

The following is a brief summary only. Before prescribing, see complete prescribing information in CEFTIN® (cefuroxime axetil, Glaxo) Tablets product labeling.

CONTRAINDICATIONS: CEFTIN® is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS: BEFORE THERAPY WITH CEFTIN® IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFTIN OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuation alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

PRECAUTIONS: General: If an allergic reaction to CEFTIN® occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, eg, antihistamines, epinephrine, or corticosteroids. As with other antibiotics, prolonged use of CEFTIN may result in overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution for individuals with a history of colitis.

Information for Patients: (Pediatric) CEFTIN is only available in tablet form. During clinical trials, the tablet was well tolerated by children who could swallow the tablet whole. Children who cannot swallow the tablet whole may have the tablet crushed and mixed with food (eg, applesauce, ice cream). However, it should be noted that the crushed tablet has a strong, persistent, bitter taste. Discontinuation of therapy due to the taste and/or problems of administering this drug occurred in 13% of children (range, 2% to 28% across centers). Thus, the physician and parent should ascertain, preferably while still in the physician's office, that the child can ingest CEFTIN reliably. If not, alternative therapy should be considered.

Interference with Laboratory Tests: A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets), but not with enzyme-based tests for glycosuria (eg, Clinistix®, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving CEFTIN.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to 50 to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime axetil. 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.

Nursing Mothers: Since cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with CEFTIN® (cefuroxime axetil, Glaxo).

ADVERSE REACTIONS: The adverse reactions to CEFTIN® are similar to reactions to other orally administered cephalosporins. CEFTIN was usually well tolerated in controlled clinical trials. Pediatric patients taking crushed tablets during clinical trials complained of the bitter taste of CEFTIN Tablets [see ADVERSE REACTIONS: Gastrointestinal and PRECAUTIONS: Information for Patients: (Pediatric)]. The majority of adverse events were mild, reversible in nature, and did not require discontinuation of the drug. The incidence of gastrointestinal adverse events increased with the higher recommended doses. Twenty-five (25) patients have received CEFTIN 500 mg twice a day for one to 2.5 months with no increase in frequency or severity of adverse events. The following adverse reactions have been reported.

Gastrointestinal: Nausea occurred in 2.4% of patients. Vomiting occurred in 2.0% of patients. Diarrhea occurred in 3.5% of patients. Loose stools occurred in 1.3% of patients. There have been rare reports of pseudomembranous colitis.

Crushed tablets have a bitter taste. In pediatric clinical studies conducted with crushed tablets, complaints due to taste ranged from 0/8 (0%) in one center to 4/71 (66%) in another center.

Hypersensitivity: Rash (0.6% of patients), pruritus (0.3% of patients), and urticaria (0.2% of patients) have been observed. One case of severe bronchospasm has been reported among the approximately 1,600 patients treated with CEFTIN. Of the patients treated with CEFTIN who reported a history of delayed hypersensitivity to a penicillin and not a cephalosporin, 2.9% of patients experienced a delayed hypersensitivity reaction to CEFTIN.

Central Nervous System: Headache occurred in less than 0.7% of patients, and dizziness occurred in less than 0.2% of patients.

Other: Vaginitis occurred in 1.9% of female patients.

Clinical Laboratory Tests: Transient elevations in AST (SGOT, 2.0% of patients), ALT (SGPT, 1.6% of patients), and LDH (1.0% of patients) have been observed. Eosinophilia (1.1% of patients) and positive Coombs' test (0.4% of patients) have been reported.

In addition to the adverse reactions listed above that have been observed in patients treated with CEFTIN, the following adverse reactions and altered laboratory tests have been reported for cephalosporin class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, fever, colitis, renal dysfunction, toxic nephropathy, and hepatic dysfunction including cholestasis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests: Increased prothrombin time, increased BUN, increased creatinine, false-positive test for urinary glucose, increased alkaline phosphatase, neutropenia, thrombocytopenia, and leukopenia.

SIGNS OF ECTOPIC PREGNANCY

To the Editor:

The excellent article describing the presentation of ectopic pregnancy by Andolsek (*Andolsek KM: Ectopic pregnancy: 'Classic' vs common presentation. J Fam Pract 1987; 24:481-85*) alluded to tachycardia in case 2 as a "clue" to this difficult diagnosis. This finding, especially when produced by postural challenge, is an extremely valuable determination in the early detection of ectopic pregnancy.

Ectopic pregnancy is usually found in young women with excellent cardiovascular reserve. By the time the blood pressure is affected by postural changes, significant intraabdominal blood loss has occurred. A more sensitive method is to measure also postural heart rates.

The method I use is, first, to determine heart rate and blood pressure in a patient who is supine for more than three minutes. Then, I sit the patient up and have her dangle her legs (standing is not necessary) and re-evaluate the pulse and blood pressure in three minutes. If the pulse increases by 20 or more beats per minute, a significant intravascular volume loss has occurred regardless of changes in blood pressure.

A postural heart rate increase of 20 beats per minute in the setting of a positive pregnancy test is an ectopic gestation until proven otherwise.

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PATIENT SATISFACTION AND CONTINUITY OF CARE

To the Editor:

Cherkin, Hart, and Rosenblatt¹ compared patients of family physicians with patients of general internists and found no differences in general satisfaction and satisfaction with access, humaneness, and technical quality of care. Analyses I performed on this same data set were consistent with those reported by Cherkin et

al.²⁻⁶ The consistent finding of no difference between family practice and general internal medicine patients for the dimensions of satisfaction reported by Cherkin et al is in part due to large correlations between the satisfaction measures they analyzed. In a confirmatory factor analysis of these data, I found correlations ranging from 0.74 to 1.00 among latent variables representing the four dimensions of satisfaction they examined.

Cherkin et al did not examine specialty differences for the satisfaction with continuity of care scale (1. This is not the doctor I usually see when I go for medical care. 2. I hardly ever see this doctor when I go for medical care. 3. I see this doctor just about every time I go for medical care. Alpha reliability = 0.89), but they included one of the scale's items as a predictor of satisfaction with the four dimensions of care they examined. When I analyzed these data, I observed specialty differences in satisfaction with continuity of care.

Ordinary least-squares regression was used to examine differences in satisfaction with continuity of care between patients of family physicians, primary care track general internists, general internists, and subspecialty internists, controlling for patient health and sociodemographics, provider expense- or income-sharing arrangements and practice type (solo office-based, single-specialty, multi-specialty, salaried academic, other). The most notable effect was a highly significant difference favoring internal medicine subspecialists over general internists ($P < .0001$). Patients of internal medicine subspecialists also tended to be more satisfied with continuity than patients of family physicians ($P < .10$). In addition, there was some indication of greater satisfaction with continuity among patients of primary care track general internists than among patients of general internists ($P < .10$).

The specialty differences observed for continuity of care may reflect different types of patients seen by providers in these specialties. Internal medicine subspecialists, for example,

may be more likely than general internists to see chronically ill patients, for whom regular visits and continuity of care are typical. An important issue for future research is explaining these specialty differences by examining potential explanatory factors such as patient characteristics (eg, chronic conditions).

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References

1. Cherkin DC, Hart G, Rosenblatt RA: Patient satisfaction with family physicians and general internists: Is there a difference? *J Fam Pract* 1988; 26:543-551
2. Hays R: The measurement of patient satisfaction in the Physician Practice Study. Medical Outcomes Study Memo No. R-22, April 11, 1984. Santa Monica, Calif. The Rand Corporation, 1988
3. Hays R: Exploratory factor analyses of Q5 patient satisfaction items. Medical Outcomes Study Memo No. R-23, April 1984. Santa Monica, Calif. The Rand Corporation, 1988
4. Hays R: Explaining patient satisfaction in terms of physician and practice characteristics: Analyses of data from the Physician Practice Study. Medical Outcomes Study Memo No. R-25, April 25, 1984. Santa Monica, Calif. The Rand Corporation, 1988
5. Hays R: Confirmatory factor analyses of patient satisfaction items fielded in the Physician Practice Study. Medical Outcomes Study Memo No. R-37, June 6, 1984. Santa Monica, Calif. The Rand Corporation, 1988
6. Hays R: Physicians-level reliability estimation for patient satisfaction ratings: Analysis of data from the Physician Practice Study. Medical Outcomes Study Memo No. R-660, February 13, 1986. Santa Monica, Calif. The Rand Corporation, 1988

The preceding letter was referred to Dr. Cherkin, who responds as follows:

It should be reassuring to readers that Dr. Hays' separate analyses of the same data set reached the same conclusion: no differences in patient satisfaction with family physicians and general internists for the dimensions of quality, humaneness, access, and general satisfaction. We did not analyze specialty differences for the "satisfaction with continuity of care"

variables, since they are measures of continuity and not measures of satisfaction. However, because having a usual physician is known to be correlated with patient satisfaction, it seemed important to include a measure of this as a control variable in the analyses. Finally, we deliberately excluded medical subspecialists from our analyses because we were concerned about comparing the proverbial apples with oranges. Family physicians and general internists provide first-contact care for a broad range of similar problems, while subspecialists often see referred patients, have a much narrower scope of practice, and see a more medically dependent patient population.

In view of these fundamental differences in the types of patients seen by generalists and specialists and in the roles these physicians play for their patients, we did not believe comparisons of patient satisfaction with physician generalists and specialists would be interpretable.

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PAPANICOLAOU SMEAR TECHNIQUES

To the Editor:

We enjoyed reviewing the findings of Reissman,¹ who demonstrated an improved yield of endocervical cells using a Milex spatula followed by a Cytobrush in Papanicolaou smears from women over 45 years of age. This study reported an endocervical recovery rate of 76 percent in women older than 45 years using this technique, compared with less than 30 percent using the Milex spatula followed by a moist saline swab, a technique we previously found to yield a 63 percent endocervical cell recovery rate in postmenopausal women.²

We believe that there are three possible explanations for the failure of Reissman to replicate our findings. First, his sample only included 65

women older than 45 years whose Papanicolaou smear samples were collected with the Milex spatula and moist swab. We calculate that the confidence interval is ± 11 percent for the 29 percent recovery rate reported. Second, we believe that the Papanicolaou smear techniques were not identical in the two studies. Our protocol included swabbing the cervix of excess mucus with a large cotton swab prior to utilizing the Milex spatula and moistened swab, whereas Reissman does not describe employing this step. We have found that swabbing the cervix of excess mucus prior to performing a Papanicolaou smear improved our endocervical cell recovery rate 4 to 5 percent in postmenopausal women.³ Finally, the outcome criteria for adequate Papanicolaou smears differed in the two studies. We considered an adequate smear as one containing the presence of endocervical or squamous metaplastic cells, whereas Reissman considered a smear adequate only if it contained endocervical cells.

Since publication of our original findings, we continue to have satisfactory Papanicolaou smear results in older women using the Milex spatula and moistened swab. Between July 1, 1984, and December 31, 1987, 910 Papanicolaou smears were performed in our family medical center on women older than 45 years with an intact uterus. Of the smears, 498 (55 percent) contained endocervical cells, and 537 (59 percent) had endocervical cells or squamous metaplastic cells. Our age-specific results are presented in Table 1.

Although Reissman's data do seem to indicate an improved yield of endocervical cells using a Milex spatula followed by a Cytobrush, caution is needed prior to widespread utilization of this technique. As he correctly suggests, the Hawthorne effect may account for some of the differences in Papanicolaou smear adequacy between those performed with the Milex spatula and Cytobrush cell collector compared with the concurrent and historical controls. In addition, the

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References: 1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension. In *Prazosin Clinical Symposium Proceedings*. Published as a special report by Postgraduate Medicine, New York, McGraw-Hill Co, 1975, pp 45-52. 2. Komajda M: Prazosin and lipids: A study of the effects of prazosin on blood lipids in hypertensive patients. *Arterioscler Thromb* 1986; (special issue): 1-4. 3. Rouffy J, Jallard J: Effects of two antihypertensive agents on triglycerolipids, apolipoproteins A and B: Comparison of prazosin and atenolol. *Am J Med* 1986; 80(suppl 2A):100-103. 4. Lovelace J, Neus J: Effects of prazosin and propranolol on serum lipids in patients with essential hypertension. *Am J Med* 1984; 76(2A):79-84. 5. Stamler R, Stamler J, Gosch FC, et al: Initial antihypertensive drug therapy: A comparison of alpha blocker (prazosin) and diuretic (hydrochlorothiazide): Final report of a randomized, controlled trial. In press. 6. Leren P, Helgeland A, Holme I, et al: Effect of propranolol and prazosin on blood lipids: The Oslo Study. *Lancet* 1980; II:4-6. 7. Grimm RH Jr, Huminghake DB: Lipids and hypertension: Implications of new guidelines for cholesterol management in the treatment of hypertension. *Ann J Med* 1986; 80(suppl 2A):56-63. 8. Kwan CM, Shepherd AMM, Johnson L, et al: Forearm arterial ring hemodynamics, blood pressure control, and lipid changes in patients with diabetic hypertension treated with atenolol and prazosin. *Clin Pharmacol Ther* 1986; 44: 202-210. 9. Leichter SB, Baumgardner B: Effects of chronic prazosin therapy on intermediary metabolism in diabetic patients. *J Cardiovasc Med* 1981; (special suppl):38-42. 10. The Working Group on Hypertension in Diabetes: Statement on hypertension in diabetes mellitus. *Final Arch Intern Med* 1987; 147:830-842. 11. Leenen FHH, Smith DL, Farkas RM, et al: Vasodilators and regression of left ventricular hypertrophy: Hydralazine versus prazosin in hypertensive humans. *Am J Med* 1987; 82:969-978.

Brief Summary

MINIPRESS (prazosin hydrochloride) CAPSULES For Oral Use

INDICATIONS AND USAGE: MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. It is mild to moderate in activity and can be used as the initial agent or in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed. **CONTRAINDICATIONS:** None known. **WARNINGS:** MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncope episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncope episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dose increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncope episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncope episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see **DOSE AND ADMINISTRATION**). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol. If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. The adverse effect is self-limiting and, in most cases does not recur after the initial period of therapy or during subsequent dose titration. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy. **PRECAUTIONS: Information for Patients:** Dizziness or drowsiness may occur after the first dose of this medicine. Avoid driving or performing hazardous tasks for the first 24 hours after taking this medicine or when the dose is increased. Dizziness, lightheadedness or fainting may occur, especially when rising from a lying or sitting position. Getting up slowly may help lessen the problem. These effects may also occur if you drink alcohol, stand for long periods, or drink coffee, if the weather is hot. While taking MINIPRESS, be careful in the amount of alcohol you drink. Also, use extra care during exercise or hot weather, or if standing for long periods. Check with your physician if you have any questions. **Drug Interactions:** MINIPRESS has been administered without any adverse drug interaction in limited clinical experience to date with the following: (1) cardiac glycosides—digitalis and digoxin; (2) hypoglycemics—insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide; (3) tranquilizers and sedatives—diazepam, diazepam, and phenobarbital; (4) antitussive—alprazolam, codeine, and probenecid; (5) anticholinergics—procainamide, propranolol (see **WARNINGS** however), and quinidine; and (6) analgesics, antipyretics and anti-inflammatories—propoxyphene, aspirin, indomethacin, and phenylbutazone. Addition of a diuretic or other antihypertensive agent to MINIPRESS has been shown to cause an additive hypotensive effect. **Drug/Laboratory Test Interactions:** False positive results may occur in screening tests for pheochromocytoma in patients who are being treated with prazosin. If an elevated VMA is found, prazosin should be discontinued and the patient retested after 1 week. **Laboratory Tests:** In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No carcinogenic potential was demonstrated in an 18 month study in rats with MINIPRESS (prazosin hydrochloride) at dose levels more than 225 times the usual maximum recommended human dose of 20 mg per day. MINIPRESS was not mutagenic in *in vivo* genetic toxicology studies. In a fertility and general reproductive performance study in rats, both males and females, treated with 75 mg/kg (225 times the usual maximum recommended human dose), demonstrated decreased fertility while those treated with 25 mg/kg (75 times the usual maximum recommended human dose) did not. In chronic studies (one year or more) of MINIPRESS in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (75 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (30 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS for up to 51 months did not have changes in sperm morphology suggestive of drug effect. **Use in Pregnancy:** Pregnancy Category C: There are no adequate and well controlled studies which establish the safety of MINIPRESS (prazosin HCl) in pregnant women. MINIPRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus. **Nursing Mothers:** MINIPRESS has been shown to be excreted in small amounts in human milk. Caution should be exercised when MINIPRESS is administered to a nursing woman. **Use in Children:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS:** Clinical trials were conducted on more than 900 patients. During these trials and subsequent marketing experience, the most frequent reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.8%, lack of energy 6.9%, weakness 6.5%, palpitations 5.2%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug. Less frequent adverse reactions which are reported to occur in 1-4% of patients are: **Gastrointestinal:** vomiting, diarrhea, constipation; **Cardiovascular:** edema, orthostatic hypotension, dyspnea, syncope; **Central Nervous System:** vertigo, depression, nervousness; **Dermatologic:** rash; **Genitourinary:** urinary frequency; **EENT:** blurred vision, reddened sclera, epistaxis, dry mouth, nasal congestion. In addition, fewer than 1% of patients have reported the following (in some instances, exact causal relationships have not been established): **Gastrointestinal:** abdominal discomfort and/or pain, liver function abnormalities, pancreatitis; **Cardiovascular:** tachycardia; **Central Nervous System:** paresthesia, hallucinations; **Dermatologic:** pruritus, alopecia, lichen planus; **Genitourinary:** incontinence, impotence, priapism; **EENT:** tinnitus; **Other:** diaphoresis, fever. Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. **OVERDOSAGE:** Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, stock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialyzable because it is protein bound. **DOSE AND ADMINISTRATION:** The dose of MINIPRESS should be adjusted according to individual blood pressure response. **Initial Dose:** 1 mg two or three times a day. **Maintenance Dose:** Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 0 mg to 20 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy. However, a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen. **Use With Other Drugs:** When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out. Revised November 1986

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poor yield of endocervical cells in all other phases of the study (less than 60 percent regardless of the setting, Papanicolaou smear method, or age of patient) indicates that his setting may not be generalizable and that other

high-risk patients to obtain influenza vaccinations (*Brimberry R: Vaccination of high-risk patients for influenza: A comparison of telephone and mail reminder methods. J Fam Pract* 1988; 26:397-400). Brimberry concludes that "if successful telephone contact can be made, this [telephone] reminder method is more effective than a letter reminder to increase influenza vaccination rates among high-risk patients."

This conclusion would be warranted only if successful telephone contact as such were unrelated to the likelihood a person would become vaccinated. This does not seem to be the case, since none of the 123 patients not successfully contacted by telephone were vaccinated (derived from the data in Table 1). Based on the 3.8 percent vaccination rate in the control group, one would have expected to find about five patients with vaccinations in this group. Hence, the relatively high vaccination rate among the telephone reminder group that was successfully contacted is in part due to the fact that persons who are more easily reached by telephone are also more likely to get vaccinations independent of the content of the telephone message. Therefore, although the telephone method may in fact be superior to the mailed reminder method, the degree of superiority is overstated in this study, which, of course, has significant implications for comparisons of the relative cost-effectiveness of the two approaches.

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TABLE 1. AGE-SPECIFIC ENDOCERVICAL CELL RECOVERY FOR PAP SMEARS FROM OLDER WOMEN

Patient Age (years)	Number	Endocervical Cells No. (%)
46-50	183	127 (69)
51-55	117	75 (64)
56-60	123	64 (52)
61-65	161	88 (55)
66-70	131	65 (50)
71-75	107	41 (38)
76-80	61	27 (44)
>81	27	11 (41)
Total	910	498 (55)

factors may have been responsible for the improvement noted in phase 3 of the study.

We believe that properly controlled trials are needed to compare the Milex spatula and moist swab with the Milex and Cytobrush instrument in unselected groups of postmenopausal women.

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References

1. Reissman SE: Comparison of two Papanicolaou smear techniques in a family practice setting. *J Fam Pract* 1988; 26: 525-529
2. Brock CD, Ornstein SM, Litchfield L: An improved technique for Papanicolaou smear sampling in postmenopausal women. *letter. J Fam Pract* 1986; 22:498, 500
3. Hamblin JE, Brock CD, Litchfield L, Dias J: Papanicolaou smear adequacy: Effect of different techniques in specific fertility states. *J Fam Pract* 1985; 20:257-260

EFFECTIVENESS OF FOLLOW-UP REMINDER METHODS

To the Editor:

In his study of the relative effectiveness of mailed and telephone reminder methods for encouraging

RESEARCH METHODOLOGIES

To the Editor:

Drs. Bell and Dippe's paper¹ on "Recognition and Treatment of Hypercholesterolemia in a Family Practice Center" states in the abstract and methods that charts were reviewed "retrospectively." The term *retro-*

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TERAZOL[®] 7 (terconazole) **Vaginal Cream, 0.4%**
TERAZOL[®] 3 (terconazole) **Vaginal Suppositories, 80 mg**

INDICATIONS AND USAGE: TERAZOL 7 Vaginal Cream and TERAZOL 3 Vaginal Suppositories are indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As TERAZOL 7 Vaginal Cream and TERAZOL 3 Vaginal Suppositories are effective only for vulvovaginitis caused by the genus *Candida*, the diagnosis should be confirmed by KOH smears and/or cultures.

HUMAN PHARMACOLOGY: Photosensitivity reactions were observed in some normal volunteers following repeated dermal application of terconazole 2.0% and 0.8% creams under conditions of filtered artificial ultraviolet light. Photosensitivity reactions have not been observed in U.S. and foreign clinical trials in patients who were treated with terconazole vaginal cream or suppositories.

CONTRAINDICATIONS: Patients known to be hypersensitive to any components of terconazole cream or suppositories.

PRECAUTIONS: *General:* Discontinue drug if sensitization or irritation is reported during use.

The base contained in the TERAZOL 3 Vaginal Suppositories formulation may interact with certain rubber or latex products, such as those used in vaginal contraceptive diaphragms, therefore concurrent use is not recommended.

If there is lack of response to TERAZOL 7 Vaginal Cream or TERAZOL 3 Vaginal Suppositories, appropriate microbiological studies (standard KOH smear and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens.

Drug Interactions: The therapeutic effect of TERAZOL 7 Vaginal Cream and TERAZOL 3 Vaginal Suppositories is not affected by oral contraceptive usage.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Studies to determine the carcinogenic potential of terconazole have not been performed.

Mutagenicity: Terconazole was not mutagenic when tested *in vitro* for induction of microbial point mutations (Ames test) or for inducing cellular transformation, or *in vivo* for chromosome breaks (micronucleus test) or dominant lethal mutations in mouse germ cells.

Impairment of Fertility: No impairment of fertility occurred when female rats were administered terconazole orally up to 40 mg/kg/day.

Pregnancy: *Pregnancy Category C:* There was no evidence of teratogenicity when terconazole was administered orally up to 40 mg/kg/day (TERAZOL 7 Vaginal Cream—100× the recommended intravaginal human dose; TERAZOL 3 Vaginal Suppositories—25× the recommended intravaginal human dose) in rats, or 20 mg/kg/day in rabbits, or subcutaneously in rats up to 20 mg/kg/day.

Dosages at or below 10 mg/kg/day produced no embryotoxicity; however, there was a delay in fetal ossification at 10 mg/kg/day in rats. There was some evidence of embryotoxicity in rabbits and rats at 20–40 mg/kg. In rats this was reflected as a decrease in litter size and number of viable young and reduced fetal weight. There was also delay in ossification and an increased incidence of skeletal variants.

The no-effect oral dose of 10 mg/kg/day resulted in a mean peak plasma level of terconazole in pregnant rats of 0.176 mcg/ml which exceeds by 44 times the mean peak plasma levels (0.004 mcg/ml) seen in normal subjects after intravaginal administration of terconazole. This assessment does not account for possible exposure of the fetus through direct transfer of terconazole from the irritated vagina to the fetus by diffusion across amniotic membranes.

Since terconazole is absorbed from the human vagina, it should not be used in the first trimester of pregnancy unless the physician considers it essential to the welfare of the patient.

Nursing Mothers: TERAZOL 7 Vaginal Cream—It is not known whether this drug is excreted in human milk. Animal studies have shown that rat offspring exposed via the milk of treated (40 mg/kg/orally) dams showed decreased survival during the first few post-partum days, but overall pup weight and weight gain were comparable to or greater than controls throughout lactation.

TERAZOL 3 Vaginal Suppositories—It is not known whether terconazole is excreted in human milk. Animal studies have shown that rat offspring exposed via the milk of treated (40 mg/kg/orally) dams showed decreased survival during the first few post-partum days.

TERAZOL 7 Vaginal Cream and TERAZOL 3 Vaginal Suppositories—Because many drugs are excreted in human milk, and because of the potential for adverse reaction in nursing infants from terconazole, 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 efficacy in children have not been established.

ADVERSE REACTIONS: TERAZOL 7 Vaginal Cream—During controlled clinical studies conducted in the United States, 521 patients with vulvovaginal candidiasis were treated with terconazole 0.4% vaginal cream. Based on comparative analyses with placebo, the adverse experiences considered most likely related to terconazole 0.4% vaginal cream were headache (26% vs 17% with placebo) and body pain (21% vs 0% with placebo). Vulvovaginal burning (5.2%), itching (2.3%) or irritation (3.1%) occurred less frequently with terconazole 0.4% vaginal cream than with the vehicle placebo. Fever (1.7%) and chills (0.4%) have been reported, but are not statistically different from placebo (0.5% and 0.0%, respectively). The therapy-related dropout rate was 1.9%. The adverse drug experience on terconazole most frequently causing discontinuation was vulvovaginal itching (0.6%), which was lower than the incidence for placebo (0.9%).

TERAZOL 3 Vaginal Suppositories—During controlled clinical studies conducted in the United States, 284 patients with vulvovaginal candidiasis were treated with terconazole 80 mg vaginal suppositories. Based on comparative analyses with placebo (295 patients) the adverse experiences considered adverse reactions most likely related to terconazole 80 mg vaginal suppositories were headache (30.3% vs 20.7% with placebo), and pain of the female genitalia (4.2% vs 0.7% with placebo). Adverse reactions that were reported but were not statistically significantly different from placebo were burning (15.2% vs 11.2% with placebo) and body pain (3.9% vs 1.7% with placebo). Fever (2.8%) and chills (1.8%) have been reported, but are not statistically different from placebo (1.4% and 0.7%, respectively). The therapy-related dropout rate was 3.5% and the placebo therapy-related dropout rate was 2.7%. The adverse drug experience on terconazole most frequently causing discontinuation was burning (2.5% vs 1.4% with placebo) and pruritus (1.8% vs 1.4% with placebo).

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spective has both a general common usage and a more precise methodological (epidemiological) definition. The general definition of retrospective is "directed to the past, looking or directed backward."² The methodological use of retrospective is to describe a research design that is longitudinal, linking current outcomes with measurements of events that occurred in the past, as in case-control studies.^{3–7} Researchers should distinguish cross-sectional study designs, which collect data on a patient at one point in time, from longitudinal designs (both retrospective and prospective), which collect data on a patient at several points in time. The study by Drs. Bell and Dippe is clearly a cross-sectional chart review, examining multiple variables from 93 patients with cholesterol levels greater than 6.2 mmol/L, but they do not link current outcomes with any events in the past.

It is vital to describe methodology precisely so that other researchers can interpret and replicate findings and inferences presented in a published article. Most researchers recognize that while the term *significant* has a general definition of "meaningful,"² in research papers it means that a finding has a statistical probability of occurring by chance at a rate less than a particular alpha level. The term *retrospective* in research papers should be limited to the description of studies that collect data at several points in time, one in the present, others in the past, and relate the present and past data for each individual studied.

We appreciate the opportunity to comment on this issue.

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References

1. Bell MM, Dippe SE: Recognition and treatment of hypercholesterolemia in a Family Practice Center. *J Fam Pract* 1988; 26: 507–513
2. McKeachnie J (ed): *Webster's New Universal Dictionary*. New York, Simon & Schuster, 1983, p 1549
3. Sartwell PE: Retrospective studies: A re-

view for the clinician. *Ann Intern Med* 1974; 81:381–386

4. Lilienfeld AM, Lilienfeld DE: *Foundations of Epidemiology*, ed 2. New York, Oxford University Press, 1980
5. Bailar JC, Louis TA, Lavori PW, Polansky M: A classification for biomedical research reports. *N Engl J Med* 1984; 311:1482–1487
6. Fletcher RH, Fletcher SW: Clinical research in general medical journals: A 30-year perspective. *N Engl J Med* 1979; 301:180–183
7. Schulsinger F, Mednick SA, Knop J: *Longitudinal Research: Methods and Uses in Behavioral Science*. Boston, Martinus Nijhoff, 1981

The preceding letter was referred to Dr. Bell, who responds as follows:

We appreciate the comments by Muncie, Sobal, and DeForge regarding our recent article in *The Journal*. We agree that our study is a cross-sectional chart review. Recognition of hypercholesterolemia was examined at one point in time rather than longitudinally.

We disagree, however, with the statement that retrospective studies are by definition longitudinal. Retrospective studies are defined by Friedman as those using observations that have been recorded in the past.¹ Marks states that there are two types of retrospective studies: case-control studies, which are longitudinal, and cross-sectional studies, which examine a single point in time.² Prospective studies, on the other hand, are by definition longitudinal and include randomized controlled clinical trials and cohort studies.

We conclude that our study is retrospective, but characterizing it as a cross-sectional chart review is more descriptive and useful. We agree that it is important to precisely describe methodology and believe that we have done so in our study.

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References

1. Friedman G: *Primer of Epidemiology*, ed 3. New York, McGraw-Hill, 1987
2. Marks R: *Designing a Research Project, the Basics of Biomedical Research Methodology*. Belmont, Mass, Lifetime Learning Publications, 1982