during 1984, there were 455 individual osteopathic physicians and basic scientists who were either the primary investigator or a collaborator in the activity. Of the 455, 193 were D.O.s, but only 101 of these were listed as the principal investigator. Also, the vast majority of projects performed by Ph.D. researchers in osteopathic institutions were funded by federal agencies, whereas the majority of funding for clinicians was through in-house support and from pharmaceutical houses.

Clearly, there is a need to increase the number of clinicians who will be prepared to conduct or participate in medical research. The efforts of several of our colleges of osteopathic medicine to develop physician-scientist programs that combine the D.O. and Ph.D. degrees should be encouraged and supported. Additional suggestions for increasing the number of clinician-scientists are proposed by D'Alonzo; they bear close reading and attention.

THOMAS W. ALLEN, D.O., FACOI

1. Northup, G.W., ed.: Osteopathic research. Growth and development. American Osteopathic Association, Chicago, 1987

The erosion of medicine

We live in an era where positive and forward thinking are popular things. But in order to achieve positive results, we sometimes have to look backwards to determine a dynamic purpose for the future.

It is useful once in a while to stop and think about terms. The word "medicine," for example, has at least three definitions: It refers to any drug or remedy; to the art and science of the diagnosis and treatment of disease and the maintenance of health; and to the treatment of disease by non-surgical means.

Certainly that broad definition has been generally accepted throughout the ages. But the unique responsibility of physicians to adhere to such a definition is being eroded and narrowed by recent advances. In no way is this meant to be critical of groups of sincere individuals who are trying to advance their cause. But at the same time, physicians should be aware of what is happening.

For example, several states throughout the country have enacted legislation permitting physical therapists to accept patients without prior medical referral. In many of these states, the legislation's impact was not studied to any extent. Of course, on the one hand, it increased the vulnerability of the physical therapist in accepting responsibility for making a diagnosis. It also increased their profes-

sional liability. But it was taken to extremes when some state boards of physical therapy began sending notices to physicians who use physical therapy modalities in their offices. They were told that they should stop using such modalities because they were practicing physical therapy without a license. Also interesting to note is that the same group is promoting courses in manipulative therapy. Could it be that same group who tried to get legislative sanction saying that manipulative therapy is a physical therapy modality only, and that it should be restricted to and licensed only by physical therapists?

Another development is the suggestion of clinical pharmacists that they be allowed greater authority in the pharmacologic management of, in particular, hospital inpatients. In some instances, they wish to have a deciding role in the selection and prescription of medications to be administered.

Before we become too critical, let us look back in history a bit and see what has happened in a couple of other areas. At least two professions have developed primarily due to a lack of interest on the part of medicine in that particular area of practice. For example, podiatrists largely filled the void created by general practitioners and some orthopedic surgeons who weren't particularly interested in disorders of the feet. And optometry developed when a number of ophthalmologists weren't too interested in refraction, and focused more concern towards eye surgery and ocular diseases. Both the podiatrists and the optometrists are constantly trying to seek legislation which would widen their turf. However, it is to their credit that they have never done anything to seek restrictive legislation that would protect their health care domain by a wall of exclusiveness.

The erosion is taking place now. And whether D.O. or M.D., our traditional turf is gradually being eroded. We need to be acutely aware of what's going on and develop programs to stop it.

GEORGE W. NORTHUP, D.O., FAAO

editorial comment

Health maintenance organizations (HMOs) have failed to reduce per capita hospital costs in the nation's major cities, according to a University of Michigan study.

As participation in HMOs rises in a major metropolitan area, so does the average cost of hospital

continued on page 409/68

DESCRIPTION: Each milliliter of NASALCROM® (cromolyn sodium nasal solution, USP) contains 40 mg cromolyn sodium in purified water with benzalkonium chloride 0.01% and EDTA (edetate disodium) 0.01%.

INDICATIONS: NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.

CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.

PRECAUTIONS: General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy.

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphylaxis.

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, perianteric vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

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"I LIKE HOW FAST IT WORKS TO STOP MY ALLERGIES, WITHOUT MAKING ME DROWSY."

NASALCROM works rapidly—usually within the first few doses—to relieve the congestion, rhinorrhea, and sneezing of seasonal allergic rhinitis. However, for many patients, the side effects of traditional medications can be as troublesome as the allergic symptoms themselves. Unlike these medications, NASALCROM is extremely well-tolerated therapy, virtually uncomplicated by serious side effects, tolerance or contraindications.

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**Stops allergic rhinitis rapidly,
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Effective control time and time again¹

Effective control of fasting and postprandial glucose—patient after patient, meal after meal, year after year.

Insulin when it's needed

Insulin levels are rapidly elevated in response to a meal, then return promptly to basal levels after the meal challenge subsides.

Timed to minimize risks

Rapidly metabolized and excreted, with an excellent safety profile.¹ As with all sulfonylureas, hypoglycemia may occur.

In concert with diet in non-insulin-dependent diabetes mellitus

Glucotrol[®]
(glipizide) 5-mg and 10-mg
Scored Tablets

**SYNCHRONIZED
SULFONYLUREA THERAPY**

Please see brief summary of Glucotrol[®] (glipizide) prescribing information on next page.

ROERIG
A division of Pfizer Pharmaceuticals
New York, New York 10017

Reference:

1. Sachs R, Frank M, Fishman SK: Overview of clinical experience with glipizide, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 163-172.

GLUCOTROL® (glipizide) Tablets

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 19, supp. 2:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including non-steroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hypoglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity was being similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

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

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas. GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.

DOSEAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100; 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

care per day and per admission. Catherine G. McLaughlin, professor of U-M's School of Public Health, analyzed data from 1972 through 1982 in 25 cities, where the popularity of HMOs has reached as much as 34 percent of the population. She found that on the average, every time the number of participants in an HMO increased by one percentage point, there were increases of \$3.58 in the average cost of hospital care per patient day, and of \$19.04 in the average hospital cost per admission. At the same time, however, the total number of annual admissions per 1,000 population fell by 5.79, and the length of hospital stay declined slightly.

McLaughlin said these results suggest that "when discussing future cost containment strategies, policymakers should consider some form of rate setting, the one factor that seemed to be associated with lower cost per capita."

A naturally occurring chemical found in fruits and vegetables may reduce the risk of skin cancer by decreasing the activity of Cytochrome P450-dependent enzymes that metabolize carcinogens in that organ. This is the result of experimental animal studies using ellagic acid, according to David Bickers, M.D., professor and chairman of the Department of Dermatology at the Case Western Reserve University School of Medicine.

This latest study shows that skin is a surprisingly active site for the metabolism of a variety of internal and external chemicals. "There is enzymatic activity in the skin that is capable of converting certain inert chemical environmental pollutants into reactive metabolites that can bind to structures in the skin, such as DNA. This enzyme-mediated reaction may initiate cancer," Dr. Bickers said. Initial studies showed that ellagic acid, derived from naturally occurring tannins, inhibits cancer by diminishing this metabolite binding. "We also showed that they could directly inhibit the ability of the enzymes that generate reactive metabolites," he continued.

Although the researchers are a long way from making any recommendations, they say it is conceivable that the repetitive use of substances like ellagic acid or its derivatives, which would reduce the metabolism of carcinogens, would be useful in diminishing the risk of cancer development.

A bed partner could save your life, especially if you're over age 60. Another person is often pivotal in noticing a major "hidden" sleep disorder. Although its episodes can even occur hundreds of times each night, the victims themselves may be

Oh, the extremes people go to.

Some people will go to any length to relieve back pain. Even if it means turning their world upside down.

Too bad she didn't come to you. Relief of painful musculoskeletal conditions can be so simple with Norflex® (orphenadrine citrate) — just one tablet b.i.d. Or one Norflex Injectable for on-the-spot relief.

Norflex effectively relieves pain and associated spasm. And it has a better safety profile — no sedation,* no danger of habituation.

*Some patients may experience transient episodes of light-headedness, dizziness or syncope, which may impair their ability to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.

NORFLEX® B.I.D.
(orphenadrine citrate) Sustained-Release
Tablets

**Relief pure
and simple.**

Please see next page for full
prescribing information.

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RK NX-1214

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3M

NORFLEX® B.I.D.

(orphenadrine citrate) TABLETS and INJECTABLE

Relief pure and simple.

Prescribing Information

DESCRIPTION: Orphenadrine citrate is the citrate salt of orphenadrine (2-dimethylaminoethyl 2-methylbenzhydrol ether citrate). It occurs as a white crystalline powder having a bitter taste. It is practically odorless, sparingly soluble in water, slightly soluble in alcohol.

ACTIONS: The mode of therapeutic action has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate also possesses anticholinergic actions.

INDICATIONS: Orphenadrine citrate is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute painful musculoskeletal conditions. The mode of action of the drug has not been clearly identified, but may be related to its analgesic properties. Orphenadrine citrate does not directly relax tense skeletal muscles in man.

CONTRAINDICATIONS: Contraindicated in patients with glaucoma, pyloric or duodenal obstruction, stenosing peptic ulcers, prostatic hypertrophy or obstruction of the bladder neck, cardiospasm (megaesophagus) and myasthenia gravis.

Contraindicated in patients who have demonstrated a previous hypersensitivity to the drug.

WARNINGS: Some patients may experience transient episodes of light-headedness, dizziness or syncope. Norflex may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; ambulatory patients should therefore be cautioned accordingly.

USAGE IN PREGNANCY: Safe use of orphenadrine has not been established with respect to adverse effects upon fetal development. Therefore, Norflex should be used in women of childbearing potential and particularly during early pregnancy only when in the judgment of the physician the potential benefits outweigh the possible hazards.

USAGE IN CHILDREN: Safety and effectiveness in children have not been established; therefore, this drug is not recommended for use in the pediatric age group.

PRECAUTIONS: Confusion, anxiety and tremors have been reported in few patients receiving propoxyphene and orphenadrine concomitantly. As these symptoms may be simply due to an additive effect, reduction of dosage and/or discontinuation of one or both agents is recommended in such cases.

Orphenadrine citrate should be used with caution in patients with tachycardia, cardiac decompensation, coronary insufficiency, cardiac arrhythmias.

Safety of continuous long-term therapy with orphenadrine has not been established. Therefore, if orphenadrine is prescribed for prolonged use, periodic monitoring of blood, urine and liver function values is recommended.

ADVERSE REACTIONS: Adverse effects of orphenadrine are mainly due to the mild anticholinergic action of orphenadrine, and are usually associated with higher dosage. Dryness of the mouth is usually the first adverse effect to appear. When the daily dose is increased, possible adverse effects include: tachycardia, palpitation, urinary hesitancy or retention, blurred vision, dilation of pupils, increased ocular tension, weakness, nausea, vomiting, headache, dizziness, constipation, drowsiness, hypersensitivity reactions, pruritus, hallucinations, agitation, tremor, gastric irritation, and rarely urticaria and other dermatoses. Infrequently, an elderly patient may experience some degree of mental confusion. These adverse reactions can usually be eliminated by reduction in dosage. Very rare cases of aplastic anemia associated with the use of orphenadrine tablets have been reported. No causal relationship has been established.

Rare instances of anaphylactic reaction have been reported associated with the intramuscular injection of Norflex injectable.

DOSAGE AND ADMINISTRATION: TABLETS: Adults—Two tablets per day, one in the morning and one in the evening.

INJECTABLE: Adults—One 2 ml. ampul (60 mg.) intravenously or intramuscularly; may be repeated every 12 hours. Relief may be maintained by 1 Norflex tablet twice daily.

HOW SUPPLIED: TABLETS: Bottles of 100 (NDC 0089-0221-10) and 500 (NDC 0089-0221-50), each tablet containing 100 mg. of orphenadrine citrate.

INJECTABLE: Boxes of 6 (NDC 0089-0540-06) and 50 (NDC 0089-0540-50) 2 ml. ampuls, each ampul containing 60 mg. of orphenadrine citrate in aqueous solution, made isotonic with sodium chloride. A.M.F.S. Category 12:08

CAUTION: Federal law prohibits dispensing without prescription.

NRF-6C

unaware of the disorder.

Sleep apnea causes repeated halts in breathing during sleep that last from 10 to 180 seconds each. It is most common in the elderly and in overweight middle-aged and older men who snore, and it usually worsens with increasing body weight and advancing age. Sleep apnea not only interrupts the flow of sleep, but it can be fatal if unchecked, especially in older persons who already have heart disease or hypertension.

Unfortunately, even if a person over 60 is not burdened with sleep apnea, sleep is found to be different from that of early adulthood. An estimated 90 percent of Americans between the ages of 60 and 80 complain that they experience chronic or occasional sleeplessness, making the elderly the largest age group with insomnia. Some factors that can interfere with a good night's sleep include physical and mental illness, evening use of alcohol, caffeine, nicotine, and dependence on nightly sleeping pills to invite drowsiness. Changes in routine and life-style, such as retirement, or changes in environment, particularly institutionalization in a hospital or nursing home, can also induce insomnia.

For more information about insomnia, the booklet, "What you should know about insomnia," is available by writing to: Insomnia/Upjohn, Department FS, P.O. Box 307, Coventry, Connecticut 06238. For the location of nearby sleep disorder centers, write to: Association of Sleep Disorders Centers, P.O. Box 2604, Del Mar, California 92014.

A new strategy for locating and monitoring hidden tumors has been devised by scientists at The University of Texas Health Science Center at Dallas. David Ranney, M.D., director of the Laboratory of Targeted Diagnosis and Therapy, report that by using a special dye, known as Gd-DTPA-dextran, researchers have been able to improve the effectiveness of MRI at locating tumors hidden in the body and at observing the action of anti-cancer drugs on tumors.

Gd-DTPA-dextran is a non-toxic, magnetic polymer, which is readily detectable by the MRI scanner and remains in the bloodstream except around tumors. Since tumors have leaky, porous blood vessels, when the dye reaches the tumor, it leaks through the blood vessels and is readily detected by the scanner. The tumor-imaging dye allows identification of tumor structures as small as half a millimeter in diameter. GD-DTPA-dextran also enables physicians to see quickly if a drug is killing all or only part of a tumor.

Dr. Ranney predicts that if current testing goes well, Gd-DTPA-dextran could be approved for use in hospitals within three years.

continued on page 411/76

***GIVE YOUR ANGINA PATIENTS
WHAT THEY'RE MISSING...***

CARDIZEM[®]
diltiazem HCl/Marion

FEW SIDE EFFECTS

CTS: CARDIZEM[®] *diltiazem HCl/Marion*

Antianginal action includes dilatation of coronary arteries, a decrease in vascular resistance/afterload, and a reduction in heart rate

Proven efficacy when used alone in angina¹

Compatible with other antianginals^{2,3*}

A safe choice for angina patients with coexisting hypertension, asthma, COPD, or PVD^{4,5}

***See Warnings and Precautions.**

Please see brief summary of prescribing information on the next page.

90 mg
NEW 120 mg
GREATER DOSAGE FLEXIBILITY

CARDIZEM[®]
diltiazem HCl/Marion
60 mg tid or qid

CARDIZEM® FEW SIDE EFFECTS diltiazem HCl/Marion IN ANTIANGINAL THERAPY

60 mg tid or qid

Brief Summary Professional Use Information

CARDIZEM®
(diltiazem HCl) 30 mg and 60 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

- Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
- Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
- Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
- Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, CPK, LDH, SGOT, SGPT, and other symptoms consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic

function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

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

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably asso-

ciated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. Issued 7/86
See complete Professional Use Information before prescribing.

References: 1. Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers. Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. *Am Heart J* 1983; 106(6): 1341-1347. 2. Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. *Consultant* 1984; 24(Dec): 150-159. 3. Johnston DL, Lesoway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. *Am J Cardiol* 1985; 55: 680-687. 4. Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): *Heart Disease: A Textbook of Cardiovascular Medicine*, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. 5. Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. *Mod Med* 1982; 50(Sept): 94-116.

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CERTIFICATION OF HOME STUDY

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This form should **not** be used, however, when CME quiz cards for the AOA Journal are submitted separately.

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Please refer to the revised CME GUIDE for additional information.

The newly recognized threat of radon gas in homes, believed to be a risk factor for lung cancer in the general population, has prompted scientists to evaluate the extent of the health hazard. National Cancer Institute (NCI) investigators and collaborating scientists are currently conducting three epidemiologic studies to assess the health risks of residential radon on populations in New Jersey, Sweden, and China. The studies are expected to be completed in about two years.

Radon is one of the world's most widely distributed natural carcinogens. The Environmental Protection Agency estimates that each year, between 5,000 and 30,000 lung cancer deaths in the United States may be attributed to radon. Recent measurements of radon in homes in various parts of the United States have shown that high levels of the gas can accumulate inside of houses built on uranium-rich soil. The invisible, odorless gas moves through small spaces in soil and rock and seeps into homes through dirt floors, cracks in concrete, floor drains, sump joints, and water drawn in from private wells. Lack of ventilation and tight insulation may contribute to indoor radon gas buildup. John Boice, M.D., chief of the NCI's Radiation Epidemiology Branch, believes that these studies will yield important information on radon risk, including information on the possible interaction of radon with cigarette smoking and the pattern of risk over time.

An artificial ligament that attaches between the thigh and lower leg bone has been approved for marketing by the Food and Drug Administration (FDA). The braided strand of synthetic fiber stabilizes the knee after the anterior cruciate ligament is torn—a common injury in football, soccer, and skiing.

The Gore-Tex[™] (W. Gore and Associates, Flagstaff, Arizona) ligament has been used experimentally on more than 1,000 patients at 27 hospitals in the United States, some of which have been followed for two years. After the device is implanted, many patients are able to walk in several weeks, as compared to the six or eight months after traditional tendon grafting surgery.

At this time, the artificial ligament is approved only for patients in whom tendon grafting has failed. The indications could be broadened as more clinical experience accumulates. Since the FDA presently has data on the performance of the ligament for only the two-year period, the agency will require the manufacturer to continue to study a group of patients for up to 5 years after implantation to confirm long-term safety and effectiveness of the device.

Proposed Amendment to the Bylaws of the American Osteopathic Association

At its meeting on May 27, 1987, the AOA Committee on Membership recommended the following addition to the AOA Bylaws for consideration by the AOA House of Delegates at its July, 1987 meeting:

HONORARY MEMBERSHIP

Honorary Members. By specific action of the Board of Trustees, or its Executive Committee, honorary membership may be granted to individuals, not eligible for any other category of membership, who support the goals and objectives of this Association. Such honorary members shall not be required to pay dues or assessments. They shall receive complimentary copies of the Association's publications and such other services as authorized by the Board of Trustees.

Honorary members shall not be eligible to membership in the House of Delegates or the Board of Trustees, or hold any elective offices of this Association. Special listing in the YEARBOOK AND DIRECTORY shall be provided.

Such membership, when conferred, shall remain in full force and effect unless revoked by action of the Executive Committee or Board of Trustees of the American Osteopathic Association.

Allergy Relief Knows No Boundaries

Spring & Summer Allergies...

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BROMFED® - BROMFED-PD®

Timed-release Capsules
(antihistamine/decongestant action)

BROMFED® CAPSULES Timed-release capsules
(antihistamine/decongestant action)

DESCRIPTION: A light green and clear capsule containing white beads.
Each capsule contains:

Brompheniramine maleate 12 mg
Pseudoephedrine hydrochloride (d-isopropylamine HCl) 120 mg

BROMFED-PD® CAPSULES Timed-release capsules
(antihistamine/decongestant action)

DESCRIPTION: A dark green and clear capsule containing white beads.
Each capsule contains:

Brompheniramine maleate 6 mg
Pseudoephedrine hydrochloride (d-isopropylamine HCl) 60 mg

Both products are in a specially prepared base to provide prolonged action.

BROMFED® TABLETS

DESCRIPTION: A white scored tablet. Each tablet contains:

Brompheniramine maleate 4 mg
Pseudoephedrine hydrochloride 60 mg

These products contain ingredients of the following therapeutic classes:
antihistamine and decongestant.

CLINICAL PHARMACOLOGY: Brompheniramine maleate is an alkylamine type antihistamine. This group of antihistamines are among the most active histamine antagonists and are generally effective in relatively low doses. The drugs are not so prone to produce drowsiness and are among the most suitable agents for day time use; but again, a significant proportion of patients do experience this effect. Pseudoephedrine hydrochloride is a sympathomimetic which acts predominantly on alpha receptors and has little action on beta receptors. It therefore functions as an oral nasal decongestant with minimal CNS stimulation.

INDICATIONS: For the treatment of the symptoms of seasonal and perennial allergic rhinitis, and vasomotor rhinitis, including nasal obstruction (congestion).

CONTRAINDICATIONS: Hypersensitivity to any of the ingredients. Also contraindicated in patients with severe hypertension, severe coronary artery disease, patients on MAO inhibitor therapy, patients with narrow-angle glaucoma, urinary retention, peptic ulcer and during an asthmatic attack.

BROMFED®/BROMFED-PD®

WARNINGS: Considerable caution should be exercised in patients with hypertension, diabetes mellitus, ischemic heart disease, hyperthyroidism, increased intraocular pressure and prostatic hypertrophy. The elderly (60 years or older) are more likely to exhibit adverse reactions.

Antihistamines may cause excitability, especially in children. At doses higher than the recommended dose, nervousness, dizziness or sleeplessness may occur.

PRECAUTIONS: General: Caution should be exercised in patients with high blood pressure, heart disease, diabetes or thyroid disease. The antihistamine in this product may exhibit additive effects with other CNS depressants, including alcohol.

INFORMATION FOR PATIENTS: Antihistamine may cause drowsiness and ambulatory patients who operate machinery or motor vehicles should be cautioned accordingly.

DRUG INTERACTIONS: MAO inhibitors and beta adrenergic blockers increase the effects of sympathomimetics. Sympathomimetics may reduce the antihypertensive effects of methyldopa, mecamylamine, reserpine and veratrum alkaloids. Concomitant use of antihistamines with alcohol and other CNS depressants may have an additive effect.

PREGNANCY: The safety of use of this product in pregnancy has not been established.

ADVERSE REACTIONS: Adverse reactions include drowsiness, lassitude, nausea, giddiness, dryness of mouth, blurred vision, cardiac palpitations, flushing, increased irritability or excitement (especially in children).

BROMFED® CAPSULES

DOSAGE AND ADMINISTRATION: Adults and children over 12 years of age—1 capsule orally every 12 hours.

HOW SUPPLIED: Bottles of 100—500

BROMFED-PD® CAPSULES

DOSAGE AND ADMINISTRATION: Children 6 to 12 years of age—1 capsule every 12 hours. Adults—2 capsules every 12 hours.

HOW SUPPLIED: Bottles of 100—500

BROMFED® TABLETS

DOSAGE AND ADMINISTRATION: Adults and children 12 and over: One tablet every 4 hours not to exceed 6 doses in 24 hours. Children 6 to 12 years: One-half tablet every 4 hours not to exceed 6 doses in 24 hours. Do not give to children under 6 years except under the advice and supervision of a physician.

HOW SUPPLIED: Bottles of 100

BROMFED® SYRUP

DOSAGE AND ADMINISTRATION: Adults and children 12 years of age and over: 2 teaspoonfuls orally every 4-6 hours. Children 6 to under 12 years of age: 1 teaspoon orally every 4-6 hours. Do not exceed 4 doses in 24 hours. Children under 6 years of age, consult a physician.

HOW SUPPLIED: Bromfed Syrup is available in 16 fl. oz. bottles.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT A PRESCRIPTION.

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Official call

To the officers and members of the American Osteopathic Association:

You are hereby notified that the annual meeting of the American Osteopathic Association will be held in Chicago, Illinois, on July 23-27, 1987, at the Chicago Marriott Hotel.

The opening session of the annual meeting of the Board of Trustees will be held at 9:00 a.m. on Thursday, July 23.

The House of Delegates will convene for the annual business session of the association at 10:00 a.m. on Sunday, July 26. All meetings of the House of Delegates will be held at the Chicago Marriott Hotel. The Committee on Credentials will register delegates and alternate delegates beginning at 8:30 a.m. on Sunday, July 26. The House will conclude its session on Monday, July 27.

At least 30 days prior to the first day of the annual meeting, the secretary of each divisional society must certify to the executive director of the American Osteopathic Association a list of the names and addresses of delegates and alternate delegates.

Eugene L. Sikorski, D.O., President

T. Eugene Zachary, D.O., Speaker of the House