\(^{102}\) There is no age or sex predilection.

Prospective identification of susceptible patients is not possible, but several high-risk subsets can be identified: patients with prior phenytoin reactions who are reexposed to the drug,\(^{103}\) patients who continue to receive phenytoin after developing unrecognized signs of drug hypersensitivity,\(^{104-106}\) and blacks.\(^{101}\) The highest incidence of severe phenytoin hypersensitivity syndrome has occurred in elderly black male patients; clinical findings include rash, fever, eosinophilia, and a systemic granulomatous vasculitis involving liver, kidneys, and spleen.\(^{102,107}\)

Phenytoin hypersensitivity syndrome develops within 3 months of initiating therapy (assuming there has not been previous exposure to the drug)\(^{101,102}\) and is frequently heralded by fever and rash. An exanthem is not only a common feature of phenytoin hypersensitivity syndrome but may be its earliest and sole manifestation. Variability in presentation makes assessment of phenytoin hypersensitivity syndrome difficult. Patients with florid phenytoin hypersensitivity syndrome may exhibit the entire spectrum of abnormalities listed in Table IV. Other phenytoin hypersensitivity syndrome patients may have only one or two of these features when first seen. Retrospective analysis of 38 patients with phenytoin hypersensitivity syndrome showed that the majority had isolated abnormalities (for example, maculopapular rash, hepatitis, eosinophilia); multisystem abnormalities were present in less than half.\(^{108}\)

The rash is usually accompanied by a high spiking fever that may persist for weeks. Localized or generalized edema is often present; massive facial edema is said to be a characteristic finding.\(^{109}\) The conjunctivitis, tonsils, and pharynx are inflamed, and "strawberry tongue" is often seen.\(^{110}\)

The cutaneous eruption of phenytoin hypersensitivity syndrome initially consists of patchy erythema, evolves into a pruritic maculopapular rash, and can later generalize into an exfoliative erythroderma.\(^{111}\) Follicular accentuation of the rash and later evolution of follicular-centered pustules have been reported.\(^{109}\) Desquamation occurs as the rash resolves.

Erythema multiforme (Fig. 5) and toxic epidermal necrolysis (Fig. 6) may occur.\(^{111-115}\) Toxic epidermal necrolysis is uncommon; it usually occurs in patients who have previously had adverse reactions to the drug and are reexposed and in patients who continue to receive phenytoin even after hypersensitivity develops.\(^{103-106}\) The high mortality associated with toxic epidermal necrolysis and exfoliative erythroderma is due to factors such as severe hepatocellular disease and sepsis.\(^{103,104,114}\) Universal cutaneous depigmentation following phenytoin-induced toxic epidermal necrolysis has been reported.\(^{115}\)

Mycosis fungoides—like lesions have been reported rarely. An 83-year-old woman developed generalized lymph node hyperplasia and mycosis fungoides—like erythematous plaques 11 months after initiation of phenytoin therapy. The eruption cleared 3 weeks after cessation of therapy.\(^{116}\)

Histologically, a nonspecific perivascular lymphocytic infiltrate is most commonly found.\(^{110,117,118}\) Biopsy findings tend to parallel lesion morphology:
biopsy of a pustular lesion revealed an intraepidermal vesiculopustule with a dense superficial perivascular lymphohistiocytic infiltrate in an edematous papillary dermis, while papular lesions were characterized histologically by psoriasiform lichenoid dermatitis with slight spongiosis. Cutaneous vasculitis has been reported.

Tender localized or generalized adenopathy is often present. The most frequent biopsy finding is benign lymphoid hyperplasia (see Table V). Benign lymphoid hyperplasia in phenytoin hypersensitivity syndrome can be distinguished from pseudolymphoma only on histologic grounds; that is, a biopsy for histopathologic interpretation is required. Ideally, the term pseudolymphoma should be used only when lymph node biopsy reveals atypical hyperplasia simulating malignancy (reticulum cell hyperplasia, loss of normal nodal architecture, abnormal cells with frequent mitotic figures) in a patient with clinical features of phenytoin hypersensitivity syndrome. Lymphadenopathy resolves following discontinuation of phenytoin in both phenytoin hypersensitivity syndrome and pseudolymphoma.

Hepatomegaly is present in the majority of cases and is frequently accompanied by splenomegaly. Liver function tests may show abnormal findings, and values may continue to rise progressively even after phenytoin is discontinued. Liver function test values are elevated in patients on chronic phenytoin therapy because of induction of hepatic microsomal enzymes by the drug. This nonspecific increase in enzyme activity occurs in 90% of patients on long-term phenytoin therapy.

Most patients initially are anicteric but may later develop frank jaundice. Severe hepatitis portends a prolonged course characterized by multiple exacerbations and remissions of both rash and liver disease. Phenytoin hepatitis is a serious reaction with an 18% overall mortality. Clinically it mimics infectious mononucleosis—fever, pharyngitis, lymphadenopathy, and atypical lymphocytosis. Drug rechallenge in these patients may be fatal. Eruptive xanthomas may appear suddenly in patients with severe hepatocellular disease. Liver biopsy reveals a broad spectrum of changes.

Deaths have been reported in patients with phenytoin hypersensitivity syndrome and severe liver disease, usually in the setting of coagulopathy and sepsis. Another major cause of severe illness and death is accidental reexposure, or continued exposure of sensitized patients to phenytoin. It should be emphasized, however, that there were no deaths in Rapp et al.'s prospective studies or in Haruda's retrospective studies.

Involvement of other organ systems is usually minimal. Pulmonary changes in patients on prolonged phenytoin therapy include interstitial infiltrates and increased bronchovascular markings. One patient developed diffuse lymphocytic interstitial pneumonia after receiving phenytoin for 14 months. Withdrawal of the medication resulted in reversal of the disease process. Myositis and reversible acute renal failure may occur. Renal biopsy shows interstitial nephritis, sparing the glomeruli, which resolves once phenytoin is withdrawn. Severe rhabdomyolysis has been reported: in one patient, creatinine phosphokinase levels peaked at 242,000 IU/L. Muscle biopsy showed muscle fiber necrosis with partial dissolution of the sarcoplasm without evidence of inflammation, vasculitis, or regeneration. This patient also reacted to phenobarbital.

Laboratory abnormalities include leukocytosis with eosinophilia and atypical lymphocytosis. A mild Coombs-negative hemolytic anemia may occur. Although hypogammaglobulinemia has been reported, immunoglobulin levels are usually normal. Sedimentation rate and complement levels are normal.

There is no specific therapy for phenytoin hypersensitivity syndrome other than immediate discontinuation of phenytoin. Corticosteroid administration has never been proved efficacious in a controlled study. Phenytoin challenge is dangerous because even milligram amounts of the drug can provoke hypersensitivity reactions in previously sensitized patients. For example, a patient who developed a mononucleosis-like syndrome 6 weeks after starting phenytoin therapy reacted with near-fatal hepatic necrosis following intravenous phenytoin rechallenge. Data pertaining to immunologic cross-reactivity are scanty, making selection of alternative anticonvulsants difficult. Phenobarbital can cause reactions indis-
tistinguishable from phenytoin hypersensitivity syndrome, and hypersensitivity to multiple anticonvulsants has been reported.112,136,139,140

To summarize, a small proportion of patients taking phenytoin will develop phenytoin hypersensitivity syndrome within 3 months of initiating therapy. The severity of associated clinical and laboratory abnormalities is related, in part, to how long phenytoin is administered after hypersensitivity develops. Most frequently seen are a maculopapular rash that generalizes and desquamates, lymphadenopathy, hepatitis, and leukocytosis with eosinophilia, all of which resolve after phenytoin is withdrawn. Total recovery without sequelae is the rule. Patients with severe hepatitis, nephritis, or persistent lymphadenopathy tend to have more prolonged and complicated courses and require more extensive diagnostic evaluation. If serious complications do not develop, hospitalization averages 2 to 4 weeks. Patients receiving phenytoin chronically should undergo yearly evaluations, including physical examination, blood chemistries, and complete blood count.

Immunologic aspects of phenytoin hypersensitivity syndrome and chronic phenytoin administration

Humoral immunity. Global or selective immunoglobulin deficiency may occur during phenytoin therapy, most commonly decreased or absent IgA.141 IgA levels decline during phenytoin administration in approximately 25% of adults and in 40% of children,142-144 and an association with human lymphocyte antigen (HLA)-A2 has been reported.146 Normal numbers of lymphocytes bearing surface IgA are present, implying failure of terminal B lymphocyte differentiation.147,148 IgA levels return to normal following discontinuation of phenytoin, with the one exception described below (Guerra et al151). No consistent changes in IgM or IgG have been found.

Phenytoin causes significant reduction in immunoglobulin secretion by human mononuclear cells.149 Isotype-specific human lymphoblastoid B cell lines differ in their sensitivity—secretion of IgA and IgG are reduced by phenytoin near therapeutic concentration, while IgM is not affected.

Inbred NFS mice, injected with phenytoin and immunized with bovine serum albumin, demonstrated a dose-dependent decreased production of IgG antibodies to bovine serum albumin.150

Guerra et al151 described a patient who, 3 weeks after initiation of phenytoin therapy, developed phenytoin hypersensitivity syndrome manifested by rash, lymphadenopathy, hepatitis, and panhypogammaglobulinemia. The patient had decreased circulating B lymphocytes as assessed by the number of lymphocytes with surface membrane immunoglobulin and by the number of lymphocytes bearing the B1 antigen. Hemolytic plaque assay revealed decreased immunoglobulin production and minimal enhancement on stimulation with pokeweed mitogen. No reversal of the immunodeficiency had occurred 3 years after discontinuation of phenytoin.

Polymorphonuclear leukocyte function was assessed in 12 patients who had received phenytoin monotherapy for more than 1 year and compared to 12 healthy age- and sex-matched control subjects. No change was found in the absolute or relative counts of polymorphonuclear leukocytes. However, a significant impairment of both polymorphonuclear chemotaxis and stimulated nitroblue tetrazolium reduction was observed in the patients compared with the control group of subjects.152

Increased T-suppressor cell activity resulting in B cell lymphopenia, arrest in B cell differentiation, and global hypogammaglobulinemia have been reported.137,138 Circulating anti–phenytoin antibodies have been identified,153,154 but their role in phenytoin hypersensitivity syndrome is not clear. Phenytoin administration is associated with absence of common specific antibodies (rubella, cytomegalovirus)141 and impairment of antibody response to vaccination with influenza virus, Salmonella typhi, and tetanus toxoid.137,141-144

Cell-mediated immunity. Phenytoin administration is associated with anergy to ubiquitous recall antigens (mumps, purified protein derivative [PPD], streptokinase-streptodornase, and trichophytin)138,141,143,144,146 and inability to sensitize to dinitrochlorobenzene.141 Phenytoin induces blast transformation in cultured lymphocytes from patients with phenytoin hypersensitivity syndrome.136,137,155 Decreased lymphocyte
Table V. Lymphoid reactions to phenytoin

I. Benign lymphoid hyperplasia
   Lymphadenopathy
   Pleomorphic cellular hyperplasia
   Preservation of normal nodal architecture
   May be an isolated finding in asymptomatic patients receiving phenytoin
   Found in most patients with phenytoin hypersensitivity syndrome
   Regresses after phenytoin is withdrawn

II. Pseudolymphoma
   Lymphadenopathy
   Atypical cellular hyperplasia simulating malignant lymphoma but lacking necessary histologic criteria for
   malignancy (i.e., no Reed-Sternberg cells or capsular invasion)
   Mixed cellular infiltrate (lymphocytes, histiocytes, eosinophils, fibroblasts)
   Mitotic figures, vascular proliferation, necrosis, and fibrosis are present
   Nodal architecture is distorted or obliterated
   Regresses after phenytoin is withdrawn

III. Pseudopseudolymphoma
   Lymphadenopathy
   Atypical cellular hyperplasia similar to pseudolymphoma
   Lymphadenopathy initially regresses after phenytoin is withdrawn
   After an asymptomatic quiescent period, lymphoma develops

IV. Malignant lymphoma

responsiveness to mitogens has also been described.143,144,146,156

In cases of tubulointerstitial nephritis associated
with phenytoin hypersensitivity syndrome, linear
deposits of IgG have been found in renal cortical
tubular basement membrane, along with scattered
focal deposits of IgG and IgM.121,133-135 An IgG
antibody reactive with human renal cortical tubular
basement membrane has been isolated in serum.134

Guerra et al.'s135 patient with phenytoin hyper-
sensitivity syndrome had normal T cell–mediated
immunity, including T cell surface markers (E ro-
settes), lymphocyte proliferation after mitogen
stimulation, and T cell phenotypes.

Abnormal mitogen-induced T-suppressor cell
activity inhibiting B cell differentiation has been
described.137,138 Since cytotoxic/suppressor T lympho-
cyties are known to be poorly responsive to
mitogen and antigen,157 it has been suggested that
phenytoin induces a selective T-suppressor lym-
phocytosis that interferes with B cell differenti-
ation.

Gleichmann158 proposed that phenytoin binds to
lymphoid cells in such a way that lymphocyte in-
teractions comparable to an allogeneic system can
be elicited between autologous cells: that is, lym-
phoid cells rendered "nonself" by phenytoin bind-
ing may simulate a form of graft-versus-host re-
action.

Phenytoin at therapeautic (10 to 20 μg/ml) and
toxic (40 μg/ml) concentrations significantly sup-
pressed natural killer cell activity in a dose-
dependent fashion in human peripheral blood
mononuclear cells in vitro. It also depressed inter-
feron augmentation of natural killer cell cyto-
toxicity in a dose-dependent manner. Antibody-
dependent cell-mediated cytotoxicity was signifi-
cantly depressed at concentrations of 20 and 40
μg/ml.159

Because of the relative immunosuppression in-
bunded by phenytoin, a pilot study was carried out
to determine its potential therapeutic utility in
treatment of rheumatoid arthritis. Only 11 patients
were treated in this initial study, and more data
are needed.23

Delayed toxic effects

Teratogenicity. Several excellent reviews of
this topic are available.160-165 This summary is not
intended to substitute for careful evaluation of
the literature because controversy in this area is rife.

Gestational exposure to phenytoin, which cros-
ses the placenta and concentrates in fetal liver, heart, kidney, and adrenal glands, may contribute to an increased incidence of congenital defects.\textsuperscript{166-167} This risk must be assessed in the context of the hazards of uncontrolled epilepsy (which frequently exacerbates during pregnancy),\textsuperscript{166} the background incidence of congenital abnormalities in the epileptic population, and the overall incidence of congenital malformations.\textsuperscript{168}

Phenytoin teratogenicity has been linked to protein binding. In vitro uptake and distribution studies suggest that only protein-bound phenytoin (and not phenytoin itself) is able to pass through the yolk sac and reach the tissue of the embryo proper.\textsuperscript{169}

The most common isolated defects initially attributed to phenytoin were cleft lip and/or cleft palate.\textsuperscript{166,170} Syndactyly and polydactyly, cardiac malformations, hydrocephalus, and diaphragmatic hernia have been described.\textsuperscript{171-172}

Fetal hydantoin syndrome is a variable pattern of dysmorphic features coupled with deficiencies in growth and developmental performance.\textsuperscript{162-164} This syndrome includes: (1) pre- and postnatal growth deficiencies, performance delays, and mental retardation; (2) craniofacial abnormalities including microcephaly, cleft lip and/or cleft palate, prominent or low-set ears, ocular abnormalities (strabismus, hypertelorism),\textsuperscript{173} and inner epicanthic folds; (3) abnormalities of the hands, including hypoplasia of the distal phalanges with absent or hypoplastic nails, fingerlike thumb, uniform deep brown pigmentation of the nail, linear longitudinal hyperpigmented nail streaks, and abnormal palmar creases; (4) miscellaneous defects including umbilical and inguinal hernias, hypospadias, bifid scrotum, webbed neck, multiple lethal cardiac defects,\textsuperscript{174} renal abnormalities, and skeletal malformations. Hanson and Smith\textsuperscript{163} prospectively studied 35 infants exposed prenatally to phenytoin: 4 of 35 (16%) had sufficient features to be classified as having the fetal hydantoin syndrome and 11 of 35 (31%) displayed isolated features compatible with the prenatal effects of phenytoin.

By altering collagenase activity,\textsuperscript{18} phenytoin may compromise the precise orchestration of the developing dermis, resulting in abnormal structural juxtapositions.\textsuperscript{164} Phenytoin has also been shown to inhibit prolyl hydroxylase, which stabilizes the triple helix via posttranslational hydroxylation of prolyl residues.\textsuperscript{55,56} The subsequent increased production of unstable collagen may adversely affect morphogenesis.\textsuperscript{164}

Fetal hydantoin syndrome is not a universally accepted entity.\textsuperscript{164,175} It is difficult to establish a specific causal relationship because similar defects have occurred in children whose mothers were taking other anticonvulsant drugs.

Carcinogenicity. Lymphoid reaction patterns to phenytoin are defined on the basis of both histology and clinical outcome (Table V). Saltstein and Ackerman\textsuperscript{176} were the first to describe severely hyperplastic lymph nodes, mimicking malignant lymphoma, that occurred during phenytoin administration. Anthony\textsuperscript{177} later reported a tenfold increased incidence of malignant lymphoma in patients who were receiving long-term phenytoin therapy.

The genotoxicity of phenytoin on human peripheral blood mononuclear cells was investigated in vitro by gravity-flow alkaline dilution.\textsuperscript{178} There was a significant increase in DNA single-strand breaks when mononuclear cells were exposed to phenytoin for 18 or 72 hours.

Sister chromatid exchanges in lymphocyte cultures from adult epileptic patients on long-term phenytoin monotherapy have been studied. There is a significantly increased frequency of sister chromatid exchanges in these patients, indicating a detectable chromosome-damaging effect of phenytoin therapy.\textsuperscript{179,180}

Benign lymphoid hyperplasia. The ability of hydantoins to produce lymphadenopathy has been described previously. Significant lymphadenopathy develops within 8 hours of intravenous challenge in patients who have previously had phenytoin hypersensitivity syndrome.\textsuperscript{124,181} The lymphoid reaction pattern that occurs most commonly in phenytoin hypersensitivity syndrome is benign lymphoid hyperplasia, a benign pleomorphic cellular response in which overall lymph node architecture is preserved.

Isolated benign lymphoid hyperplasia may occur in otherwise asymptomatic patients receiving long-term phenytoin therapy, although the inci-
Pseudolymphoma. Because phenytoin hypersensitivity syndrome shares clinical features in common with lymphoma (lymphadenopathy, fever, rash, hepatosplenomegaly), cases of phenytoin hypersensitivity syndrome have been reported in the literature as pseudolymphoma. Loose use of the term pseudolymphoma, in this descriptive sense, has resulted in confusion.

The lymphoid reaction pattern most commonly found in phenytoin hypersensitivity syndrome is benign lymphoid hyperplasia. The term pseudolymphoma applies only to patients who have clinical and histologic features suggestive of lymphoma. Atypical lymph node hyperplasia characterizes pseudolymphoma—a hyperplastic, malignant-appearing infiltrate distorts or obliterates normal nodal architecture. As currently defined, pseudolymphoma is not a premalignant state; later development of malignancy necessitates a change in the diagnosis to pseudopseudolymphoma. Whether this is a real or an artificial distinction is moot.

Phenytoin–associated pseudolymphoma was first described by van Wyk and Hoffman. Lymph node biopsy revealed distorted nodal architecture, capillary proliferation, and a pronounced eosinophilic infiltrate. Histologic features of phenytoin–associated pseudolymphoma, as reviewed by Saltzstein and Ackerman, include distortion or destruction of lymph node architecture by a pleomorphic infiltrate consisting predominantly of hyperplastic reticulum cells (often showing mitotic figures), vasculitis, and areas of necrosis.

Pseudopseudolymphoma. Pseudopseudolymphoma describes a small number of patients who develop severely hyperplastic lymph node changes while taking phenytoin. These initially resolve after withdrawal of the drug. Later, recurrent lymphadenopathy develops. Finally, malignant lymphoma intervenes. Two of seven pseudolymphoma patients originally described by Saltzstein and Ackerman later died of malignant lymphoma. In both cases the lymphadenopathy initially regressed after discontinuation of phenytoin but later recurred.

Gams et al found “chronic reactive adenitis” in a patient who developed right neck swelling 6 months after starting phenytoin and phenobarbital. The lymphadenopathy completely resolved after discontinuation of phenytoin. Poorly differentiated lymphoma was diagnosed 5 months later when lymphadenopathy recurred.

Pseudopseudolymphoma is, by definition, a retrospective diagnosis that can be made only after a patient with a presumed drug-related syndrome develops malignant lymphoma.

Lymphoma. There is an unexplained increased incidence of lymphoma in patients taking phenytoin. It is not yet known whether phenytoin acts as an inciting agent lighting up a dormant malignancy, allows expression of an oncogene or oncogenic virus by altering the helper/suppressor ratio, is genotoxic, or predisposes to malignant change by virtue of persistent antigenic stimulation coupled with immunosuppression.

Animal studies have shown that phenytoin may be carcinogenic. Young adult mice fed phenytoin showed early thymic atrophy, distortion of lymph node architecture, and hyperplastic lesions (atypical histiocytic giant cells). Mice susceptible to spontaneous lymphoreticular tumor development (SJL/SJ strain) developed early lymphosarcomas after 3 to 5 months of phenytoin administration. Spontaneously arising Hodgkin’s-like lesions occurred earlier in phenytoin-treated mice than in untreated mice. Mice with a medium or low spontaneous incidence of lymphoreticular malignancy (C57Bl, C3Hf strains) showed an increased incidence and earlier onset of lymphomas when fed phenytoin.

Long-term phenytoin therapy has been associated with small intestinal lymphoma, hairy cell leukemia, and mycosis fungoides.
Anthony reviewed all cases of autopsy-proved malignant lymphoma occurring between 1958 and 1968 at Cincinnati General Hospital. Using the lowest prevalence estimate for epilepsy in the general population (0.5%), the expected incidence of epilepsy in lymphoma is one case of epilepsy for every 200 cases of lymphoma. Four of 85 patients with lymphoma were found to have epilepsy, or ten times the incidence expected. Hyman and Sommers reported that patients with lymphoma superimposed upon a seizure disorder outnumbered those in whom pseudolymphoma was found.

Tashima and de los Santos reported two cases of Hodgkin’s disease developing in patients taking phenytoin. Sorrell and Forbes speculated that chronic antigenic stimulation and immunosuppression by phenytoin were involved in the induction of Hodgkin’s disease in a patient who was taking phenytoin. Lapes et al described a patient with a salivary gland benign lymphoepithelial lesion who developed lymphoblastic lymphoma after therapy with phenytoin was initiated. They proposed that chronic lymphoid stimulation by phenytoin led to proliferation of a malignant clone of lymphocytes.

Charlton and Lunsford reported that 2.3% of 300 patients with lymphoma had received chronic phenytoin therapy, compared to 0.6% of 300 control patients. Li et al found a history of prolonged phenytoin therapy in 10 of 516 patients (1.9%) with Hodgkin’s or non-Hodgkin’s lymphoma compared to 3 of 516 patients (0.6%) with other types of cancer, and to 2 of 516 (0.4%) tumor-free individuals. Discontinuation of phenytoin did not result in tumor regression. The excess risk was two- to fourfold and appeared more evident in adult patients.

CONCLUSION

Unusual and potentially serious cutaneous and immunologic abnormalities are associated with phenytoin therapy. Phenytoin effects on collagenase and connective tissue are clinically manifest as gingival hyperplasia, coarse facies, and heel pad thickening. Phenytoin is utilized in treatment of recessive dystrophic epidermolysis bullosa because it is thought to inhibit the synthesis and/or secretion of collagenase by fibroblasts. Hypersensitivity is associated with hyperplastic lymph node responses, histologically benign or atypical, which may sometimes simulate malignant lymphoma. These changes occur in conjunction with abnormalities in both cell-mediated and humoral immunity. In the light of current concerns about acquired immunodeficiency syndrome, immunomodulating drugs such as phenytoin should be used with some caution. The other side of the coin is that the immunosuppressive effects of phenytoin may be useful in treating disorders such as rheumatoid arthritis. Recent studies suggest that phenytoin may play an etiologic role in development of malignant lymphoma. Whether this results from alteration of immune surveillance, chronic antigenic stimulation, direct interaction with cellular DNA, or perhaps even activation of an oncogenic virus or oncogene is not known. Further investigation hopefully will clarify these issues.

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REFERENCES

Cutaneous and immunologic reactions to phenytoin


