THOMAS WESLEY ALLEN, DO
Editor in Chief

Accuracy of rapid dipstick tests in predicting urinary tract infection

This study summarizes the diagnostic accuracy data for dipstick nitrite and leukocyte esterase tests (or both), known as the index tests, as predictors of bacterial urinary tract infection, defined by quantitative culture (the reference test).

Researchers identified 1017 citations from an online search, 51 of which were relevant and contained sufficient data for further analysis. From each citation, the researchers extracted 2 × 2 tables of true-positive, true-negative, false-positive, and false-negative results. They assessed four categories of index test: nitrite only, leukocyte esterase only, disjunctive pairing (dipstick positive if nitrite, leukocyte esterase, or both were positive), and conjunctive pairing (dipstick positive only if both nitrite and leukocyte esterase were positive).

The authors calculated true-positive and false-positive rates from each 2 × 2 table. Plots of true-positive rates versus false-positive rates demonstrated widely scattered points, indicating heterogeneity. A receiver-operating characteristic curve was fitted to the data using logistic transforms and weighted linear regression.

This analysis revealed that the disjunctive pair is the most accurate index test. However, in many clinical settings, the posterior probability of urinary tract infection given a negative dipstick is too high to exclude. Within most clinically relevant ranges of true-positive and false-positive rates, a negative urine dipstick test cannot exclude the diagnosis of urinary tract infection in patients with high prior probabilities of contracting this infection. For lower prior probabilities, the clinical efficacy of these rapid tests would best be determined by decision analysis, conclude the researchers. These receiver-operating characteristic functions would serve as valuable analytic tools.

Hurlbut TA III, Littenberg B, Diagnostic Technology Assessment Consortium: The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. *Am J Clin Pathol* 1991;96:582-588.

Maternal, perinatal costs of cocaine abuse

No reports to date exist on the direct and indirect costs of maternal cocaine abuse. In this study, the authors compared hospital charges of a cocaine-abusing population with those of a control group. Specifically, 91 mother-infant pairs who tested positive for cocaine at delivery were compared with a screened drug-free control population matched for socioeconomic status, age, and parity.

Cocaine-positive mothers were more likely to deliver prematurely than control mothers (37% vs 2%) and to have low-birth weight infants (2613 g vs 3340 g). Cocaine-abusing mothers were also more likely than control subjects to deliver growth-retarded infants (12% vs 0%) with Apgar scores less than 7 at 5 minutes (8% vs 1%). Compared with control mothers, cocaine-positive subjects had prevalent signs of cocaine abuse (63% vs 0%). Similarly, neonatal intensive care was required more often of infants of cocaine-abusing mothers than nonabusers' infants (30% vs 3%), as was an extended hospital stay (11 days vs 3 days).

As expected, a substantial cost difference occurred between the study and control groups. Hospital charges for labor, delivery, and postpartum care of cocaine-positive mothers averaged $3608, compared with an average of $3147 for mothers in the control group ($P < .05$). Neonatal charges from the cocaine-positive study group averaged $13,222, whereas control subjects' charges averaged only $1297 ($P < .03$). Most of the statistically significant differences in perinatal cost between the cocaine-positive and control populations were traced to the

(continued on page 20)

Thousands of neurologists go by the same name.

Neurologists write "Dilantin" more often than any other name in anti-convulsant therapy[1]—and for good reasons:

- **Unsurpassed control of generalized and partial seizures**[2-4]
- **Convenient once-daily dosing for many patients***
- **Significantly lower cost than carbamazepine or valproic acid**†

When you add billions of successful patient therapy days, it's clear why so many neurologists independently write the same prescription: Dilantin Kapseals for effective seizure control.

*For adult patients already controlled on 100 mg tid of Dilantin Kapseals.
†Adapted from *IMS National Pharmacy Audit Basic Data Book*, 4/91-6/91.[1]

Please see next page for a brief summary of full prescribing information.

Dilantin® Kapseals®

(extended phenytoin sodium capsules, USP) 100 mg

For control, compliance, and cost

PARKE-DAVIS

Dilantin® Kapseals®

(extended phenytoin sodium capsules, USP) 100 mg

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar compounds (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, and immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution—Federal law prohibits dispensing without prescription. 0362G280

 Revised October 1989

References **1.** Data on file, Market Research Dept, Parke-Davis. **2.** Ramsay RE, Wilder BJ, Berger JR, Bruni J. A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology.* 1983;33:904-910. **3.** Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin T. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *J Neurol Neurosurg Psychiatry.* 1985;48:639-644. **4.** Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med.* 1985;313:145-151.

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950

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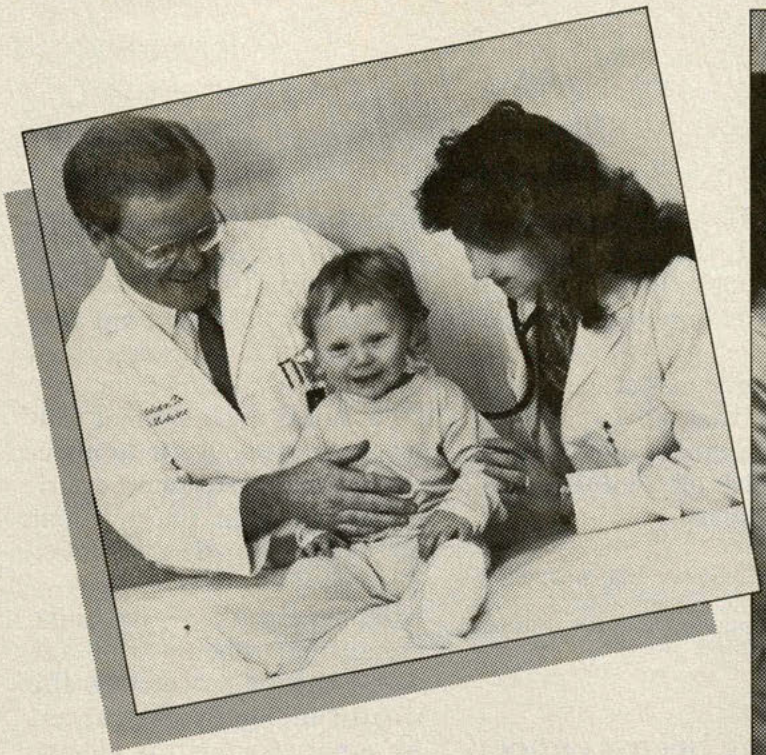

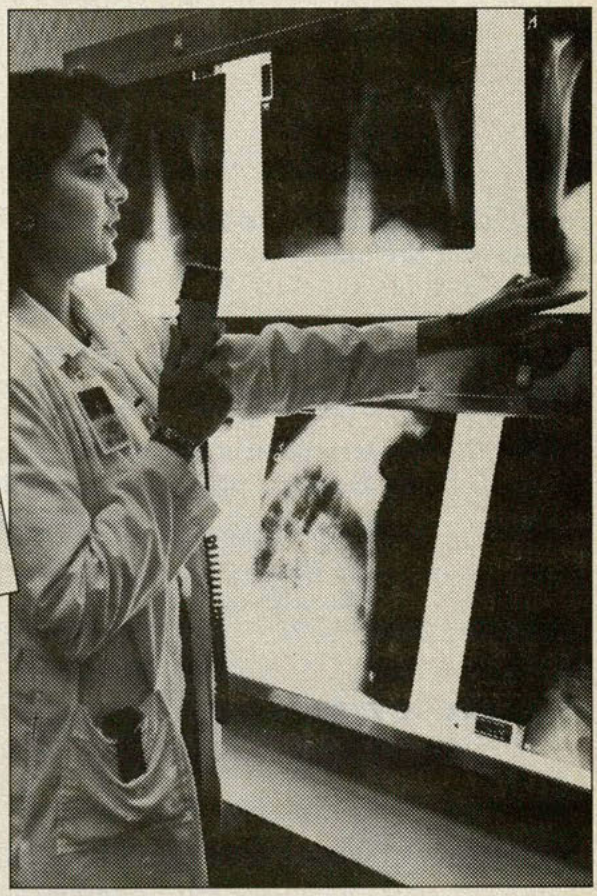

Your education is important to us!

Left Photo: Don Middleton, D.O., Resident, Tracy Middleton, D.O., Resident and "small" patient at FOH.

Right Photo: Sucheta Kulkarni, D.O., Intern

"Flint Osteopathic Hospital has provided acute and general health care for the Flint community for 50 years. The hospital is affiliated with Michigan State University and offers a full range of medical, surgical, emergency, and intensive care services. All medical and surgical subspecialties are covered. At FOH the intern and resident receives training in both outpatient ambulatory care as well as inpatient practices.

FOH, with 359 beds, is the largest osteopathic hospital in Michigan offering intern and residency training programs for osteopathic physicians. The medical education program is designed to provide a structured curriculum and experience in diagnosis and treatment. Morning reports and guest physician lectures occur daily. Reading lists and objectives have been developed for each service. A monthly journal club is conducted by each clinical department. EKG conferences are scheduled twice monthly. The FOH Congdon Lecture Series brings both D.O. and M.D. physicians to the hospital each month. Prominent practitioners, representative of both medical communities, share expertise in research findings during these monthly, day-long seminar presentations.

Ambulatory clinics have been established and provide longitudinal continuity training for interns and residents. Both traditional and alternative track internships are available at FOH. The hospital is a charter member of the Consortium of Osteopathic Graduate Medical Education and Training (COGMET) in association with Michigan State University."

Residencies

- Anesthesia
- Family Practice
- Gastroenterology
- Internal Medicine
- Obstetrics/Gynecology
- Ophthalmology
- Orthopedics
- Otorhinolaryngology
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- Radiology
- Surgery
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- Gastroenterology

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Vice President of Medical Education

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FLINT OSTEOPATHIC HOSPITAL
3921 Beecher Rd.
Flint, MI 48532

Where family matters

association between cocaine abuse and premature birth.

The authors conclude that this information should benefit institutions and organizations trying to assess cost-benefit aspects of programs for the prevention and treatment of cocaine abuse during pregnancy.

Calhoun BC, Watson PT: The cost of maternal cocaine abuse: I. Perinatal cost. *Obstet Gynecol* 1991;78:731-734.

Antigen diversity threshold in onset of AIDS?

Longitudinal studies of patients infected with the human immunodeficiency virus 1 (HIV-1) reveal a long, variable incubation period between infection and the development of the acquired immunodeficiency syndrome (AIDS). Data from two HIV-infected patients in this study show temporal changes in the number of genetically distinct strains of the virus throughout the incubation period, with a slow, but steady, rise in diversity during the progression to AIDS.

Researchers developed a mathematical model of the dynamic interaction between viral diversity and the human immune system that suggests an antigen diversity threshold exists. Below this threshold, the immune system can regulate the viral population growth. However, above the threshold, the virus population induces the collapse of the CD4+ lymphocyte population.

Their mathematical model suggests that antigen diversity is the cause—not the consequence—of immunodeficiency disease.

Nowak MA, Anderson RM, McLean AR, et al: Antigenic diversity thresholds and the development of AIDS. *Science* 1991;254:963-969.

Treating breast cancer in elderly women

The authors retrospectively reviewed the medical records of 150 women, aged 80 years or older, in whom breast cancer was diagnosed between 1970 and 1980 at the Massachusetts General Hospital. These patients tolerated surgery or radiation therapy well.

Of the 103 women who had mastectomies, only one patient died during the postoperative period. The complication rate from mastectomy was similar to that reported for younger women. All of the patients who began radiation therapy completed their treatment courses. Complications from radiation therapy were generally transient and easily tolerated.

Five-year actuarial survival rates for patients with stage I and II disease were similar among women undergoing primary radiation therapy (67%) or modified radical mastectomy (65%). However, the comparable survival rate for those women treated with lumpectomy alone was only 39%. Local and regional failures occurred with lumpectomy, total mastectomy, or primary radiation therapy, but not with modified radical mastectomy.

Based on these findings, the authors conclude that age alone should not dictate the treatment for breast cancer. An otherwise healthy elderly woman should be offered the same treatment options for the treatment of carcinoma of the breast as those options offered to younger patients.

Swanson RS, Sawicka J, Wood WC: Treatment of carcinoma of the breast in the older geriatric patient. *Surg Gynecol Obstet* 1991;173:465-469.

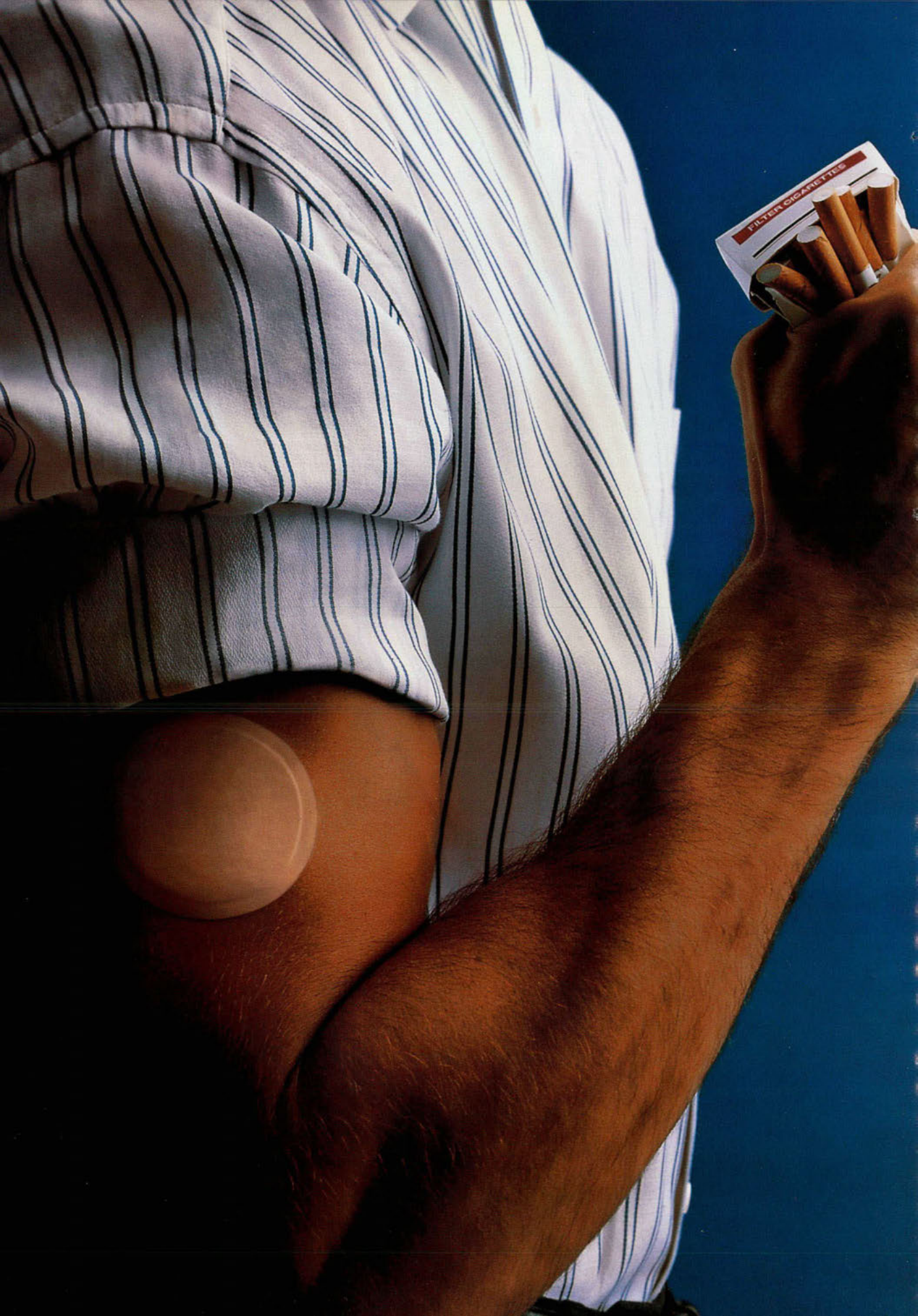
Long-term evaluation of patients undergoing extracapsular cataract surgery

Investigators evaluated the 2-year outcome of extracapsular cataract surgery with posterior chamber intraocular lens insertion performed by a single surgeon in Kathmandu, Nepal. During this follow-up period, 610 eyes were evaluated.

Patients included in this study had undergone manual irrigation and aspiration by use of a modified J-loop poste-

(continued on page 30)


NEW
FILTER CIGARETTES
INTRODUCING
Habitrol™
nicotine
FINALLY THE
END OF SMOKING
DEPENDENCE MAY
BE AT HAND...


FILTER CIGARETTES

New Habitrol™ nicotine

THE PATCH THAT BEATS THE PACK

National statistics show that of the 17 million Americans who attempt to quit smoking each year, only 1.3 million are successful.[1] Now you have the power to give your motivated patients a better chance at quitting. New Habitrol provides a simple, once-a-day therapy that significantly reduces craving for cigarettes, and significantly increases abstinence rates.[2]

Please see brief summary of Prescribing Information at end of this advertisement.

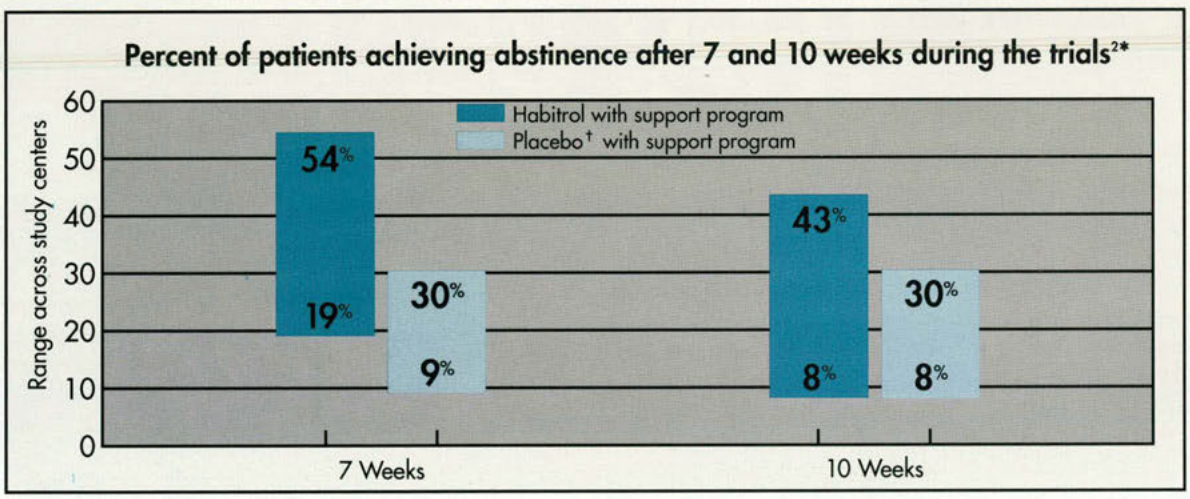
For the motivated patient...

New Habitrol™ nicotine

Significantly increases abstinence rates when used with support[2]

- In two 10-week, double-blind, placebo-controlled trials of smokers who wanted to quit and received behavioral support,

  Quit rates were significantly greater for Habitrol after 7 weeks and after weaning (10 weeks)[2*]

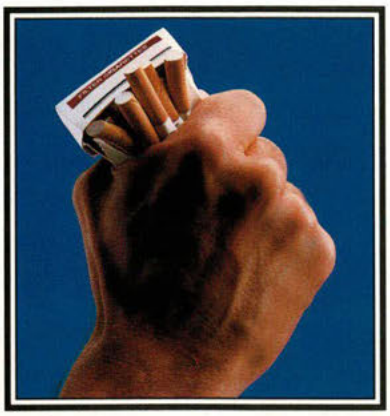


- Total abstinence from smoking was measured by patient diary entries and verified by breath carbon monoxide levels

*Two trials with 9 study centers, number of patients per treatment ranged from 44 to 76.

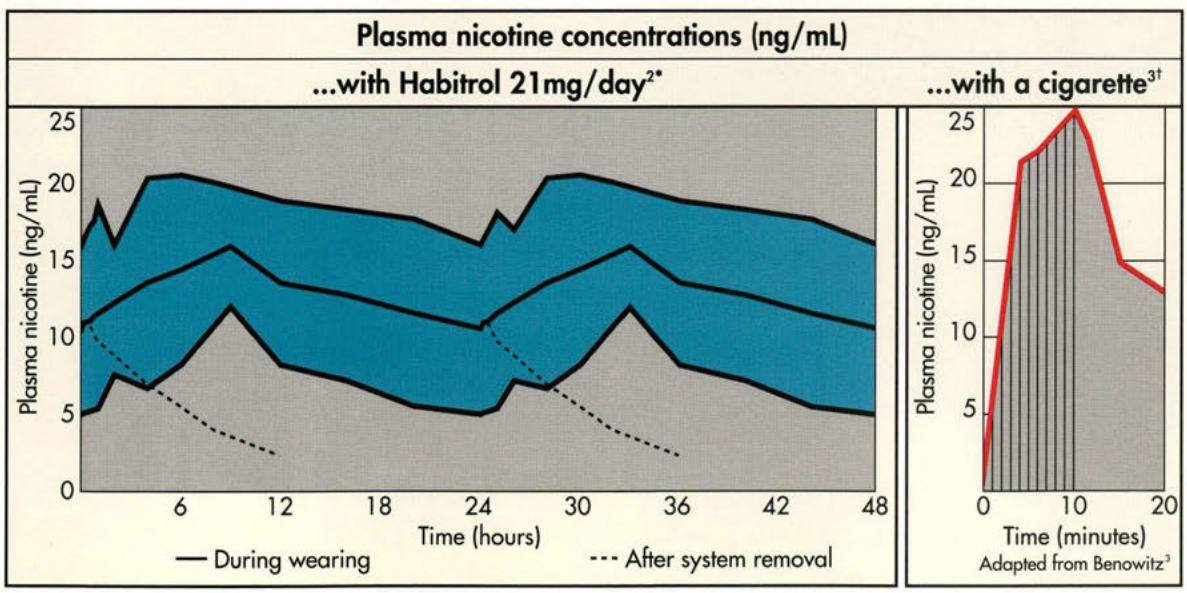
†Placebo contained a subtherapeutic (ST) amount of nicotine (13% of the nicotine found in the active system).

THE PATCH THAT BEATS THE PACK



Significantly reduces cigarette craving through controlled nicotine release

- Reduction in craving for cigarettes was significantly greater with Habitrol than with placebo throughout the study period[2]
- Maintains steady blood levels of nicotine for a full 24 hours to...
  - —avoid the peaks and troughs produced by cigarette smoking
  - —maintain early morning nicotine levels



- Systematic step-down therapy with three dosages helps wean patients off nicotine

*Steady-state plasma nicotine concentrations for two consecutive applications of Habitrol 21mg/day (Mean ± 2SD).

†Patient inhaled from a cigarette once every minute for 10 minutes.

Please see brief summary of Prescribing Information at end of this advertisement.

For the motivated patient...

New Habitrol™ nicotine

A simple and convenient once-daily therapy for your patients

- During the course of therapy the dosage of nicotine is gradually reduced to help patients overcome dependence

21 mg/day* ($30\ cm^2$)†

14 mg/day ($20\ cm^2$)†

7 mg/day ($10\ cm^2$)†

- Safe and well tolerated
- Topical reactions are the most commonly reported side effects — seen at least once in 35% of patients[2]
  - — 97% of topical reactions (short-lived erythema, pruritus and burning) were mild to moderate[2]
- 7% of Habitrol patients (29 of 401) discontinued trials due to side effects[2]

The most frequently observed adverse reaction is skin irritation.

Because Habitrol, transdermal therapeutic system, contains nicotine, it should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. It should be kept out of the reach of children and pets.

*For patients with coronary artery disease or who weigh less than 100 lbs or smoke less than 1/2 pack of cigarettes/day, please see Individualization of Dosage Section of Prescribing Information.

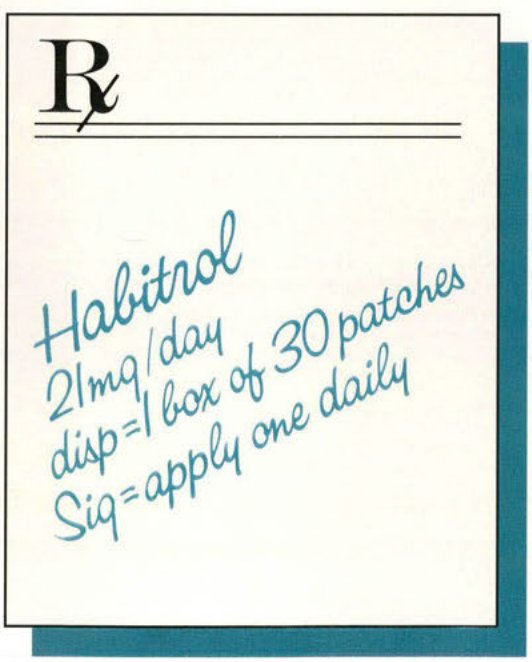
†Patches shown 50% of actual size.

THE PATCH THAT BEATS THE PACK

...plus a patient support program that's easy for you to implement

Comprehensive program includes...

- Patient Starter Kit — provides materials that can help patients overcome the behavioral and social components of smoking dependence
- Office Support Kit — provides tools that make it easy for you and your staff to identify the motivated patient, initiate therapy, and follow up on your patient's progress



BASEL Pharmaceuticals
Division of CIBA-GEIGY Corporation

Please see brief summary of Prescribing Information at end of this advertisement.

Printed in U.S.A. (11/91)

273-12357-A

Habitrol™
nicotine
Transdermal Therapeutic System
Systemic delivery of 21, 14, or 7 mg/day over 24 hours

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Habitrol treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Habitrol treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of Habitrol systems for longer than 3 months has not been studied.

CONTRAINDICATIONS
Use of Habitrol systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS
Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking while using Habitrol systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning
Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Habitrol treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Habitrol systems has not been examined in pregnancy (see PRECAUTIONS, Other Effects). Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Habitrol therapy is used during pregnancy, or if the patient becomes pregnant while using Habitrol treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children
The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Habitrol systems are applied or ingested by children or pets. Used 21 mg/day systems contain about 60% (32 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused Habitrol systems out of the reach of children and pets.

PRECAUTIONS
General
The patient should be urged to stop smoking completely when initiating Habitrol therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using Habitrol systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Habitrol dose should be reduced or Habitrol treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of Habitrol systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions: In a 6-week open-label dermal irritation and sensitization study of Habitrol systems, 22 of 220 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 3 patients exhibited mild-to-moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking. In the efficacy trials, erythema following system removal was typically seen in about 17% of patients, some edema in 4%, and dropouts due to skin reactions occurred in 6% of patients.

Patients should be instructed to promptly discontinue the Habitrol treatment and contact their physicians if they experience severe or persistent local skin reactions at the site of application (e.g., severe erythema, pruritus or edema) or a generalized skin reaction (e.g., urticaria, hives, or generalized rash).

Skin Disease: Habitrol systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases: The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Habitrol treatment was reported occasionally. If serious cardiovascular symptoms occur with Habitrol treatment, it should be discontinued.

Habitrol treatment should generally not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency: The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Endocrine Diseases: Habitrol treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease: Nicotine delays healing in peptic ulcer disease; therefore, Habitrol treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension: Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Habitrol treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patients
A patient instruction sheet is included in the package of Habitrol systems dispensed to the patient. It contains important information and instructions on how to use and dispose of Habitrol systems properly. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions
Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation

May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
Adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Carcinogenesis, Mutagenesis, Impairment of Fertility
Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D (see WARNINGS)
The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Habitrol treatment on fetal development are unknown. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Habitrol treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity
Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg/day IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects
Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low-birth-weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate, and decreased uterine blood flow and fetal breathing movements. Habitrol treatment has not been studied in pregnant humans.

Labor and Delivery
Habitrol systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother or the fetus during labor are unknown.

Nursing Mothers
Caution should be exercised when Habitrol therapy is administered to nursing women. The safety of Habitrol treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk-to-plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with Habitrol treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Habitrol systems should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother

Coming in. . .

THE DO

The February issue of The DO will focus on continuing medical education in the osteopathic medical profession. The issue will explain changes in AOA CME requirements that go into effect this year. It will also examine the concerns that DOs in small states and in the military have regarding CME.

The February issue will also carry articles on living wills and euthanasia.

Future issues of JAOA

- "Recognizing patients at risk or already infected with HIV"
- "Bacterial patterns found in surgery patients with chronic sinusitis living in Iowa"
- "The planning, development, and implementation of a worksite health promotion program: A case study"
- "Acute severe asthma: Part 1. Pathophysiology and clinical assessment"
- "Acute severe asthma: Part 2. Current therapy"
- "Regulation of the tension of human chorionic vasculature by histamine and prostaglandin $F_2\alpha$"
- "The office diagnosis of lower extremity venous insufficiency and treatment with the use of nonprescription support hose"
- "Laterally transposed pelvis: A new and proper name for an old problem"
- "The physical fitness of first-year osteopathic medical students"
- "Nociceptive considerations in the mechanism of counterstrain"
- "Periorbital and orbital infections in children"
- "Group A *Streptococcus* detection: Office versus reference laboratory"

rior chamber intraocular lens. Almost 50% of the patients had uncorrected visual acuities of 20/50 or better after surgery.

Sight-threatening complications in seven eyes (1.2%) included retinal detachment, corneal decompensation, and endophthalmitis. Although this rate compares with that in developed countries, posterior capsular opacification occurred in 21% of the patients at follow-up.

Extracapsular cataract surgery with intraocular lens insertion may be an alternative to intracapsular cataract surgery in developing nations, where aphakic spectacles are expensive, not easily obtainable, or difficult to replace, conclude the authors.

Ruit S, Robin AL, Pokhrel RP, et al: Extracapsular cataract extraction in Nepal: 2-year outcome. *Arch Ophthalmol* 1991; 109:1761-1763.

Pediatric psychosomatic musculoskeletal pain

Investigators here report the clinical and psychological findings of 100 children with psychosomatic musculoskeletal pain at a major pediatric rheumatology referral center. Most patients were girls (76%) with a median age of 13 years and a median duration of symptoms of 1 year.

Multiple pain sites were common (66%), with the pain being constant or intermittent among 63% and 37% of the children, respectively. Hyperesthesia occurred in 45% of the children; yet nearly all of them maintained a cheerful disposition despite complaints of severe pain.

Two predominant abnormal family milieus were observed: One was cohesive, stable, and organized, but intolerant of separation and individuation. The second family type was chaotic, and emotionally unsupportive, with high conflict levels. Members of the cohesive family type reported significantly less distress than members of chaotic families. Enmeshment between mother and child was common in both family types.

Although frequently viewed as bright, these children generally had normal intelligence levels; some of them had unrecognized academic difficulty. These children, compared with those youngsters with arthritis, had a significantly lower global well-being score. Clinical depression was diagnosed in only 11% of the children.

Most youngsters (97%) responded favorably to intensive physical and occupational therapy along with individual or family psychotherapy; 78% became symptom-free or fully functional.

Children with these signs and symptoms should have full psychological evaluations, conclude the authors. Those who do receive such evaluations respond well to treatment directed toward decreasing pain and restoring function.

Sherry DD, McGuire T, Mellins E, et al: Psychosomatic musculoskeletal pain in childhood: Clinical and psychological analyses of 100 children. *Pediatrics* 1991;88:1093-1099.

Morbidity associated with radical lymphadenectomy treatment for gastric carcinoma

Recent studies suggest an improved survival in patients who undergo radical lymph node dissection for the curative treatment of gastric carcinoma. This retrospective review compares morbidity and mortality between patients who underwent radical lymph node dissection with those patients who underwent resections of lesser scope.

Of the surgically related events compared in this study, only the amount of postoperative abdominal drainage differed significantly among patients in the group who underwent radical lymph node dissection. Forty-four percent of patients who underwent radical lymph node dissection and 35% of patients who underwent a less-extensive procedure had a major complication. With a total of two 30-day in-hospital deaths (1.1%),

(continued on page 34)

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ONCE-A-DAY

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PELLET-FILLED CAPSULES

P ROTECTS your hypertensive patients for 24 hours[1]

R EDUCES wide variations in BP control[2]

N EGLIGIBLE discontinuation due to side effects[1]

D OSED once daily at all doses

Constipation, which can easily be managed in most patients, is the most frequently reported side effect of verapamil.

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Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on adjacent page.

American Osteopathic Association—Continuing Medical Education

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Please refer to the revised CME GUIDE for additional information.

References: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144–150. **2.** Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In

VERELAN® verapamil HCl

patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following-reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain.

Cardiovascular: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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In non-insulin-dependent diabetes...

24-HOUR CONTROL..

ONE DOSE A DAY

Steady, round-the-clock glycemic control can begin with breakfast

All sulfonylureas, including MICRONASE, can cause severe hypoglycemia. Proper patient selection, dosage, and instruction are important.

Micronase®
Tablets (glyburide)

Usual starting dosage: 2.5mg-5mg once a day

Upjohn

Please see adjacent page for brief summary of prescribing information.

no significant difference in the postoperative death rate occurred.

Based on these results, the authors conclude that radical lymph node dissection can be performed as safely as lesser operations for gastric carcinoma. The former procedure should not be avoided for fear of complications.

Smith JW, Shiu MH, Kelsey L, et al: Morbidity of radical lymphadenectomy in the curative resection of gastric carcinoma. *Arch Surg* 1991;126:1469-1473.

D-dimer, thrombin-antigen as diagnostic tests for pulmonary embolism

The value of D-dimer and thrombin-antithrombin III was evaluated as a screening tool before lung scanning for pulmonary embolism. Specifically, the authors of this study investigated how well these tests discriminated between patients with clinically suspected pulmonary embolism and patients with other diseases mimicking pulmonary embolism.

Investigators performed Data-Fi Dimertest latex assay, MAbCO Dimertest enzyme immunoassay (EIA), and thrombin-antithrombin III (TAT) complex EIA testing in 100 consecutive patients who were sent to one institution for lung scanning by their attending physicians because of clinically suspected

(continued on page 36)

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pulmonary embolism. Twenty-six percent of these subjects were treated as outpatients.

The D-dimer latex assay was positive (>500 ng/mL) in 12 of 25 patients (48%) with high probability of pulmonary embolism and in 1 of 9 patients (11.1%) with intermediate probability. Only one patient (1.5%) with a scan showing no abnormality had a positive latex assay, presumably related to inapparent bleeding after a computed tomographic (CT)-guided liver biopsy.

Using 120 ng/mL as the upper limit of normal (mean ± 2 SD of healthy controls), researchers determined the D-dimer EIA to be positive in 21 of 25 patients (84%) with high probability, in 6 of 9 patients (66.7%) with intermediate probability, and in 40 of 66 patients (60.6%) with normal/low probability of pulmonary embolism.

The TAT EIA was positive (>mean ± 2 SD of healthy controls; 3.53 ng/mL) in 18 of 25 patients (72%) with high probability, in 5 of 9 patients (55.6%) with intermediate probability, and in 16 of 66 patients (24.2%) with normal/low probability of pulmonary embolism. A normal result in one of these hemostaseologic tests did not predict a low probability of pulmonary embolism after lung scanning.

The authors conclude that exclusion of patients with clinically suspected pulmonary embolism from further investigation by lung scanning because of a normal result of one of the aformentioned tests is not justified.

Leitha T, Speiser W, Dudczak R: Pulmonary embolism: Efficacy of D-dimer and thrombin-antithrombin III complex determinations as screening tests before lung scanning. *Chest* 1991;100:1536-1541.

Biomechanical differences in obese, nonobese men's gait

The purpose of this study was to identify and compare the kinematic components of the walking gait of obese men with those of nonobese men. Using cinematography, researchers recorded the self-paced walking trials of 12 obese volunteers, aged 30 to 47 years, who weighed 70% to 99% above their ideal body weight.

Their findings were as follows: Obese men walked significantly slower (1.09 m/s; $P < .001$) than nonobese men (1.64 m/s). Obese subjects take significantly shorter strides (1.25 m; $P < .001$) than nonobese men (1.67 m). Similarly, obese men had step widths twice those of normal-weight individuals (0.16 m vs 0.08 m).

Mean hip abduction angles of the obese men are significantly different ($P < .001$) at some events of the walking cycle from the hip angles of nonobese persons. The mean hip and knee flexion angles are not significantly different for obese and nonobese subjects. Obese individuals have a walking gait pattern with significantly greater mean magnitude of ankle dorsiflexion ($P < .001$) and lesser mean magnitude of ankle plantar flexion ($P < .001$) than nonobese men throughout the walking cycle.

The authors conclude that obese individuals display a walking gait that follows a normal pattern but some of the temporal and angular components of their gait are different from those of nonobese persons, primarily because of the excessive adipose tissue inside their thighs.

Spyropoulos P, Pisciotta JC, Pavlou KN, et al: Biomechanical gait analysis in obese men. *Arch Phys Med Rehabil* 1991;72:1065-1070.

Rate of HIV infection among patients undergoing elective surgery

To determine the prevalence of antibody to the human immunodeficiency virus (HIV), investigators conducted an anonymous survey of patients who underwent elective surgery in a large metropolitan hospital. Of the 4087 patients evaluated, 18 patients (0.4%) were found to be infected with the HIV as confirmed by a positive Western Blot antibody test.

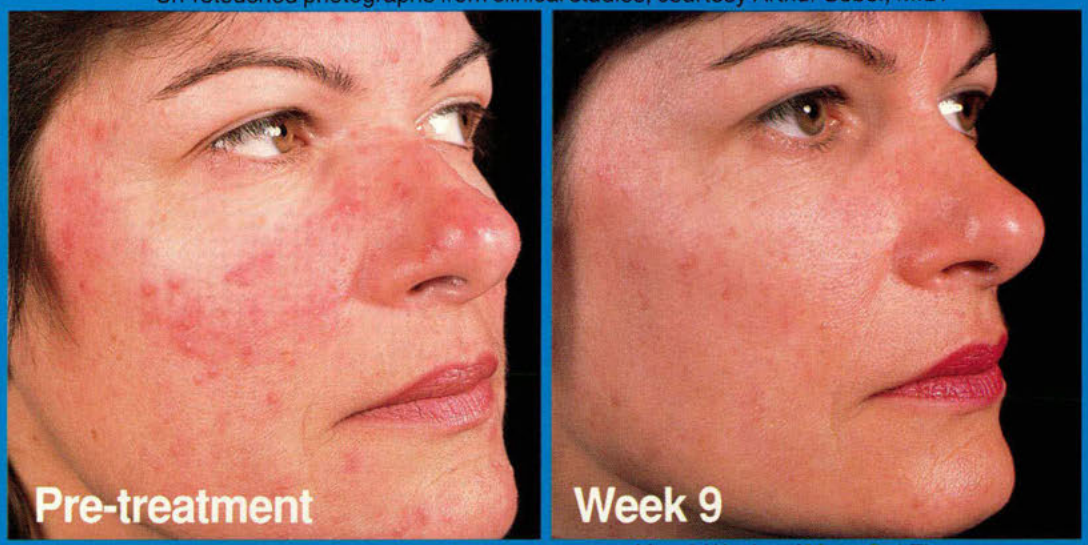
Assessment of risk factors demonstrated that patients

(continued on page 39)

Now

#1 THERAPY FOR ROSACEA

Un-retouched photographs from clinical studies, courtesy Arthur Sober, M.D.



After 9 Weeks of MetroGel Therapy

MetroGel®
(metronidazole) 0.75% Topical Gel

PROVEN EFFECTIVE[2,3,4]

- 9 weeks BID yields excellent initial efficacy. Some rosacea patients may see significant improvement within 3-6 weeks of MetroGel therapy
- Over 70% of patients experience significant reductions of papules, pustules and erythema

EXCELLENT SAFETY PROFILE

- No reports of systemic side effects
- Avoids common side effects associated with oral antibiotics, such as GI distress, vaginal candidiasis and phototoxicity

FORMULATED FOR PATIENT ACCEPTANCE

- Elegant gel is 95% water and contains no oils, alcohols or fragrances
- MetroGel can be used under make-up, sunscreens or moisturizers

CONVENIENT BID DOSING

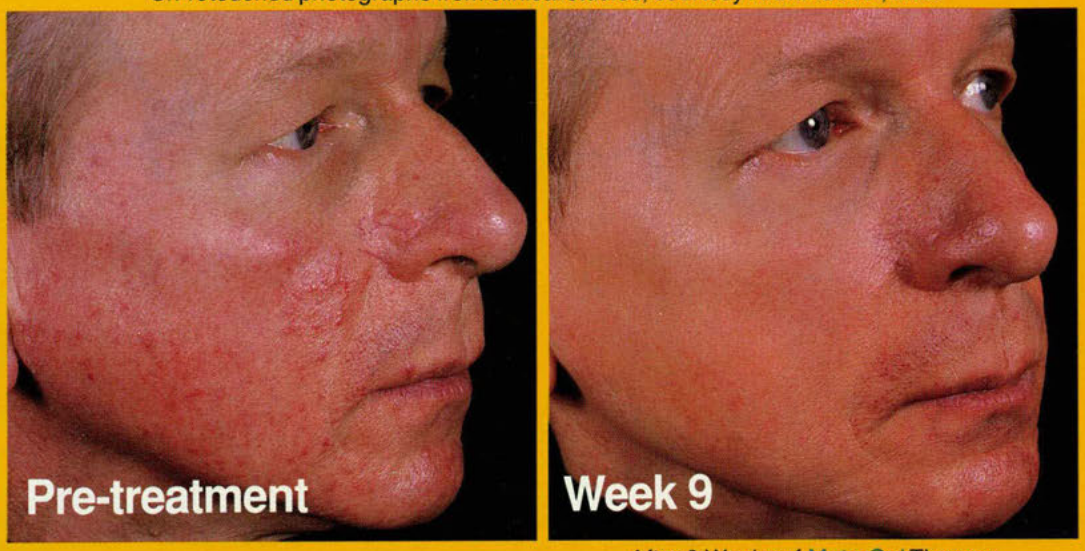
- Apply a thin film of MetroGel morning and evening
- Initial therapy for 9 weeks. Continued BID maintenance therapy as needed

MetroGel For Rosacea

Curatek

Now #1 THERAPY FOR ROSACEA[1]

Un-retouched photographs from clinical studies, courtesy Arthur Sober, M.D.



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- Proven Effective[2,3,4]
- Excellent Safety Profile
- Formulated For Patient Acceptance
- Convenient BID Dosing

Brief Summary

MetroGel®
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(NOT FOR OPHTHALMIC USE)

CLINICAL PHARMACOLOGY The mechanisms by which METROGEL acts in reducing inflammatory lesions of rosacea are unknown, but may include an anti-bacterial and/or an anti-inflammatory effect.

INDICATIONS AND USAGE METROGEL is indicated for topical application in the treatment of inflammatory papules, pustules, and erythema of rosacea.

CONTRAINDICATIONS METROGEL is contraindicated in individuals with a history of hypersensitivity to metronidazole, parabens, or other ingredients of the formulation.

PRECAUTIONS Because of the minimal absorption of metronidazole and consequently its insignificant plasma concentration after topical administration, the adverse experiences reported with the oral form of the drug have not been reported with METROGEL.

General METROGEL has been reported to cause tearing of the eyes. Therefore, contact with the eyes should be avoided. If a reaction suggesting local irritation occurs, patients should be directed to use the medication less frequently, discontinue use temporarily, or discontinue use until further instructions. Metronidazole is a nitroimidazole and should be used with care in patients with evidence of, or history of, blood dyscrasia.

Drug Interactions Drug interactions are less likely with topical administration but should be kept in mind when METROGEL is prescribed for patients who are receiving anticoagulant treatment. Oral metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time.

Carcinogenesis: Tumorigenicity in Rodents Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic, oral administration in mice and rats but not in studies involving hamsters. These studies have not been conducted with 0.75% metronidazole gel, which would result in significantly lower systemic blood levels than oral formulations.

Mutagenicity Studies Although metronidazole has shown mutagenic activity in a number of *in vitro* bacterial assay systems, studies in mammals *(in vivo)* have failed to demonstrate a potential for genetic damage.

Pregnancy This drug should be used during pregnancy only if clearly needed.

Nursing Mothers Even though METROGEL blood levels are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS Adverse conditions reported include watery (tearing) eyes if the gel is applied too closely to this area, transient redness, and mild dryness, burning, and skin irritation. None of the side effects exceeded an incidence of 2% of patients.

DOSAGE AND ADMINISTRATION Apply and rub in a thin film of METROGEL twice daily, morning and evening, to entire affected areas after washing. Significant therapeutic results should be noticed within three weeks. Clinical studies have demonstrated continuing improvement through nine weeks of therapy.

Areas to be treated should be cleansed before application of METROGEL. Patients may use cosmetics after application of METROGEL.

HOW SUPPLIED METROGEL (0.75% metronidazole) is supplied in a 1 oz. (28.4 g) aluminum tube – NDC 55326-100-21.

Caution: Federal law prohibits dispensing without a prescription.

STORE AT CONTROLLED ROOM TEMPERATURES: 59° to 86° F; 15° to 30° C.

Consult package insert for full disclosure. Package insert issued 10/88.

References:

1. Independent market research shows dermatologists prescribe MetroGel for rosacea more often than any other medication. Data on file, Curatek Pharmaceuticals, 1991.
2. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol.* 1987; 123:609-614.
3. Aronson IK, Rumsfield JA, West DP, Alexander J, Fischer JH, Paloucek FP. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm.* 1987;21:346-351.
4. Lowe NJ, Henderson T, Millikan LE, Smith S, Turk K, Parker F. Topical metronidazole for severe and recalcitrant rosacea: a prospective open trial. *Cutis.* 1989;43(3): 283-286.

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with a history of a blood transfusion did not differ in demographics or rate of HIV infection from the population as a whole. Of the 18 HIV-infected patients, 13 gave an admission history of one or more risk factors, including 10 patients with a history of a prior positive test. Only five patients (0.12%) provided no history of a risk factor or a history of transfusion only.

The authors conclude that the prevalence of HIV infection among patients undergoing elective surgery is low; therefore, no substantial benefit would be gained from screening such patients.

Charache P, Cameron JL, Maters AW, et al: Prevalence of infection with human immunodeficiency virus in elective surgery patients. *Ann Surg* 1991;214:562-568.

Effects of menstrual cycle, gender on alprazolam pharmacokinetics

The authors of this study evaluated the effects of menstrual cycle phases and gender on alprazolam pharmacokinetics in healthy volunteers. They administered alprazolam (1 mg) to seven women during the late follicular and luteal phases of the menstrual cycle. This same alprazolam dosage was given to eight men on one occasion.

No difference was observed in the alprazolam pharmacokinetic parameters during the menstrual cycle phases. Mean alprazolam clearance (±SD) was 0.0037 ± 0.0009 mL/h during the follicular phase and 0.0036 ± 0.001 mL/h during the luteal phase ($P > .05$, difference not significant).

Using weight as a covariant, the investigators found no difference in alprazolam pharmacokinetic parameters between women and men. Mean alprazolam clearance (±SD) was 0.0036 ± 0.0009 mL/h in women, compared with 0.0041 ± 0.0006 mL/h in men ($P > .05$, difference not significant).

Researchers concluded that although alprazolam metabolism was similar among the two groups on the 2 days tested, alterations may occur in women at other times during the menstrual cycle. They concede, however, that further investigation is needed to understand the effects of the menstrual cycle phases on gender and drug metabolism.

Kirkwood C, Moore A, Hayes P, et al: Influence of menstrual cycle and gender on alprazolam pharmacokinetics. *Clin Pharmacol Ther* 1991;50:404-409.

JAOA CME QUIZ APPLICATION FORM

COMPLETE THE APPLICATION FORM AND ANSWER SHEET BELOW FOR CME CREDIT (1 HOUR).

"Certification of Home Study" may be submitted with this application form to save postage.

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Answer Sheet to January 1992 *JAOA* CME Quiz

1. a b	2. a b c d	3. a b c d e	4. a b c d e	5. a b c d
6. a b c d	7. a b c d	8. a b	9. a b c d	10. a b

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Please see brief summary of Prescribing Information on the next page.

References:
1. Walson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.