

CUTANEOUS MEDICINE  
FOR THE PRACTITIONER  
A YORKE  
MEDICAL JOURNAL  
CAHNERS  
PUBLISHING COMPANY  
VOL. 48 NO. 5  
NOVEMBER 1991

# cutis®



\*\*\*\*\* 5-DIGIT 55455  
007 01943227  
MINNESOTA UNIVERSITY  
505 ESSEX STREET S E  
MINNEAPOLIS MN 55455



Pseudohorn Associated with Basal Cell Carcinoma

Philodendron-Induced Dermatitis

Aquagenic Pruritus

Complications of Ear Piercing

Dr. Reddy's Laboratories, Ltd., et al.  
v.  
Galderma Laboratories, Inc.  
IPR2015-\_\_\_\_\_  
**Exhibit 1067**



# Second-Generation Tetracyclines, A Dermatologic Overview: Clinical Uses and Pharmacology

Howard Maibach, MD, San Francisco, California

Tetracycline and its derivatives are frequently used in the treatment of acne, soft tissue bacterial infections, Lyme disease (borreliosis), chlamydial infections, and respiratory tract infections. Several pharmacologic and microbiological properties of these antibiotics make them particularly suitable for such uses. First-generation tetracyclines have long been in use; however, the second-generation tetracyclines minocycline, doxycycline hyclate, and doxycycline monohydrate have also become widely prescribed, and can offer advantages to the dermatologist over tetracycline.

This paper reviews the important pharmacologic and microbiological characteristics of these three commonly used second-generation tetracyclines, and their clinical applications in dermatology.

**M**inocycline and doxycycline, which are tetracycline structural analogs, have been used in human medicine for twenty-five years. Doxycycline and minocycline are differentiated from the original tetracyclines by structural differences in positions 5 and 6 (doxycycline) and by the substitution of a dimethylamino group in position 7 (minocycline). These substitutions cause few variations in the bacteriologic properties, but significantly enhance the physicochemical and pharmacokinetic properties, in particular, increasing their lipophilicity.

These compounds are obtained semisynthetically from oxytetracycline or methacycline and are significantly more lipophilic than tetracycline, which permits excellent tissue penetration. Higher lipophilicity results in a large volume of distribution, substantial binding to plasma proteins, and reabsorption in the renal tubules and gastrointestinal tract. This gives the drugs longer elimination half-lives. Excellent absorption after oral administration allows the use of low oral dosages and minimizes the side effects of tetracycline derivatives on the gastrointestinal tract.

Doxycycline is available in two forms: doxycycline hyclate, a salt form combining doxycycline (a weak base), hydrochloric acid (a strong acid), plus ethanol and water; and the more recently available doxycycline monohydrate, which is doxycycline free base with an associated water molecule.

## Pharmacologic Characteristics

**Antimicrobial Activity**—The tetracyclines are bacteriostatic through their ability to inhibit protein synthesis. This group of antibiotics is active against a broad range of gram-positive and gram-negative bacteria as well as *Mycoplasma*, *Ureaplasma*, and *Chlamydia*.

**Mechanism of Microbial Resistance**—Inherent in the use of all antibiotics is the appearance of resistant strains of micro-organisms. The degree of resistance is dependent upon several factors, including resistance of the host, concentration of the antibiotic, and even the location of the bacteria in the body. As with other antibiotics, resistant strains of micro-organisms have been observed with all tetracyclines.

Resistance to tetracycline is thought to occur as a result of either an altered ribosome (although tetracycline-resistant ribosomes have yet to be isolated) or the presence of a plasmid that decreases uptake of the antibiotic by the bacterium.<sup>1</sup> Resistance is usually conferred upon the bacteria in the form of R-plasmids.<sup>2,3</sup>

Resistance is defined within the parameters of the minimum inhibitory concentration of a drug required to inhibit bacterial growth. Minimum inhibitory concentration levels under 4 µg/ml are defined as "susceptible," from 4 to 16 µg/ml as "partially resistant," and levels over 16 µg/ml as "resistant."<sup>4</sup> Two types of resistance may be identified: a broad high-level resistance to all tetracyclines, and a moderate-level resistance in which the minimum inhibitory concentration of various micro-organisms increases in resistance from minocycline, through doxycycline, demethylchlortetracycline, and tetracycline to oxytetracycline.<sup>5,6</sup> Organisms resistant to tetracycline have been shown to be susceptible to doxycycline and minocycline.<sup>1,2</sup> In some instances of progressive resistance, the minimum inhibitory concentration for doxycycline is lower than for minocycline.<sup>7</sup>



**Absorption/Distribution**—Doxycycline and minocycline are the best absorbed of the tetracyclines because of their high lipophilicity. This lipid solubility facilitates the transport of the drug across lipid-rich cell membranes and allows far better tissue penetration than all other tetracyclines. Distribution in body tissues is widespread and well documented.<sup>1,2,8</sup>

Absorption of orally administered doxycycline in a dose of 100 to 200 mg is greater than 80 percent, the mean values being closer to 95 percent. Doxycycline absorption is rapid, and is detectable in the blood fifteen to thirty minutes after administration.<sup>1,9-11</sup>

Minocycline is also 95 percent available following a 200 mg loading dose and maintenance dosages of 100 mg every twelve hours. Serum levels are detectable within one hour of administration.<sup>2,8,12,13</sup>

The major absorption site for both antibiotics is thought to be in the duodenum.<sup>1,2</sup> Several studies have shown that, at the same dosage, minocycline serum levels appear to peak somewhat earlier (approximately two hours) than those of doxycycline (approximately three hours), while the peak concentration of doxycycline is higher (approximately 7 µg/ml) than that of minocycline (approximately 5.5 µg/ml).<sup>14,15</sup>

No difference has been found in the absorption or bioavailability of the two derivatives of doxycycline, the monohydrate free base and the hydrochloride salt.<sup>9,16</sup>

**Fasting Not Required**—Doxycycline and minocycline may be administered with food or dairy products without causing a major reduction in absorption. Tetracycline absorption, however, is significantly influenced by food and dairy products. Welling et al studied the influence of various test meals and fluid volumes on the relative bioavailability of commercial formulations of tetracycline and doxycycline. Serum levels of tetracycline were uniformly reduced by 50 percent by all test meals, whereas serum levels of doxycycline were reduced by only 20 percent. The 50 percent reduction in tetracycline serum levels was found to have clinical significance.<sup>17</sup> Leyden investigated serum concentrations of tetracycline and minocycline when administered with water, milk, a meal, and 300 mg ferrous sulfate, and found absorption of tetracycline to be significantly decreased by administration with milk (–65 percent) and food (–46 percent). Minocycline absorption was affected less (27 percent and 13 percent reduction, respectively).<sup>18</sup>

Other studies have shown that the extent to which doxycycline and minocycline absorption is reduced when administered with food or dairy products is not clinically significant.<sup>1,2,9,10,14,17-24</sup> Pelletized minocycline and doxycycline are absorbed at a slower rate when taken with food than by a patient who has fasted.<sup>25,26</sup>

Because these antibiotics may be taken with meals, the incidence of gastric upset is reduced.<sup>1,2</sup> Patient compliance may be enhanced in two ways: a reduction in gastrointestinal distress, and the "memory jog" of taking their medication with, for example, their evening meal.

**Elimination**—Drug elimination may occur via two routes: metabolism or excretion. Efficient drug elimination is essential to avoid toxic accumulation in body tissues.

**Metabolism**—No doxycycline metabolites have been found in blood, urine, or feces.<sup>1,9</sup> Minocycline is partially degraded to three inactive metabolites in the liver.<sup>2,9</sup>

**Excretion**—Excretion of tetracycline takes place pri-

marily through glomerular filtration. Renal excretion of doxycycline and minocycline takes place in the kidney to a lesser extent than tetracycline, and both have a higher gastrointestinal excretion component than tetracycline.<sup>1,2,9,24</sup> Both doxycycline and minocycline concentrate in the bile, although this accounts for only a small portion of the administered dose, with primary gastrointestinal excretion resulting from secretion into the lumen.

Consistent with this elimination pattern, doxycycline serum levels are only minimally affected in patients with renal insufficiency and require no adjustment in dosage.<sup>1,24</sup> Minocycline elimination in patients with renal insufficiency also appears to be little changed due to the small amount normally excreted via that route, although several studies have presented conflicting data, some suggesting that a lowered dose may be warranted in patients with renal insufficiency.<sup>2,13,14,27-34</sup>

Doxycycline and minocycline have a longer half-life than the other tetracyclines, with reported half-lives for doxycycline varying between fifteen and twenty-five hours, while the half-life of minocycline is reported to be twelve to sixteen hours.<sup>2,9</sup>

## Physiological Variables

**Age and Gender**—Serum and tissue concentrations of doxycycline in elderly subjects are higher than those observed in young adults, and are thought to be due to decreased fecal elimination. The clinical significance of this accumulation is not clear, but adjustment of the dosage is probably unnecessary due to the drug's low toxicity. Adolescents appear to require a higher dosage than adults, although the specific mechanism involved is not known. No data are available concerning the use of minocycline in the elderly.<sup>9</sup>

There do not seem to be any gender-related modifications in the pharmacokinetic parameters of doxycycline. No data are available on minocycline.<sup>9</sup>

**Pregnancy and Lactation**—Doxycycline and minocycline are both excreted in breast milk.<sup>2,9</sup> Like other tetracyclines, doxycycline and minocycline are known to cause tooth discoloration (yellow-gray-brownish) during tooth development (last trimester of pregnancy, neonatal period, and early childhood). Use of tetracyclines should be avoided in pregnant and nursing women, and in infants and young children unless other therapeutic options are contraindicated.

**Drug Interactions**—Doxycycline and minocycline absorption is generally decreased by antacids, although they have less effect than on the other tetracyclines. Waiting three hours between administration of these drugs and an antacid should enable drug absorption to be virtually complete.<sup>9,14,35</sup> Iron also inhibits the absorption of doxycycline and minocycline, and should also only be administered after a three-hour interval.

## Adverse Reactions

Some of the adverse reactions associated with the use of second-generation tetracyclines are listed in Table I.

**Gastrointestinal**—Nausea, vomiting, and diarrhea are typical reactions that may occur with the tetracyclines, and appear to be dose related.<sup>1,2,24</sup>

**Central Nervous System**—Minocycline can produce

**TABLE I**  
**ADVERSE REACTIONS**

Drug	Potential Adverse Reactions				
	Esophageal Injury	Vertigo, Vestibular Symptoms	Photosensitivity	Photo-Onycholysis	Tissue Pigmentation
Minocycline	—	+	+/-	+/-	+
Doxycycline Hyclate	+	—	+	+	—
Doxycycline Monohydrate	—	—	+	+	—

dizziness, vertigo, or lightheadedness, which are apparently more common than those occurring after the administration of antihistamines, tranquilizers, sedatives, rifampin, penicillin, and the other tetracyclines.<sup>1,2,3,14,19,36-38</sup> Patients who experience this side effect should be cautioned not to drive or operate hazardous machinery while receiving therapy.<sup>26</sup> These vestibular effects are rarely seen in patients taking doxycycline.<sup>1,39</sup>

**Other**—Minocycline use, usually for prolonged periods, has been associated with hyperpigmentation of skin, thyroid, teeth, and bone. Pigmentation of the skin and mucous membranes occurs as a blue-gray discoloration at either the site of previous inflammation or in previously normal skin. A darker blue-gray or muddy brown discoloration may also occur in areas exposed to the sun. This effect is reported to fade with time. Thyroid discoloration is not known to cause any dysfunction.<sup>14,40-46</sup>

Of more concern, blood urea nitrogen concentrations during therapy with minocycline should be carefully monitored in patients with significant renal impairment due to the product's antianabolic activity.<sup>14</sup> Elevation in blood urea nitrogen levels in these patients appears to be dose related.<sup>26</sup> This problem has not been reported with doxycycline administration.<sup>1,47-57</sup>

**Phototoxicity**—Most currently prescribed tetracyclines are phototoxic to some extent. The mechanism of phototoxic reactions is not known, but may be associated with production of reactive oxygen radicals. Individual factors may also be of significance in the relationship of tetracycline derivatives and phototoxicity.

Most phototoxic reactions are manifest as an exaggerated sunburn or, more rarely, photo-onycholysis. The reported incidence with the use of doxycycline and minocycline is low (minocycline, less than 2 percent, doxycycline, less than 5 percent).<sup>2,14,39,58,59</sup> Doxycycline is widely used for the prevention of traveler's diarrhea in the tropics. The rate of reported photosensitivity is low.<sup>60</sup>

The relationship of tetracycline dosage, serum levels, and tissue levels with phototoxicity remains to be defined. Since this is a phototoxic and not an allergic reaction, there may be a dosage-dependent relationship. In the meantime, patients should be advised to minimize exposure to the sun while taking these antibiotics.

**Esophageal Irritation**—The acidic doxycycline hyclate salt (pH 2 to 3) is one of the most common causes of drug-induced esophageal ulceration. Most patients who experi-

enced esophageal ulcers reported that they had taken doxycycline with little or no water and then reclined.<sup>61-63</sup> The hyclate formulation is soluble at neutral pHs; hence, should the tablet or capsule become lodged in the esophagus due to insufficient liquid intake, reclining after taking the medication, or due to an esophageal stricture, it will dissolve rapidly and can cause esophageal irritation or ulceration.

Results of preclinical studies have shown that doxycycline monohydrate may significantly reduce the risk of esophageal injury due to its virtually neutral pH profile (pH 5 to 6). Furthermore, the monohydrate is not as soluble at esophageal pH, but is freely soluble in the gastric milieu, thereby dissolving more slowly than other salts in the esophagus but rapidly in the stomach. The substitution of doxycycline monohydrate for doxycycline hyclate may therefore reduce the risk of esophageal adverse reactions, particularly for patients who may have difficulty taking medication or following instructions.<sup>24,61-64</sup>

## Clinical Uses

Given the pharmacokinetics and in vitro spectrum of activity, the second-generation tetracyclines doxycycline and minocycline are ideally suited for treatment of two common dermatologic conditions: soft tissue infections and acne. In addition, doxycycline has been recommended by the Centers for Disease Control as the drug of choice for the treatment of genital chlamydial infections and for Lyme disease.

The simpler dosage regimen of these two compounds compared with tetracycline (twice daily rather than four times a day) and lowered dose (200 mg instead of 1000 mg) may enhance patient compliance. Furthermore, a once daily schedule at reduced doses for the treatment of acne has come under investigation and appears to show promise.

## Skin and Soft Tissue Infections

**Doxycyclines**—Doxycycline has been shown to be effective in treating a range of soft tissue infections, including infectious ulcers, cellulitis, gangrene, and a variety of abscesses, due to its broad spectrum of antibacterial activity and high lipid solubility.<sup>1</sup>

As part of a larger study, sixteen patients with acute traumatic infectious ulcers of the lower extremities were treated with oral doxycycline; fifteen of the patients' conditions (94 percent) responded to treatment.<sup>1,65</sup> In another



study of soft tissue infections, primarily cellulitis and abscess, the clinical response was good in 81 percent of the patients, satisfactory in 16 percent, and poor in 4 percent. *Staphylococcus aureus*, beta-hemolytic *Streptococcus*, and *Escherichia coli* were the most frequently isolated pathogens and showed an excellent bacteriologic response. The small number of less favorable responses resulted from cases in which *Proteus*, *Klebsiella*, or *Pseudomonas* sp. were isolated.<sup>1,66</sup>

A further study evaluated combined intravenous and oral doxycycline in the treatment of soft tissue infection, primarily perirectal abscess, cellulitis, gangrene, and pedal or other superficial abscesses. A good clinical response was seen in 78 percent of the patients, 22 percent showed satisfactory results, and no clinical failures were noted.<sup>1,67</sup>

**Minocycline**—Minocycline has demonstrated efficacy in soft tissue infections caused by *Staphylococcus aureus*, although tetracyclines are not the drug of choice in patients with any type of staphylococcal infection.<sup>14</sup>

Minocycline has also been successfully used in treating infections due to *Mycobacterium marinum*, although optimal dosages have not been established.<sup>14,68-72</sup> Pyoderma gangrenosum has been successfully treated with a higher dosage minocycline (300 mg/day) over an extended period of time.<sup>14,73,74</sup> Minocycline has also been used to treat mycetoma and *Serratia* granuloma.<sup>14,75,76</sup>

**Acne**—The use of antibiotics in the treatment of acne vulgaris is based on research on the interaction of hormones, sebaceous glands, and bacteria. Free fatty acids are generally considered the primary source of irritation, and are produced both in the pilosebaceous canals and on the skin surface by the hydrolysis of triglycerides in sebum. The hydrolyzing agents are lipases of aerobic coagulase-negative *Staphylococcus epidermidis* and anaerobic *Propionibacterium acnes*, both of which are flora of normal skin. Successful treatment of acne with antibiotics may prevent bacterial lipases from forming the irritant free fatty acids or may eliminate the causative bacteria.<sup>77</sup>

Tetracyclines have been used successfully for years in the treatment of acne.<sup>77-79</sup> They are believed to lower the production of free fatty acids either indirectly by interfering with nucleic acid metabolism and protein synthesis, thus decreasing the bacterial population and attendant lipases, or directly by binding lipases so that they cannot hydrolyze triglycerides. In fact, both processes may be involved.<sup>77</sup>

The doxycyclines and minocycline have an advantage over tetracycline because of their higher degree of lipophilicity/absorption. A lower dosage regimen than with tetracycline is therefore possible, providing for greater patient compliance. The ability of doxycyclines and minocycline to be administered with food further enhances patient compliance, as has been discussed already. The efficacy of doxycycline and minocycline in the treatment of acne will be summarized.

**Doxycycline vs. Placebo**—In an early double-blind crossover study of sixty-two patients with acne vulgaris that compared doxycycline at 50 mg twice daily to placebo, Plewig et al<sup>80</sup> showed a highly significant improvement in the twenty-eight patients initially randomized to receive doxycycline ( $p$  is less than 0.001). During the four-week rest period, the twenty-eight patients initially treated with doxycycline showed significant worsening of their symptoms ( $p$  is less than 0.05). In phase 2, the thirty-four subjects initially treated with placebo showed significant improvement ( $p$  is less than 0.05) in reduc-

tion of inflammatory lesions when crossed over to receive doxycycline. Patients receiving placebo in either phase 1 or 2 showed no significant reduction in number of lesions.

Another double-blind twelve-week study compared two dosages of doxycycline, 50 mg daily and 100 mg daily, to placebo.<sup>81</sup> After four weeks of treatment, 68 percent of patients treated with 100 mg doxycycline were judged to be "cured" compared with 27 percent of placebo-treated patients. In the 50 mg doxycycline-treated group, 72 percent were judged "cured" after six weeks of therapy compared to 27 percent of those receiving placebo. At week twelve, the percentage of "cured" patients was 90 percent compared with 89 percent for the 100 mg and 50 mg doxycycline-treated groups, respectively.

**Minocycline vs. Placebo**—A double-blind crossover study was conducted in fifty patients with acne vulgaris. In the first phase, minocycline or placebo was administered to patients: 200 mg daily for seven days, followed by 100 mg daily for five weeks. The two groups' treatments were switched for the last five weeks of therapy. There was a significant decrease ( $p$  is less than 0.05) in baseline acne lesion counts in the group taking minocycline, while the decrease in placebo-treated patients was not significant.<sup>14,82</sup>

**Minocycline vs. Tetracycline**—Minocycline has been compared in a number of studies to tetracycline in the treatment of acne and has been equally effective or superior in some respects.<sup>14,83-86</sup> A few are summarized here.

In one double-blind six-month study, 104 patients received either minocycline 50 mg/twice daily or tetracycline 250 mg/twice daily.<sup>14,84</sup> Although there were no statistical differences between the groups in the number of patients who reached and maintained grade I (noninflammatory) status, a higher percentage of the minocycline-treated patients (92 percent) reached that status more quickly (sixty-three days) than did tetracycline-treated patients (75 percent at seventy-six days). Seventeen patients reported side effects; these occurred equally in the two treatment groups.

In another study, fifty patients were treated with either 50 mg minocycline twice daily or 250 mg tetracycline twice daily for eighteen weeks. Eighty-six percent of the minocycline-treated patients and 80 percent of the tetracycline-treated patients exhibited a satisfactory clinical response. Two patients from each group experienced drug-related side effects.<sup>14,83</sup>

**Doxycycline vs. Minocycline**—In an early study,<sup>87</sup> sixteen patients with acne were treated with either minocycline or doxycycline at 100 mg/day for twelve days. Both drugs appeared to have similar efficacy; no patients dropped out of the study due to adverse side effects.

In 1988, Harrison completed an observer-blinded twelve-week study comparing doxycycline 50 mg/once daily to minocycline 50 mg/twice daily.<sup>88</sup> Treatment efficacy was considered good or excellent in 73 percent of the doxycycline-treated group compared with 84 percent in the minocycline-treated group; the difference was not statistically significant. Side effects were minimal in both groups; only one patient in the doxycycline-treated group and two patients in the minocycline-treated group experienced treatment-related side effects.

More recently, doxycycline and minocycline were compared in an open study over a twelve-week period, with 100 patients receiving either doxycycline 50 mg once daily or

50 mg minocycline twice daily.<sup>89</sup> Attending physicians evaluated the doxycycline-treated group as healed or improved in 78 percent of the patients, and in 82 percent of the minocycline-treated patients.

In another recent study, sixty-four patients with acne were treated with either doxycycline or minocycline at 50 mg twice daily for the first four weeks, then 50 mg once daily for the remaining eight weeks.<sup>90</sup> A significant reduction of all types of lesions was observed in all areas during the twelve weeks of treatment for both groups, with no statistical difference occurring at any time between the doxycycline-treated and minocycline-treated groups. Both patients and physicians rated the doxycycline therapy as effective or very effective in 85 percent of the cases; this was true for minocycline in 87 percent and 90 percent of the cases as rated by physicians and patients, respectively. Investigators concluded that doxycycline and minocycline were equally effective in the treatment of moderate to moderately severe acne vulgaris. Five patients (two in the doxycycline-treated group and three in the minocycline-treated group) withdrew from the study due to treatment-related side effects.

**Chlamydia**—Chlamydia is the most prevalent bacterial sexually transmitted disease in the United States, with about four million cases occurring annually.<sup>91</sup> In women, *Chlamydia trachomatis* can lead to pelvic inflammatory disease, which can further result in infertility and an increased risk of ectopic pregnancy. In men, *C. trachomatis* is the most common cause of nongonococcal urethritis, which can lead to acute epididymitis and reduced fertility.<sup>92</sup> Chlamydial infections do not always present symptomatically or the symptoms may be mild; thus it is often referred to as "the silent sexually transmitted disease."<sup>93</sup> In fact, studies have shown that 50 percent of male sexual partners of infected women are asymptomatic.<sup>92,94</sup>

Doxycycline is the Centers for Disease Control's drug of choice for the treatment of *Chlamydia*. The recommended regimen is 100 mg twice daily for seven days. Because the tetracyclines are **contraindicated in pregnancy**, erythromycin is the recommended drug for pregnant patients.<sup>95</sup> Although minocycline is also effective against *C. trachomatis*, its association with vestibular side effects and high cost have restricted its use.<sup>91</sup>

## Summary

The tetracycline group of antibiotics is useful to the dermatologist for the treatment of acne, soft tissue infections, and chlamydia. Although first-generation tetracycline remains useful, the second-generation tetracyclines in the form of minocycline and doxycycline hyclate and, most recently, doxycycline monohydrate, offer a number of advantages over tetracycline.

The newer tetracyclines have markedly increased bioavailability, greatly improved absorption in the presence of foods, and a broader range of antibacterial activity. The increased bioavailability allows for once-daily administration in the treatment of acne and a twice-daily regimen for soft tissue infections and chlamydia.

Doxycycline lacks the vestibular side effects of minocycline, but has a higher incidence of exaggerated sunburn reaction than minocycline. With the exception of esophageal injury, seen with the hyclate form but apparently absent with the monohydrate form, the doxycyclines appear to be identical

to one another and closely comparable in efficacy to minocycline.

## REFERENCES

1. Cunha BA, Sibley CM, Ristuccia AM: Review doxycycline. *Ther Drug Monit* 4: 115-135, 1982.
2. Jonas M, Cunha BA: Review minocycline. *Ther Drug Monit* 4: 137-145, 1982.
3. Krucers A, Bennet N: The Use of Antibiotics, 3rd ed. Philadelphia, JB Lippincott, 1979.
4. Lennette EH, Balows A, Hausler WJ Jr, et al (eds): Manual of Clinical Microbiology. Washington DC, American Society of Microbiology, 1985.
5. Scavizzi MR: Existence de deux caractères transférables de résistance aux tétracyclines. *Ann Inst Pasteur* 122: 3-17, 1972.
6. Levy SB: Resistance to the tetracyclines. In: Antimicrobial Drug Resistance (Bryan LE, ed), p 191. Orlando, Florida, Academic Press, 1984.
7. Lebeck G, Forter Z: Empfindlichkeit tetrazyklin-resistenter krankheitserreger des menschen gegen minozyklin und doxyzyklin. *Schweiz Med Wochenschr* 104: 1124-1139, 1974.
8. Macdonald II, Kelly RG, Allen ES: Pharmacokinetic studies of minocycline in man. *Clin Pharmacol Ther* 14: 852, 1973.
9. Saivin S, Houin G: Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 15: 355-366, 1988.
10. Fabre J, Milek E, Kalfopoulos P, et al: The kinetics of tetracyclines in man. Digestive absorption and serum concentrations. *Schweiz Med Wochenschr* 101: 593-598, 1971.
11. Lowenthal W, Vitsky BL: Computer program for a double exponential equation to determine biological constants. *J Pharm Sci* 56: 169-173, 1967.
12. Cartwright AC, Hatfield HL, Yeader A, et al: A comparison of the bioavailability of minocycline capsule and film coated tablets. *J Antimicrob Agents Chemother* 1: 317, 1975.
13. Lang W: Pharmacokinetics of minocycline. Proceedings of the Minocycline Symposium, Germany, 1971.
14. Lederle Laboratories. Minocin: minocycline hydrochloride, 1987.
15. Green R, Brown JR, Calvert RT: The disposition of four tetracyclines in normal subjects. *Eur J Clin Pharmacol* 10: 245-250, 1976.
16. Malmborg AS: Bioavailability of doxycycline monohydrate. *Chemotherapy* 30: 76-80, 1984.
17. Welling PG, Koch PA, Curtis CL, et al: Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. *Antimicrob Agents Chemother* 11: 462-469, 1977.
18. Leyden JJ: Absorption of minocycline hydrochloride and tetracycline hydrochloride. *J Am Acad Dermatol* 12: 308-312, 1985.
19. Allen JC: Minocycline. *Ann Intern Med* 85: 482, 1976.
20. Fabre J, Milek E, Kalkopoulos P, et al: The kinetics of tetracycline in man. Symposium on the mechanism of action of antibiotics. Saragosa, October 9, 1970.
21. Okhubo II, Fujimoto Y, Okamoto Y, et al: Fundamental and clinical studies on doxycycline. *Chemotherapy* 17: 216-219, 1969.
22. Rosenblatt JE, Barrett JE, Brodie JL, et al: Comparison of *in vitro* activity and clinical pharmacology of doxycycline with other tetracyclines. *Antimicrob Agents Chemother* 1966: 134-141, 1967.
23. Schach von Wittenau M: Some pharmacokinetic aspects of doxycycline metabolism in man. *Chemotherapy (Basel) (Suppl)* 13: 41-50, 1968.
24. Pallett AP, Smyth EG: Clinician's guide to antibiotics. Tetracycline. *Br J Hosp Med* 40: 385-390, 1988.
25. Williams DB, O'Reilly WJ, Boehm G, et al: Absorption of doxycycline from a controlled release pellet formulation: the influence of food on bioavailability. *Biopharm Drug Dispos* 11: 93-105, 1990.



26. Lederle Laboratories: Minocin package insert, 5/90.
27. Bernard B, Jong Yin E, Simon HJ: Clinical pharmacologic studies with minocycline. *J Clin Pharmacol* 5: 332-348, 1971.
28. George CRP, Guinness MDG, Lark DJ, et al: Minocycline toxicity in renal failure. *Med J Aust* 1: 640-641, 1973.
29. Carney S, Butcher RA, Dawborn JK, et al: Minocycline excretion and distribution in relation to renal function in man. *Clin Exp Pharmacol Physiol* 1: 299-308, 1974.
30. Heaney D, Eknayan G: Minocycline and doxycycline kinetics in chronic renal failure. *Clin Pharmacol Ther* 24: 233-239, 1978.
31. Welling PG, Shaw WR, Uman SJ, et al: Pharmacokinetics of minocycline in renal failure. *Antimicrob Agents Chemother* 8: 532-537, 1975.
32. McHenry MC, Gavan TL, Vidt G, et al: Minocycline in renal failure. *Clin Pharmacol Ther* 13: 146, 1972.
33. Spring P, Sclenarc I: The elimination of minocycline, a tetracycline derivative, in patients with normal and reduced renal function. *Schweiz Med Wochenschr* 104: 1764-1766, 1974.
34. Sklenar I, Spring P, Dettli L: One-dose and multiple-dose kinetics of minocycline in patients with renal disease. *Agents Actions* 7: 369-377, 1977.
35. Neuvonen PJ: Interactions with the absorption of tetracyclines. *Drugs* 11: 45-54, 1976.
36. Fanning WL, Gump DW, Sofferan RA: Side effects of minocycline: a double-blind study. *Antimicrob Agents Chemother* 11: 712, 1977.
37. Gump DW, Ashikaga T, Fink TJ, et al: Side effects of minocycline: different dosage regimens. *Antimicrob Agents Chemother* 12: 642, 1977.
38. Brodgen RN, Speight TM, Avery GS: Minocycline: a review of its antibacterial and pharmacokinetic properties and therapeutic use. *Drugs* 9: 251-291, 1975.
39. Oclassen Pharmaceuticals: FDA adverse reaction file analysis, 1990.
40. Basler RSW: Minocycline pigmentation. *Schoch Lett* 29: 1, 1979.
41. Basler RSW, Kohlen PW: Localized hemosiderosis as a sequela of acne. *Arch Dermatol* 114: 1695-1697, 1978.
42. Caro I: Discoloration of the teeth related to minocycline therapy for acne. *J Am Acad Dermatol* 3: 317-318, 1980.
43. Fenske NA, Mills JL, Greer KE: Minocycline-induced pigmentation at sites of cutaneous inflammation. *JAMA* 244: 1103-1106, 1980.
44. Sauer GC: Muddy skin from minocycline. *Schoch Lett* 29: 3, 1979.
45. Simons JJ, Morales A: Minocycline and generalized cutaneous pigmentation. *J Am Acad Dermatol* 3: 244-247, 1980.
46. Gordon G, Sparano BM, Iatropoulos MJ: Hyperpigmentation of the skin associated with minocycline therapy. *Arch Dermatol* 121: 618-623, 1985.
47. Whelton A, Schach von Wittenau M, Twomey TM, et al: Pharmacokinetics of doxycycline in the absence of renal function. In: Doxycycline (Vibramycin): A Compendium of Clinical Evaluations. New York, Pfizer, 1973.
48. Merier G, Laurencet FL, Rudhardt M, et al: Behaviour of doxycycline in renal insufficiency. *Helv Med Acta* 35: 124-134, 1969, 1970.
49. Fabre J, Milek E, Kalkopoulos P, et al: Kinetics of tetracyclines in man: II. Excretion, penetration in normal and inflammatory tissues, behaviour in renal insufficiency and hemodialysis. *Schweiz Med Wochenschr* 101: 625-633, 1971.
50. Laurencet FL, Fabre JP: Influence de l'insuffisance rénale sur le comportement de la doxycycline. *J Urol Nephrol* 74: 1038-1047, 1968.
51. Stein W, Schoog M, Franz HE: Doxycycline serum levels in patients with renal insufficiency. *Arzneimittelforschung* 19: 827-828, 1969.
52. Morgan T, Ribush N: The effect of oxytetracycline and doxycycline on protein metabolism. *Med J Aust* 1: 55-58, 1972.
53. Whelton A, Nightingale SD, Carter GG, et al: Pharmacokinetic characteristics of doxycycline accumulation in normal and severely diseased kidneys. *J Infect Dis* 132: 467-471, 1975.
54. Knoche JP, Dempsey W, Fetter C, et al: The effect of tetracycline and doxycycline on excretion of urea and creatinine and on muscle protein synthesis in chronic renal failure. In: Doxycycline (Vibramycin): Recent Investigations and Clinical Experience, vol 2, New York, Pfizer, 1975.
55. Mahon WA, Wittenberg JVP, Tuffnell PG: Studies on the absorption and distribution of doxycycline in normal patients and in patients with severely impaired renal function. *Can Med Assoc J* 103: 1031-1034, 1970.
56. Cunha BA: The pharmacokinetics of doxycycline. *Postgrad Med J (Suppl)* 1: 63-72, 1979.
57. Cox CE: Intravenously administered doxycycline therapy of infections of the genitourinary tract. In: Doxycycline (Vibramycin): A Compendium of Clinical Evaluations. New York, Pfizer, 1973.
58. Frost P, Weinstein GD, Gomez EC: Phototoxic potential of minocycline and doxycycline. *Arch Dermatol* 105: 681, 1972.
59. Henderson CA, Cunliffe WJ: Unusual side effects in patients receiving doxycycline. *J Dermatol Treat* 1: 95-96, 1989.
60. Sack DA, Kaminsky DC, Sack RB, et al: Prophylactic doxycycline for traveler's diarrhea. *N Engl J Med* 14: 758-763, 1978.
61. Delpre G, Kadish U, Stahl B: Induction of esophageal injuries by doxycycline and other pills. *Dig Dis Sci* 34: 797-800, 1989.
62. Bott S, Prakash C, McCallum RW: Medication-induced esophageal injury: survey of the literature. *Am J Gastroenterol* 82: 758-763, 1987.
63. Lanza FL: Esophageal ulceration produced by doxycycline. *Curr Ther Res* 44: 475-484, 1988.
64. Carlborg B, Farmer J: Esophageal corrosion tests with doxycycline monohydrate tablets. *Curr Ther Res* 34: 110-116, 1983.
65. Marks G, Mervine TB: Non-healing ulcers of the extremities. Scientific exhibit. American College of Surgeons Annual Meeting, October 14-18, 1968, Atlantic City, New Jersey.
66. Britt LA: Use of doxycycline in surgical infections—report of 117 case studies with 13 different organisms. *J Tenn Med Assoc* 62: 37-40, 1969.
67. Brigg LA: Intravenously administered doxycycline in the treatment of soft tissue infections. In: Doxycycline (Vibramycin): A Compendium of Clinical Evaluations. New York, Pfizer, 1973.
68. Loria PR: Minocycline hydrochloride treatment for atypical acid-fast infection. *Arch Dermatol* 112: 517-519, 1976.
69. Leroy JP, et al: Deux cas de pigmentation cutanée au cours de traitements par la minocycline. *Ann Dermatol Venerol* 108: 871-875, 1981.
70. Contorer P, Jones RN: Minocycline therapy of aquarium granuloma. Case reports and literature review. *Cutis* 23: 864-868, 1979.
71. Horn MS: *Mycobacterium marinum* infection. *J Assoc Milit Dermatol* 7: 25-27, 1981.
72. Hanke CW, Bergfeld WF, Shear H: Sporotrichoid *Mycobacterium marinum* skin infection treated with minocycline hydrochloride. *Cleve Clin Q* 47: 339-342, 1980.
73. Lynch WS, Bergfeld WF: Pyoderma gangrenosum responsive to minocycline hydrochloride. *Cutis* 21: 535-538, 1978.
74. Davies MG, Piper S: Pyoderma gangrenosum. Successful treatment with minocycline. *Clin Exp Dermatol* 6: 219-223, 1981.
75. Hubler WR Jr, Hubler WR: Actinomycotic mycetoma treated with minocycline: case report. *Tex Med* 72: 79-83, 1976.
76. Epstein E, Carson TE: *Serratia* granuloma. *JAMA* 223: 670-671, 1973.
77. Becker FT: Treatment of tetracycline-resistant acne vulgaris. *Cutis* 14: 610-613, 1974.

78. Lane P, Williamson DM: Treatment of acne vulgaris with tetracycline hydrochloride: a double-blind trial with 51 patients. *Br Med J* 2: 76-79, 1969.
79. Akers WA, Allen AM, Burnett JW, et al: Systemic antibiotics for treatment of acne vulgaris: efficacy and safety. *Arch Dermatol* 111: 1630-1636, 1975.
80. Plewig G, Petrozzi JW, Berendes U: Double-blind study of doxycycline in acne vulgaris. *Arch Dermatol* 101 (4): 435-437, 1980.
81. Suh JI, Kim KS, Kim YP, et al: Evaluation of effectiveness of low-dose long-term vibramycin on acne vulgaris in a double-blind study. *Korean J Dermatol* 16 (2): 121-130, 1978.
82. Hersle K, Gisslen H: Minocycline in acne vulgaris: a double-blind study. *Curr Ther Res* 19: 339-342, 1976.
83. Cullen SI, Cohan RH: Minocycline therapy in acne vulgaris. *Cutis* 17: 1208-1214, 1976.
84. Hubbell CG, Hobbs ER, Rist T, et al: Efficacy of minocycline compared with tetracycline in treatment of acne vulgaris. *Arch Dermatol* 118: 989-992, 1982.
85. Leyden JJ, McGinley KJ, Kligman AM: Tetracycline and minocycline treatment. Effects on skin-surface lipids and *Propionibacterium acnes*. *Arch Dermatol* 118: 19-22, 1982.
86. Rossman RE: Minocycline treatment of tetracycline-resistant and tetracycline-responsive acne vulgaris. *Cutis* 27: 196, 197, 201, 207, 1981.
87. Smit F: Minocycline versus doxycycline in the treatment of acne vulgaris. A double-blind study. *Dermatologica* 157: 186-190, 1978.
88. Harrison PV: A comparison of doxycycline and minocycline in the treatment of acne vulgaris. *Clin Exp Dermatol* 13: 242-244, 1988.
89. Laux B: Treatment of acne vulgaris. A comparison of doxycycline versus minocycline. *Dermatologist* 40: 577-581, 1989.
90. Olafsson JH, Gudgeirsson J, Eggertsdottir GE, et al: Doxycycline versus minocycline in the treatment of acne vulgaris: a double-blind study. *J Dermatol Treat* 1: 15-17, 1989.
91. Toomey KE, Barnes RC: Treatment of *Chlamydia trachomatis* genital infection. *Rev Infect Dis* 12 (Suppl) S645-S655, 1990.
92. McGregor JA: Chlamydial infection in women. *Obstet Gynecol Clin North Am* 16: 565-592, 1989.
93. National Institute of Allergy and Infectious Diseases: Chlamydial infections. National Institutes of Health, Pub No 87-909B, 1987.
94. Thelin I, Wennstrom AM, Mardh PA: Contact tracing in patients with genital chlamydial infection. *Br J Vener Dis* 56: 259-262, 1980.
95. 1989 Sexually transmitted diseases treatment guidelines. *MMWR* 38: 27-29, 1989.

Now you can run  
Classified Ads in

# cutis®

to reach the Physicians  
you need . . . and get  
3 ads for the price of 2!

Let **Cutis'** targeted audience and high readership give your **Classified Advertising** more reach and impact than ever before in these categories:

**Career Opportunities**  
**Business Opportunities**  
**Practice for Sale**  
**Real Estate**

**Beginning this October,**  
**save money when you run Classified!**

**ACT NOW. . .**

**Buy 2 ads, Get a 3rd one at no charge.**

(Ad units must be identical and placed in consecutive issues. Offer ends March 31, 1992.)

**ALL-NEW CLASSIFIED SECTION.**

Also beginning in **Cutis'** October issue: All classified ads will appear in a newly designed, high-impact classified section.

Don't miss this very special opportunity to reach **Cutis'** 50,000+ readers!

**For Information Call:**  
**LENI TEAMAN, Classified Ad Manager**

**1 (800) 344-7775**

**Or: (212) 463-6485 ■ Fax: (212) 463-6470**