

Medical Tribune



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News Summary



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CDC survey detects new cases of allergic reaction to latex during operations on children with congenital defects. Page 3.

Treating cystitis

Experts offer best treatment strategies for urinary tract infections. Page 2.

New prostate regimen

Prostate cancer halted by heat and radiation. Page 3.

Too many Rh+ babies

Too many babies are born with Rh hemolytic disease, according to government researchers. Page 4.

Drugs increase hip fractures

Thiazide diuretics increase the risk of hip fractures in the elderly, Washington study reveals. Page 4.

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Antihypertensive launched

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Low-fat debate

Cutting dietary fats may prolong life by only three to four months, investigators find. Page 13.

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DR. WILLIAM BOGGS

Beads release antibiotic

Nova Pharmaceuticals has submitted an IND application to the FDA to conduct trials of a new antibiotic-bead treatment for osteomyelitis. Page 12.

THE PHYSICIAN'S NEWSPAPER

Hospitals fight TB epidemic

In some U.S. cities, isolation wards used to stem tuberculosis spread

By John Carpi

Rising rates of tuberculosis are forcing hospitals across the country to fall back on decades-old ways of controlling the spread of the disease, health experts say.

Hospitals in major U.S. cities are on the verge of setting up special TB wards, akin to the tuberculosis sanatoriums of the early 1900s, to contain the disease and treat the growing number of infected people, said a spokesman at the American Hospital Association in Chicago, Ill.

The AHA said that an increasing number of its members are requesting information on TB control measures.

The new precautions are meant in part to deal with infected people who refuse to remain hospitalized or take medications, according to Gordon Trenholme, M.D., of Rush-Presbyterian-St. Luke's Medical Center in Chicago.

"A lot of hospitals are being faced with a growing number of

TB patients who are also infected with the AIDS virus and have a history of IV drug use, and are finding that many of these people are noncompliant with therapy," he said.

In some U.S. cities, cases of tuberculosis have more than doubled since 1980, according to the CDC.

Miami, one of the first U.S. cities to experience near-epidemic TB rates, was one of the first to deal with the problem.

"We have had special infection-control units set up for

nearly a decade now," said Horst Baier, M.D., director of pulmonary medicine at Jackson Memorial Hospital.

Jackson, which began giving chest X-rays to all people admitted to the hospital in 1981, forwards any suspicious findings to a TB review board. If the X-ray's findings are confirmed, the board orders the patient isolated in specially ventilated rooms for three to seven days while they receive antibiotic therapy.

Administrators at San Francisco General Hospital Medical Center have plans to develop a TB isolation ward within the hospital, according to Henry Chambers, M.D., co-director of infection control.

In New York, up to 30 TB patients wait to be admitted to 10 TB rooms at Brooklyn's Woodhull Hospital at any given time.

Beth Israel Hospital, also in New York, has ordered TB-bacteria killing ultraviolet lights and is considering forming a special unit where people with the disease are educated about ways to prevent infection.

Taxol anticancer hope questioned

By Peggy Peck

Disappointing reports surfaced on the highly touted anti-cancer drug, taxol, even as chemists and cell biologists reported sharp progress in the race to provide enough of the yew-tree derivative to complete definitive trials.

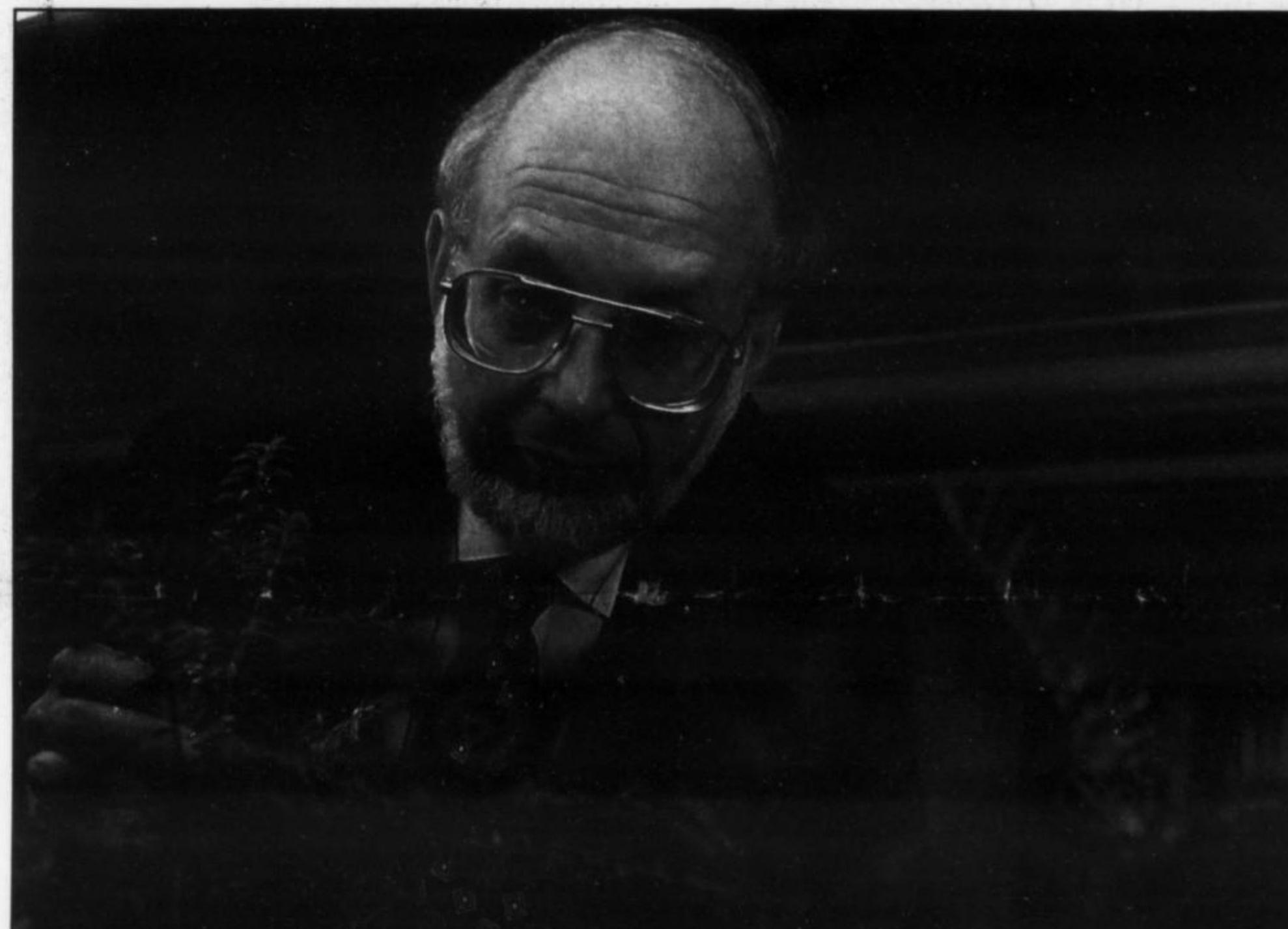
Within two years, the drug may be produced in commercial quantities by newly patented cell-culture or synthesis technologies, said a pharmaceutical company spokesperson.

But Maurie Markman, M.D., of New York's Memorial Sloan-Kettering Cancer Institute, said that while the drug shows promise, it "hasn't translated into long-term, disease-free survival rates."

Many of his patients with refractory ovarian cancer relapsed after less than a year, Dr. Markman said.

William McGuire, M.D., of Johns Hopkins University

See back of section, page 8



MICHAEL SCARABAN/ABA

Dr. Walter Goldstein of ESCAgenetics with yew cuttings used to culture taxol. Employing giant fermentation tanks, the company may be able to produce commercial quantities fairly soon.

Study 'legitimizes' chiropractic care

A RAND corporation study has concluded that chiropractic manipulation is an effective treatment for acute, uncomplicated low-back pain.

But while the study does legitimize that aspect of chiropractic care, it doesn't reflect one way or another on osteopathic manipulation, according to Raymond Hraby, D.O.

Dr. Hraby, a professor at the University of New England School of Osteopathic Medicine in Biddeford, Maine, said osteopathic manipulation has been considered "mainstream" since the mid-1970s.

The nine-member RAND panel reviewed 1,577 cases of spinal manipulation performed by chiropractors on patients with lower-back pain.

The panel found that patients with uncomplicated low-back pain for no more than three weeks benefited from spinal manipulation.

But the RAND panel agreed that the procedure was "extremely inappropriate" when low-back pain was complicated by evidence of major neurological

damage, defined as progressive neurological deficits and signs of bowel and bladder paralysis and cord compression.

Caveats aside, panelist Scott Haldeman, M.D., said the study has "brought spinal manipulation into the mainstream in that [the procedure] is no longer something that could be called quackery or unscientific."

Dr. Haldeman is a medical doctor who originally trained as a chiropractor.

"The science of manipulation is just starting to be tapped," said panelist John Triano, D.C., of the National College of Chiropractic in Lombardi, Ill.

Spinal manipulation has long been a source of medical and legal controversy.

The U.S. Supreme Court announced last year that it would not review a lower court's finding that the AMA had been guilty of an unlawful boycott of chiropractors.

In arguing for a denial of the review, the plaintiffs cited studies showing the benefits of chiropractic care, even in patients with chronic or severe pain.

High-definition television provides sharper detail HDTV guides endoscopic surgery

By David A. Danar, M.D.

Two endoscopic operations performed at a New York hospital mark the first time that high-definition television has guided the procedure.

"The clarity of detail was excellent," said Arthur Smith, M.D., who performed a laparoscopic pelvic lymphadenectomy for the staging of prostate cancer

and a percutaneous removal of a staghorn calculus from the kidney using a nephroscope.

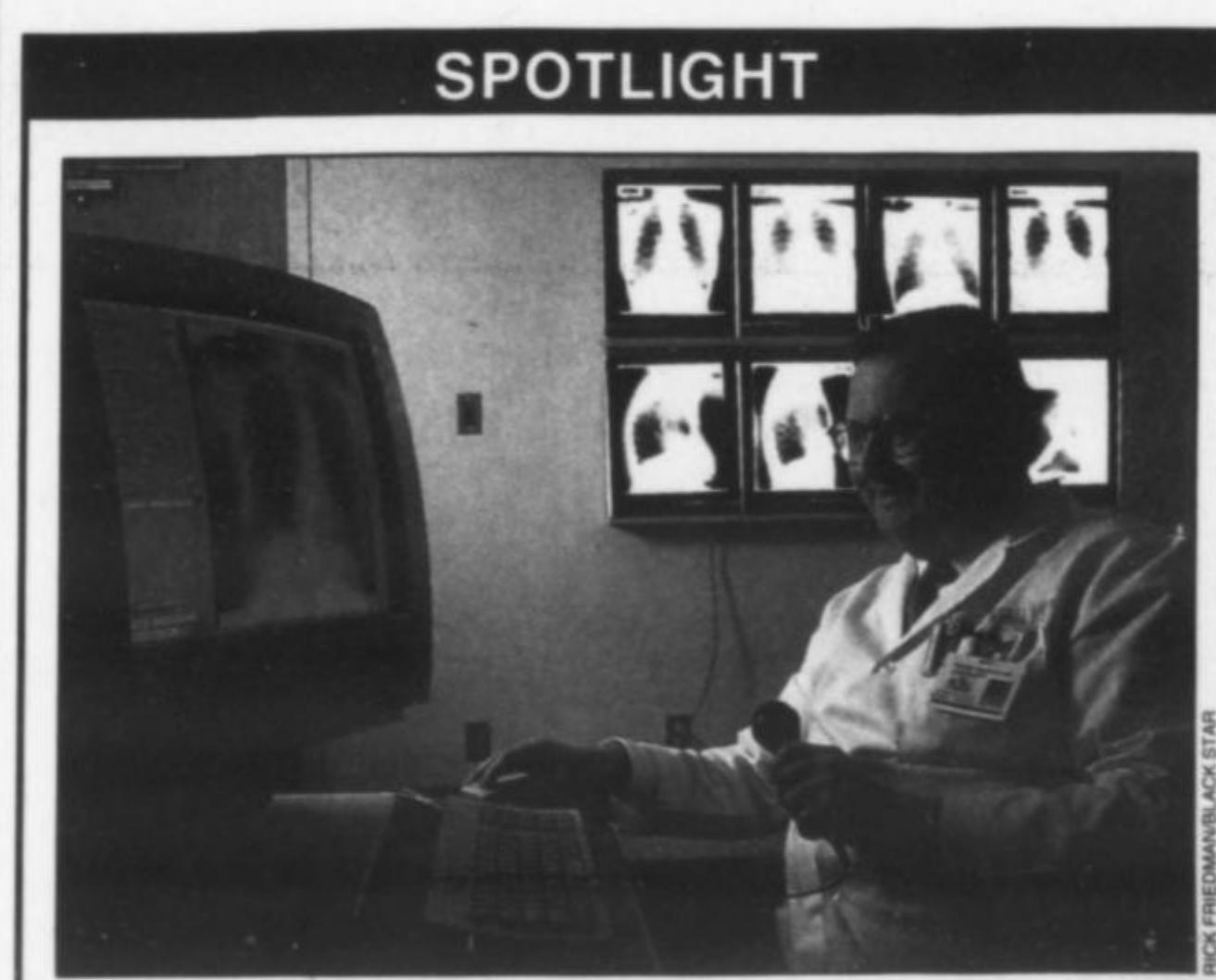
In both operations, he used an HDTV camera connected to a high-resolution monitor to guide surgery.

High-definition television produces sharper pictures that contain about five times the information of ordinary television, according to a spokesperson at Rebo Studio, a New York

Expert answers

In this issue, a panel of experts offers answers to your questions on hypothyroidism, the relationship between hypercholesterolemia and psoriasis and how Trichomonas vaginalis is transmitted (Q & A, page 10).

To get your questions answered quickly, phone 800-937-8838, fax 212-505-6542 or write Medical Tribune at 257 Park Ave. South, New York, N.Y. 10010.



Dr. Roger Bauman, a radiologist, uses a new computer network installed at four Boston hospitals. Page 7.

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Experts offer cystitis strategies

By Brianna Politzer

Most urinary tract infections can be effectively prevented or treated with drug therapy and some home remedies, infectious-disease specialists say.

Primary-care physicians can use the regimens for the more than 40% of women who, according to a recent Rand Corporation study, have a history of kidney, bladder or urinary tract infections (UTIs).

The majority of UTIs are linked temporally to sexual intercourse, according to David Richardson, M.D., assistant professor of obstetrics and gynecology at Wayne State University in Detroit, Mich.

About 90% of cases are caused by E. coli; an additional 9% are thought to be colonization of *Staphylococcus saprophyticus*, he said.

While experts agree that the use of a contraceptive diaphragm and

spermicide seem to predispose women to infection, the mechanism remains unclear. Dr. Richardson said his research has shown that the diaphragm may cause infection by decreasing urinary-flow rate.

Spermicides used with the device may also play a role, according to Ann Stapleton, M.D., an infectious-disease specialist at the University of Washington, Seattle.

"Diaphragms with spermicide cause changes in the bacterial flora in the vagina in favor of ones that cause UTI, especially E. coli," she said. "It's not clear how. Several factors are probably involved."

Diaphragm users with recurrent UTIs who can take advantage of other birth-control options might be better off switching to another method, both physicians agreed.

Low-dose antibiotic prophylaxis with trimethoprim/sulfamethoxazole, nitrofurantoin macrocrystals (Macrodantin), Norwich Eaton

Pharmaceuticals), norfloxacin (Noroxin, Merck Sharp & Dohme) or ciprofloxacin (Cipro, Miles Pharmaceutical) are effective in most cases, Dr. Stapleton said.

Depending on the patient's history and frequency of sexual intercourse, physicians may prescribe post-coital, thrice-weekly or nightly antibiotic regimens. If infection does occur, a single-dose regimen or three-day course of antibiotics is probably sufficient, she said.

It is not necessary to wait for a culture result to begin treatment for UTI, said Allan Ronald, M.D., professor of internal medicine and medical microbiology at the University of Manitoba in Winnipeg, Canada.

"I generally treat before I get any culture results. That makes the woman feel better," he said. "By the end of single-dose therapy, the patient will have responded, or I'll have my culture results back."

If a patient's culture is negative, he or she is examined in the office prior to any further antibiotic therapy, he said.

Dr. Ronald said that it is important to obtain cultures, since many women mistake the symptoms of vaginitis, yeast infections or chlamydial infections for UTIs.

Women may also subscribe to a number of myths about the prevention or treatment of bladder infections, he said.

Almost all of the prevention myths (i.e., wearing pants or skirts, riding bicycles, the way women wipe, the way they void, drinking coffee or tea) don't help, Dr. Ronald said. "They just drive patients crazy. I tell them to take the [antibiotic] pill and void when they want to void."

Certain home remedies, however, such as drinking cranberry juice or lots of water, may be effective. "I do think cranberry juice



Culture results may not be required to begin antibiotic therapy.

works," he said. "Not as well, however, for most women as taking antimicrobials."

"The principle is to acidify the urine, so the organisms won't get a chance to establish residence and multiply."

"In terms of drinking lots of water, the data is weak, but it has a lot of historical credibility."

"However, a woman shouldn't drink 20 glasses of water a day or become obsessive about it," Dr. Ronald said.



Assay may cut vaccination costs.

Rapid test for measles advocated

By Tom Yulsman

A new monoclonal antibody test, which was shown recently to be a sensitive and rapid method for diagnosing measles, may prove useful in efforts to contain the spread of the disease.

Of 21 nasopharyngeal-throat swab specimens tested in a study, 15 were positive for measles by the monoclonal test, and 14 of the positives were confirmed by culture tests, said C. George Ray, M.D., of the University of Arizona, Tucson.

Dr. Ray reported the results in a recent issue of the Journal of Clinical Microbiology.

The monoclonal test, which detects measles antigen via indirect immunofluorescence, takes about two hours. The standard PRMK culture method takes two or more weeks, said Dr. Ray.

Doctors have traditionally diagnosed measles based on symptoms, including cough, coryza and conjunctivitis with high fever, Koplik's spots, and florid rash.

"But there's a generation of physicians today that has seen no measles, and their diagnostic acuity is not so good," Dr. Ray said.

A sensitive and rapid test for measles is thus needed, especially in light of the recent surge in cases, Dr. Ray said.

PRMK culture may not be adequate, he added, because an infected patient can transmit measles to many contacts by the time the test produces results. With a positive result available in two hours, in contrast, the patient could be isolated to contain the infection.

"From a public health standpoint, the biggest value of the test would be to tell who does not have measles," said William Atkinson, M.D., a CDC epidemiologist.

Dr. Atkinson said that when a student at a school is suspected of having measles, the entire student body is vaccinated. With a rapid test, however, the student could be definitively diagnosed. Ruling out infection would avoid an expensive vaccination program.

According to Dr. Ray, most commercial diagnostic laboratories probably can do the monoclonal test, which costs about \$20.

Physicians can call state health departments for more information.

BRIEF SUMMARY

Nicorette® (nicotine polacrilex)

CAUTION: Federal law prohibits dispensing without prescription.
DESCRIPTION: Each piece of Nicorette contains nicotine polacrilex equivalent to 2 mg nicotine and also contains flavors, propylene, gum base, sodium bicarbonate, sodium carbonate, and sorbitol.

INDICATION AND USAGE: Nicorette is indicated as a temporary aid to the cigarette smoker seeking to give up his or her smoking habit while participating in a behavioral modification program under medical or dental supervision. For further information, please see Full Prescribing Information.

CONTRAINDICATIONS: Nicorette is contraindicated in non smokers.

Nicorette is contraindicated in patients during the immediate post myocardial infarction period, patients with life-threatening arrhythmias, and patients who are asymptomatic or who have a history of angina pectoris. (See **WARNINGS**.)

Also, Nicorette is contraindicated in patients with active temporomandibular joint disease.

Current medical opinion indicates that nicotine in any form may be harmful to an unborn child. Nicorette and cigarettes both contain nicotine.

Nicorette may cause fetal harm when administered to a pregnant woman.

Use of cigarettes or Nicorette during the last trimester has been associated with a decrease in fetal breathing movements.

These effects may be the result of decreased placental perfusion caused by nicotine. Rare reports of miscarriages have been received. Nicorette should not be used during pregnancy unless the potential hazard to the fetus clearly outweighs the benefit to the patient.

WARNINGS: The use of Nicorette in patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease). Prinzmetal variant angina should be carefully screened and evaluated before Nicorette is prescribed.

Occasional reports of tachyarrhythmias occurring in association with the use of Nicorette have been reported; therefore, if an increase in cardiovascular symptoms occurs with the use of Nicorette, it should be discontinued.

As the action of nicotine on the adrenal medulla (release of catecholamines) does not appear to be affected by tolerance, Nicorette should be used with caution in patients with hypertension, pheochromocytoma or insulin-dependent diabetes.

Cigarettes should be used with particular care in patients with hypertension and peptic ulcer disease. Therefore, Nicorette should be used in patients with systemic hypertension or peptic ulcer (active or inactive) only when the benefits of including Nicorette in a smoking cessation program outweigh the risks.

PRECAUTIONS: Nicorette should be used with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer.

The dosage of Nicorette dictates that it be used with caution in patients whose dental problems might be exacerbated by chewing gum. In such patients prior dental evaluation may be advisable.

Nicorette is supplied in strips and has a tendency to stick to the tongue to minimize stickiness. As with other gums, however, the degree to which Nicorette sticks to the tongue and has a tendency to stick may depend on the materials used in the gum, the amount of saliva and other factors such as amount of saliva produced, possible interaction with denture adhesive, denture cleaning compounds, dryness of mouth due to other causes and salivary constituents. Should an excessive degree of stickiness to dental work occur, there is a possibility that as with other gums, Nicorette may damage dental work; if this should occur, the patient should discontinue its use and consult a physician or dentist.

The sustained use of Nicorette by ex-smokers is not to be encouraged because the chronic consumption of nicotine is toxic and addictive. The physician must, however, weigh the relative risks of a possible return to smoking versus continued, long-term use of the gum.

Information for the Patient: The patient instruction sheet is attached at the end of the professional labeling text. It is intended for detachment by the pharmacist and inclusion in the package of Nicorette dispensed to the patient. It contains important selected information on patient selection, risks and adverse effects and instructions on how to use Nicorette properly.

Drug Interactions: Smoking cessation, with or without nicotine substitutes, may alter response to concomitant medication in ex-smokers. Smoking is considered to increase metabolism and thus lower blood levels of drugs such as phenacetin, caffeine, theophylline, imipramine and pentazocine, through enzyme induction. Cessation of smoking may result in increased levels of these drugs. Absorption of glutethimide may be decreased, and the "first pass" metabolism of propantheline may be decreased by smoking cessation. Other reported effects of smoking, which do not involve enzyme induction, include reduced duration of tarsal conjunctival and nasal mucocutaneous output, and increased blood pressure with propantheline, which may also relate to the hemodynamic effects of nicotine. Smoking and nicotine can increase circulating cortisol and catecholamines. Therapy with adrenergic agonists or with adrenergic blockers may need to be adjusted according to changes in nicotine therapy or smoking status.

Carcogenesis, Mutagenesis, Impairment of Fertility: Nicotine was not mutagenic in the Ames Salmonella test.

Literature reports indicate that nicotine is neither an initiator nor a tumor-promoter in mice. There is inconclusive evidence to suggest that nicotine, an oxidized metabolite of nicotine, may be carcinogenic in rats. Cytidine was not mutagenic in the Ames Salmonella test.

Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilization.

Pregnancy: Nicotine is Category X. (See **CONTRAINDICATIONS**.)

Nursing Mothers: Nicotine passes freely into the breast milk. Because of the potential for serious adverse reactions in nursing infants from nicotine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children and adolescents who smoke have not been evaluated.

ADVERSE REACTIONS: Adverse reactions reported in association with the use of Nicorette include both local effects and systemic effects representing the pharmacological action of nicotine. Rare reports of an apparent severe allergic reaction have been received.

Local side effects: Mechanical effects of gum chewing include traumatic injury to oral mucosa or teeth, jaw ache, and eructation secondary to air swallowing. These side effects may be minimized by modifying chewing technique. Oral mucosal changes such as stomatitis, glossitis, gingivitis, pharyngitis, and aphthous ulcers, in addition to changes in taste perception, can occur during smoking cessation efforts with or without the use of Nicorette.

Systemic side effects: Although the systemic effects seen in trials were generally similar, the reported frequency of adverse drug effects was highly variable, as illustrated by the variation observed in adverse event incidences estimated from the results of two well controlled studies (one performed in the United States, and the other in England) designed to evaluate the safety and efficacy of Nicorette. (See table below.) Given this variability, the table can be used only as an indication of the relative frequency of adverse events reported in representative clinical trials. It can not predict expected incidences of these effects during the course of usual medical practice.

Treatment Emergent Symptom Incidence for the 2 mg Gum

Number of Subjects Reporting	Symptom Incidence for the 2 mg Gum			
	U.S.	British	Drug	Placebo
Percent of Subjects Reporting	94	95	58	58
Autonomic				
Excess Salivation	2.1	0.0		
CNS				
Insomnia	1.1	1.1		
Dizziness/Light-headedness	2.1	2.1	19.0	13.8
Irritable/Fussy	1.1	1.1		
Headache	1.1	5.3	24.1	29.3
Gastrointestinal				
Nonspecific GI Distress	9.6	6.3		
Eructation	6.4	1.1		
Indigestion	18.1	4.2	31.0	15.5
Nausea/Vomiting				
Mouth/Throat Soreness	37.2	31.6	56.9	53.4
Jaw/Muscle Ache	18.1	9.5	44.8	44.8
Other				
Anorexia	1.1	1.1		
Hiccups	14.9	0.0	22.4	3.4

The only potentially serious systemic adverse effect observed among the 152 patients evaluated in the controlled clinical trials used to support the efficacy of Nicorette was cardiac irritability; a patient displayed what may have been nicotine-induced, but reversible, atrial fibrillation. Cardiac irritability is a well known consequence of cigarette smoking.

A 46-year-old male patient participating in a clinical trial of Nicorette was reported to have developed nicotine intoxication requiring his hospitalization. He was discharged, fully recovered. He died suddenly one month later. Nicorette was being taken one month prior to his death. The cause of death is undetermined.

Since the marketing of Nicorette in the U.S., reports of several other deaths and reports including myocardial infarction, congestive heart failure, cerebrovascular accident and cardiac arrest have been received. A cause and effect relationship between these reports and the use of Nicorette has not been established.

In addition to the reported effects listed above, the following events have been reported: CARDIOVASCULAR—edema, flushing, hypertension, palpitations, tachyarrhythmias, tachycardia, CNS—confusion, convulsions, depression, euphoria, numbness, paresthesia, syncope, tinnitus, weakness. DERMATOLOGIC—erythema, itching, rash, urticaria. GASTROINTESTINAL—alteration of liver function tests, constipation, diarrhea. RESPIRATORY—breathing difficulty, cough, hoarseness, sneezing, wheezing, wheezing.

Rare reports of mesothelioma have been received, and a relationship to drug therapy as a contributing factor cannot be excluded.

DRUG ABUSE AND DEPENDENCE/OVERDOSE/TREATMENT OF OVERDOSE: For further information, please see full prescribing information.

DOSAGE AND ADMINISTRATION: Most patients require approximately 10 to 12 pieces of gum per day during the first month of treatment. Patients should be instructed not to exceed 30 Nicorette pieces per day. Patients should be assessed after one month of treatment to determine smoking status, and the use of Nicorette as an adjunct should be reevaluated. Gradual withdrawal from Nicorette should be initiated after 3 months' usage and completed by 6 months. The use of Nicorette beyond 6 months is not recommended.

Product Information as of May, 1989

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Innovators in nicotine reduction therapy

Study finds 75 cases of latex allergy in children

By Saralie Faivelson

ATLANTA—Months after Wisconsin physicians reported a cluster of anaphylactic reactions in children exposed to latex, a nationwide survey showed that the number of reported cases has climbed to 75.

"It appears that children with spina bifida and congenital urinary tract abnormalities are at increased risk for allergic reactions to latex," said Michele Pearson, M.D., a medical epidemiologist at the Centers for Disease Control.

A team of Wisconsin health experts reported the survey findings in a recent CDC Morbidity and Mortality Weekly Report.

Among patients with spina bifida or urinary problems, those with a history of allergy, asthma or repeated surgery face an even higher risk of allergic reaction, she said.

The cluster of 11 allergic reactions occurred at the Children's Hospital of Wisconsin in Milwaukee, according to Jeffrey Davis, M.D.

Ten of the patients had spina bifida, and one had a congenital genitourinary tract abnormality.

The children all reacted within minutes of exposure to latex, he said. It is not known whether the children reacted to latex present in surgical gloves, sheets used on operating tables, catheters or anesthesia circuitry, Dr. Davis said.

Ten of the 11 patients reportedly had skin and in vitro tests suggesting latex allergy.

The nationwide survey of children's hospitals showed that 25 other institutions have reported allergic reactions in about 75 patients since January 1990.

As in the Wisconsin cases, the children had either spina bifida or genitourinary tract infections, according to the CDC report.

Physicians at the Wisconsin hospital now administer H₂-blockers, corticosteroids, and diphenhydramine hydrochloride during the 24 hours before and after all surgical procedures on all patients with spina bifida or congenital genitourinary dysplasia, according to Dr. Davis.

Physicians also are advised to use non-latex products on sensitive patients and to wipe and wash surgical gloves with water before a procedure, Dr. Pearson said.

"The powder on the gloves may release the latex proteins that cause the reaction," she said.

Patients should watch for the symptoms of latex allergy and report them to their doctors, Dr. Pearson said.

Swollen lips, runny nose or tearing eyes after handling balloons may signal a latex allergy.

Irritated, reddened skin, cracks in the skin or blisters after using



Latex in gloves, sheets or anesthesia tubing may cause anaphylaxis.

rubber household-cleaning gloves also may suggest signs of a latex allergy, she added.

Physicians are requested to report all episodes of anaphylaxis during procedures requiring gen-

eral anesthesia through state health departments to the Epidemiology Branch, Hospital Infections Program, at the CDC's National Center for Infectious Diseases (404) 639-1550, according to the MMWR.

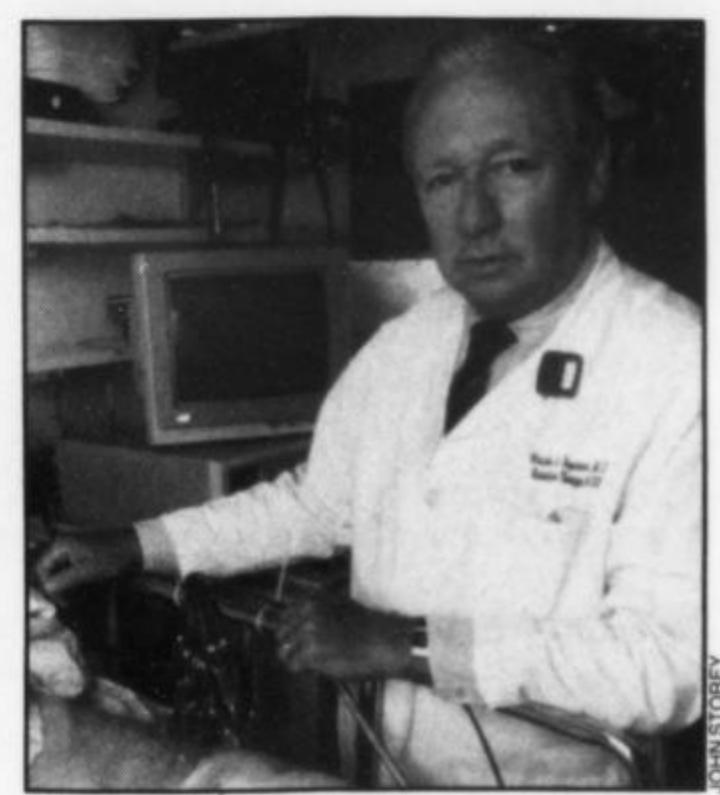
Aspirin cuts preeclampsia

Low-dose aspirin may reduce the risks of pregnancy-induced hypertension (PIH) and severe low birth weight, Ohio researchers report.

An analysis of six trials showed that women at high risk of PIH, also called preeclampsia, who took 60 to 150 mg of aspirin every day during the second and third trimesters reduced their risk of the condition by up to 65%.

Aspirin also cut the risk of severe low birth weight by 44%, Cleveland researchers reported in the Journal of the American Medical Association.

"There's no doubt that aspirin is helpful in women at high risk for PIH, but do the benefits outweigh the risks for low-risk women?" said James M. Roberts, M.D., of the University of California at San Francisco. "Aspirin inhibits prostaglandins, which are important in terms of fetal homeostasis."



Computer controls procedure.

Gland cancer halted by heat and radiation

SEATTLE—Complete responses of advanced non-metastatic prostate cancer have been reported via external beam radiation, interstitial implants and radiofrequency hyperthermia.

The eighteen previously untreated patients in the study given the combination therapy remain free of clinical disease, said Don Goffinet, M.D., of Stanford University.

Follow-up has ranged from one month to six years—too short to claim an advantage over radiation therapy alone, Dr. Goffinet said.

However, "if a larger experience confirms our results, interstitial hyperthermia could become the treatment of choice," he reported at a recent conference at the Swedish Hospital here.

The combination treatment may hold more promise than radiation alone for patients with carcinomas that are very advanced, but have not spread beyond the gland.

"We weren't satisfied with the results of standard external beam radiation," said Malcolm Bagshaw, M.D., also of Stanford. "So about six years ago we supplemented it by adding an interstitial implant of 192-iridium."

The computer-controlled procedure takes several days from start to finish, according to Dr. Goffinet.

Recently, the procedure made national headlines when Senator Alan Cranston (D-Calif.), a patient of Dr. Bagshaw, praised the treatment for eliminating his tumor.

William Catalona, M.D., of Washington University School of Medicine in St. Louis, said he is "not too enthusiastic" about the procedure. "I don't think it can kill every cell. In my opinion, it won't withstand the test of time."

E. Darracott Vaughan, M.D., chairman of urology at Cornell University Medical School in New York, said, "I would be terribly cautious. Our experience here with iodine [radioisotope] implantation was better; eight years after the procedure many patients had recurrences."

Correction

In the story "Antibiotics tested for periodontitis" in the June 13 issue, John Riebler III, M.D., associate director of medical development for Lederle Laboratories, was misquoted regarding the status of the company's antibiotic minocycline. Phase III plans for the drug are on hold indefinitely.

in Their Blood...

■ In the average smoker (20 to 30 cigarettes a day), physiologic nicotine addiction is reinforced with every cigarette



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

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CDC report: too many Rh-negative infants die

ATLANTA—Although the number of infants with Rh hemolytic disease has dropped sharply, too many babies are born with the potentially fatal genetic condition, according to government researchers.

Preventive therapy is available, but not used widely enough, said Gilberto Chavez, M.D., of the Centers for Disease Control.

He reported his findings in a recent issue of the Journal of the American Medical Association.

Rh hemolytic disease affected about 11 babies per 10,000 in 1986, down from 45 babies per 10,000 in 1970, according to Dr. Chavez.

But even that decrease is not enough, he said. "It's totally unnecessary that so many babies should be born with Rh disease. With the therapy we have today, the rate should be no higher than three per 10,000," he said.

"The rate of Rh babies has probably decreased since 1986, but it's still too high," agreed Sherwin Kevy, M.D., director of Transfusion Services at Children's Hospital in Boston.

There are marked differences in the rate of hemolytic disease in var-



Women need more access to preventive therapy for hemolytic disease.

ious areas of the country, according to Dr. Kevy. "New England physicians started giving women antenatal Rh(D) immune globulin in 1979, about five or six years before it was routinely recommended by ACOG, so rates of Rh hemolytic disease are lower here," he said.

Pregnant Rh negative women should be identified and given im-

mune globulin at 27 or 28 weeks, Dr. Kevy said. "An Rh negative woman who had a miscarriage or tubal pregnancy should be given immune globulin unless you're sure the father is negative," he added.

"Pregnant women, especially poor pregnant women, need better access to preventive therapy," ac-

cording to Dr. Chavez.

Drugs cut migraines in children

WASHINGTON—Two drugs may reduce the painful, often debilitating migraine attacks suffered by children.

Thirty children, aged five to 12, suffering from recurrent migraines were given either amitriptyline, propranolol or cyproheptadine on a daily basis for three months, according to Bennett Lavenstein, M.D., of Georgetown University in Washington, D.C. Children kept headache diaries listing frequency, intensity and duration of attacks.

Children receiving either amitriptyline or propranolol reported moderate to excellent improvement; the group on cyproheptadine reported only moderate to minimal improvement, which decreased in children older than nine.

Dr. Lavenstein presented his findings here at the 5th International Headache Congress meeting.

Between 4% and 8% of pre-teenage children may have migraines, researchers report.

Vitamin reduces nausea, vomiting

IOWA CITY—Vitamin B₆ may reduce nausea and vomiting during the first few months of pregnancy, a study suggests.

Thirty-one pregnant volunteers received 25 mg of vitamin B₆ every eight hours for three days, and 28 patients received placebo in the same regimen.

Fifteen of 31 patients in the vitamin B₆-treated group had vomiting before therapy, compared with 10 of 28 placebo-treated patients.

After therapy, only eight of 31 patients in the vitamin B₆ group had any vomiting, compared with 15 of 28 patients in the placebo group, reported researchers here at the University of Iowa College of Medicine.

Overall, the mean "difference in nausea" score in patients with severe nausea and the total number of patients with vomiting were significantly reduced following vitamin B₆ therapy, wrote study leader Vicki Sahakian, M.D., in a recent issue of the journal *Obstetrics and Gynecology*.

Women with mild to moderate nausea before therapy did not show significant improvement, Dr. Sahakian reported.

Vitamin B₆ has been shown to reduce nausea and vomiting in pregnancy in a handful of small studies, according to Dr. Sahakian, but the Iowa study was the first to compare treatment with vitamin B₆ versus a placebo.

The recommended daily allowance of B₆ for pregnant women is 2.2 mg a day, and for non-pregnant women who are not nursing, 1.6 mg a day.

Vitamin supplements would be needed to get the equivalent amount of B₆ consumed by the women in the study.

To reduce nausea and vomiting, Dr. Sahakian also recommended dividing food intake into frequent small meals that are rich in carbohydrates and low in fat. He warned against the use of iron tablets, which often cause nausea.

Judith Brown, a maternal-nutrition expert at the University of Minnesota in Minneapolis, cautioned that very little is known about the long-term side effects of the vitamin.

Thus, it may be prudent to follow the researchers' dietary recommendations before self-medication with vitamin B₆, she said.

Study ties thiazides to increased risk of hip fractures

SEATTLE—Some antihypertensive drugs may increase the risk of hip fractures in the elderly, Washington researchers reported.

In a study of 462 elderly hospital patients, those given thiazide diuretics had a 60% greater risk of hip fracture, while furosemide users had a four-fold risk over non-users.

Findings spur disagreement

modestly increase the risk for fracture," Dr. Heidrich said.

Hydrochlorothiazide and chlorothalidone accounted for 93% and 7% of all thiazide prescriptions, respectively, he reported.

The study did not show why patients taking thiazide diuretics and furosemide experienced an increased number of fractures. The thiazides may cause problems because the drugs cause fainting spells, leading to falls and fractures, Dr. Heidrich said.

Patients given diuretics were also more apt to trip and fall during frequent trips to the bathroom, he said.

Unlike thiazides, furosemide promotes calcium excretion by the kidney, and therefore may place users at an increased risk for hip fracture, Dr. Heidrich.



Elderly patients on diuretics had a 60% greater risk of hip fractures.

"I don't think thiazide increases the risk of fracture," said Joseph Zerwekh, Ph.D., of the University of Texas Southwestern Medical Center in Dallas. "A good randomized placebo trial of bone density hasn't been done. I wouldn't hesitate to give thiazide based on this report."

A UW researcher disagrees. "Even though you could get a beneficial effect on bone mass, it may not be as important as not having to get up at night and taking a fall," said Charles Chestnut III, M.D., director of the osteoporosis clinic at the University.

Unvaccinated travelers found at risk

Many travelers lack immunity against polio, measles, tetanus and other vaccine-preventable diseases, putting them at risk when visiting developing countries, according to a new study.

Twenty-eight of 233 people visiting a travel clinic were found to have inadequate immunity against polio, according to Eileen Hilton, M.D., of the Long Island Jewish Medical Center in New Hyde Park, N.Y.

"Polio outbreaks still occur in underdeveloped countries," she reported in a recent issue of the Annals of Internal Medicine.

All adults should have completed a primary series of polio vaccinations, consisting of three doses of vaccine, said Dr. Hilton, who added that adults ought to receive a polio booster before traveling to countries where the disease is prevalent.

The elderly were more likely than younger people to lack immunity to tetanus, Dr. Hilton said, adding that all people should receive tetanus boosters every five years. The CDC recommends boosters every ten years.

The study also found that adults born after 1956 were less likely to have immunity against measles and mumps.

These people should therefore receive additional measles, mumps and German measles vaccines before travel, Dr. Hilton said.

10 Questions you should ask before purchasing practice management software.

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* The antihypertensive effect may diminish at the end of the dosing interval.

Please see adjacent page for brief summary of prescribing information.



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Medicare payments limit erythropoietin treatment

WASHINGTON—Many kidney dialysis patients may not be receiving adequate doses of a drug that lowers their risk of developing anemia and reduces their need for drug transfusions, a government report found.

By August 1990, less than 45% of dialysis patients receiving erythropoietin for six months or longer showed a significant increase in the number of red blood cells, according to researchers from the Office of Technology Assessment, a congressional agency that assesses the effectiveness of government programs.

Erythropoietin, made by Amgen Inc., is a genetically engineered compound that stimulates red blood cell production.

Medicare's low payments for the drug discourage dialysis centers from using sufficient doses, and prevents adequate dosage monitoring of patients, the researchers wrote in the *Journal of the American Medical Association*.

The researchers found that doses of erythropoietin averaged 2,700 units at dialysis facilities, while the indicated dosage is 3,400 to 6,800 units per treatment.

In 1989, the Health Care Financing Administration said that it would pay for treatment for patients with a red cell count of less than 0.30. The approved amount would be \$40 for doses of 10,000 units or less and \$70 for higher doses.

Amgen Inc. set its price to wholesalers at \$10 per 1,000 units.

The fixed rate per treatment pressured providers to control or "even



Many dialysis patients are receiving insufficient erythropoietin doses.

skimp on the dose," according to the researchers.

The annual cost for a patient receiving three treatments each week was \$6,240 of which Medicare paid 80% or \$4,992 and the patient was billed for the balance.

Since its initial approval of the drug, the FDA has approved it for treatment of anemia in predialysis patients and for AIDS patients whose anemia is a side effect of receiving zidovudine. In both instances the payment rate is the same.

Although Medicare changed its payment method in January to pay providers more for the drug, it still does not cover the expenses of administering it, such as the use of staff and syringes, according to the

researchers. That resource cost could be as much as \$4 a treatment.

To assure quality, such as adequate dosage, the authors conclude that Medicare payment should factor in the resource cost.

"The brief history of the biologic also demonstrates the need for federal policy makers to recognize the incentives of their payment policies and to establish mechanisms to monitor undesirable effects and to counter them if necessary," they wrote.

Because fewer than 45% of patients reached the target hematocrit, "increased doses for many patients would be expected to improve patient response and to constitute better quality care," the researchers said.

Malpractice pay system proposed

WASHINGTON—Injured people in malpractice cases involving childbirth would receive their awards much faster if states instituted a new system where payments for certain injuries are made without going to trial, a report said.

Beyond providing prompt, fair compensation for injuries, the proposed system, described in a recent issue of the *Journal of the American Medical Association*, would provide data that would help doctors prevent injuries, and would reduce administrative costs of malpractice claims.

The system "offers a major improvement for handling obstetrical injuries for practitioners and patients alike," said Randall Bovbjerg and Daniel Gaylin of the Washington-based Urban Institute and Laurence Tancredi of the University of Texas Health Science Center at Houston.

Currently, the average delay between injury and completion of the case is almost three years, and the average case costs \$13,000 to resolve.

Under the system most obstetric cases would not go to trial. Instead, medical experts would develop a list of easily identifiable, preventable injuries, and victims suffering from those injuries would be compensated quickly, without a trial.



More physicians are turning away from family medicine.

Ways to draw MDs to primary-care field

Unless more doctors start to practice family medicine instead of becoming specialists, health care will remain out of reach for poor Americans, a government report suggests.

The federal government could improve the situation by helping medical schools expand their family medicine-training programs and offering financial incentives to primary-care residents, said Robert Politzer of the Department of Health and Human Services (HHS) in Rockville, Md. He presented his views

generalists are concentrating in large academic health centers," Politzer wrote.

To halt the steady decline of primary-care doctors, HHS developed seven recommendations designed to attract more residents to the primary-care field:

- Establish medical-school scholarship and loan-repayment programs in underserved areas that need primary-care doctors.
- Incorporate primary-care training programs with graduate medical studies.
- Give medical school admission preference to those planning to specialize in primary care.

HHS suggests promoting more research

in a recent issue of the *Journal of the American Medical Association*.

The past 20 years have seen a growing imbalance between the number of doctors training in primary-care fields like family medicine and those training in specialties, such as orthopedic surgery or obstetrics/gynecology, he said.

"Experts believe the situation will deteriorate because interest in primary-care careers, both by pre-medical students and by medical students, is waning," said Politzer.

"Physicians are choosing high-paying, technology-based specialties in place of the primary-care specialties, particularly general/family practice," he said.

"Rather than moving into underserved or unserved areas, even

physicians are turning away from family medicine," Politzer said.

• Promote clerkships in primary care to third-year undergraduate medical students who have not yet chosen a specialty.

• Promote primary-care research.

• Train and develop community-based faculty in primary-care medicine.

• Establish financial incentives for graduate primary-care training.

In the early 1980s, nearly 40% of graduating seniors chose primary-care careers. By 1989, that percentage had dropped to about 25%, the report said. A 77% increase in the number of general internists is expected between 1978 to 1998, along with a 20% rise in the number of subspecialty internists, Politzer said.



Airbags can prevent damage to the aorta, the surgeons said.

Surgeons see need for stricter highway laws

Surgeons should push lawmakers to pass stricter laws on airbags, seatbelt restraints and drunk driving to prevent motor vehicle deaths, according to a vascular surgery group.

Studies suggest that the high-velocity impact of the body against a dashboard can cause damage to the aorta, said Francis Duhaylongsod, M.D., a vascular surgeon at Duke University Medical Center in Durham, North Carolina.

"Preventative measures such as mandatory seatbelt restraints, driver's side airbags and drunk driving laws may ultimately hold the solution to the lower incidence" of damage to the aorta, said Dr. Duhaylongsod.

Dr. Duhaylongsod and his associates examined all patients brought to the Duke center in Durham, N.C., from 1970 to 1990.

Comparing the 1970s with the 1980s, they found a 50% increase in the number of aortic injuries. More women have the damage though they are still outnumbered by men three-to-one.

ZESTRIL® (lisinopril)

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: ZESTRIL® is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has been associated with a disulfiram-like reaction or liver damage or collagen vascular disease.

WARNINGS: Angioedema: Angioedema of the face, extremities, lips, tongue, glottis and/or eyes has been reported in patients treated with other ACE converting enzymes, including ZESTRIL. In such cases, ZESTRIL should be promptly discontinued and appropriate therapy initiated to relieve symptoms and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with ZESTRIL may be similar to that associated with other ACE inhibitors.

Fetal/Neonatal Mortality and Mortality: ACE inhibitors, including ZESTRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Hypotension: Hypotension was rarely seen in these treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia. If hypotension occurs, discontinuation of ZESTRIL should be started under very close medical supervision. Such patients should be followed closely for the first 6 weeks of gestation and whenever the dose of ZESTRIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty.

Hepatotoxicity: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of ZESTRIL are insufficient to determine whether ZESTRIL causes agranulocytosis and bone marrow depression in which a causal relationship to lisinopril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Fetal/Neonatal Mortality and Mortality: ACE inhibitors, including ZESTRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Lisinopril crosses the placenta. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypertension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has been associated with oliguria and/or death in the newborn. There have been reports of oligohydramnios and renal tubular acidosis in association with ZESTRIL.

Other: ZESTRIL should be discontinued if the patient becomes pregnant while taking ZESTRIL. The patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ZESTRIL should be monitored carefully and discontinued if necessary.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually transitory and resolve after discontinuing ZESTRIL or other drugs containing ACE inhibitors.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine and/or transient oliguria and/or anuria. This may be associated with an increase in serum potassium.

This is more likely to occur in patients with preexisting renal impairment. Duration of therapy should be limited to 2 days.

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Fiber-optic technology allows doctors to consult by computer Imaging software speeds care

By Brianna Politzer

Four Boston hospitals and a telephone company are using fiber-optic telephone networks to transmit and share patient records with attached radiological images.

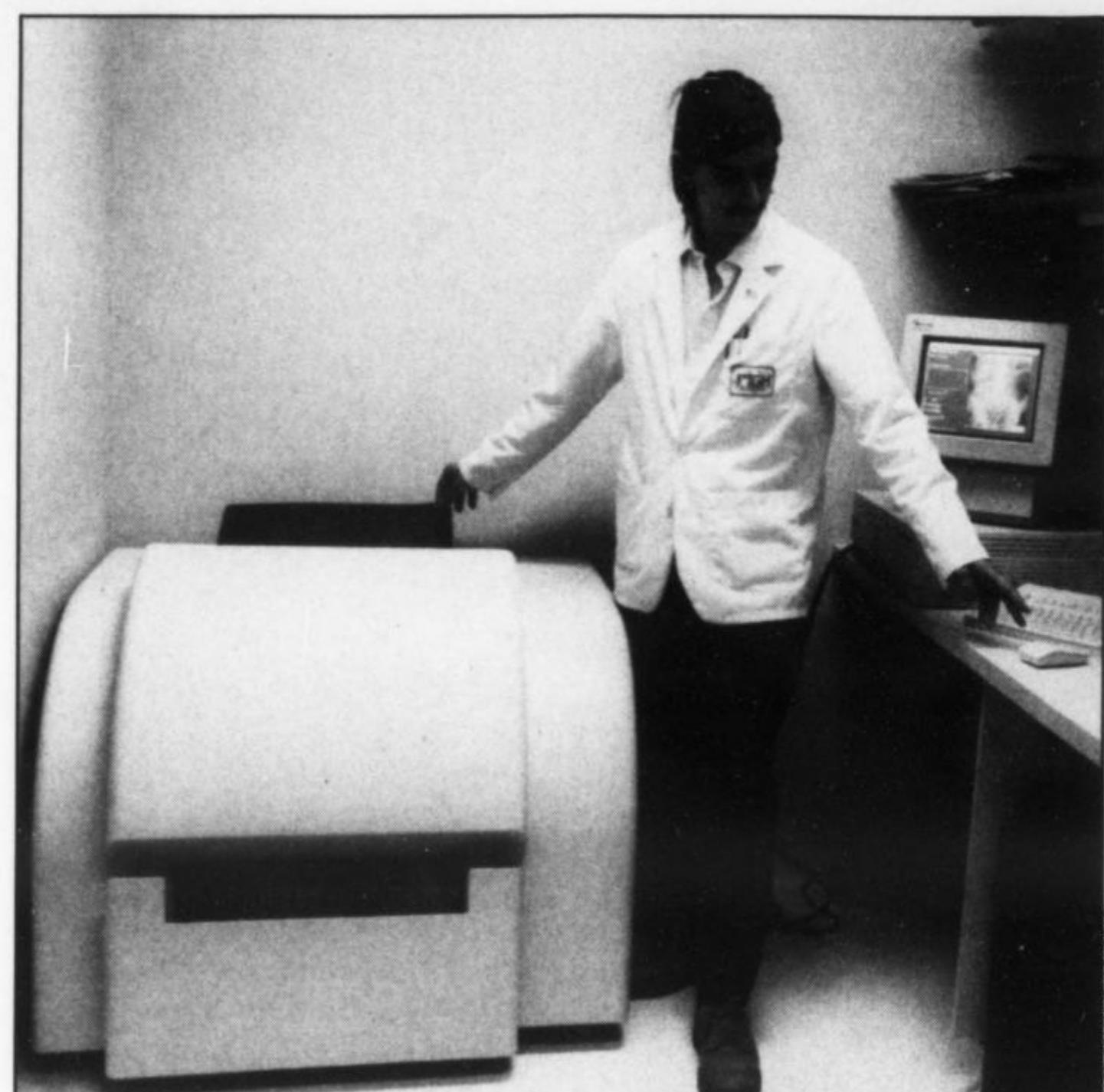
The new software will allow physicians to send a complete patient file to several other specialists, or to view and discuss CT-scans, MRIs and PET scans via computer with two or more colleagues at the same time.

"Radiology today is just like the circular memo," said Jaime Taaffe, director of computing in the department of radiology at Massachusetts General Hospital in Boston, referring to the type of memo circulated through an office and initiated by each reader.

Only a third of the staff who want to see a particular film can do so on the day it's taken because the original can only be in one place at one time, said Taaffe. "If we can make instant electronic copies, we can send them anywhere in the hospital, the country or the world."

The high-tech networks allow complicated radiological images to be transmitted accurately and almost instantaneously.

Massachusetts General, along with The Children's Hospital, New England Medical Center and Brigham and Women's Hospital, are working with New England Telephone, a Nynex subsidiary, to develop three computer-software programs, according to Jim Robin-



Technician inputs x-rays into a scanner to be viewed on computer.

son, a project manager for Nynex Science and Technology, Inc.

In a project called Media Broadband, an application named Report allows a physician to create a computerized patient record, according to Robinson.

The doctor may enter details of a patient visit, including relevant history from past visits. Radiological or nuclear-medicine images are scanned into the computer, where they can be enhanced and magnified to best highlight the site of a lesion.

Once image and patient data have been combined, the physician can add a recorded voice message to the file.

The message can be routed electronically to a transcriptionist, and later entered into the file as text.

The completed report file may be stored for later use by the physician, or may be sent as electronic mail to other specialists who wish to view it. When others later retrieve the file, they use the Review application to read the text, view the im-

ages and even play back the physician's recorded voice annotation, Robinson said.

Finally, the Consult program sends files over fiber-optic telephone networks to allow two or more physicians to view the electronic patient record simultaneously on their computer screens while discussing the case over the telephone.

The consulting physicians can use colored electronic pointers to zero in on sites of interest on the radiological image.

"If Media Broadband is implemented smoothly and if it works as we envision it, it will change the practice of imaging," said Ted Treves, M.D., chief of the division of nuclear medicine at The Children's Hospital. "It will be easier to transform information into knowledge. We can get to the point quicker and better, and hopefully, better action will follow."

The project is in its second year and is in different stages of development at each hospital.

Many hospitals would probably be interested in implementing the Media Broadband technology if it proves cost-effective, if the products are sufficiently standardized and if reliable technical support is available, according to Dr. Treves.

"Medical imaging has grown so fast that the mechanisms for managing that information haven't caught up with the technology," he said. "We should take the opportunity to improve the management of the information and make it more streamlined, more efficient."



Patients discharged from hospitals early heal as fast at home.

DAVID TOWARD/CHICAGO

Recovery not linked to time in hospital

It is possible to reduce the amount of time in the hospital without compromising the health and safety of patients, according to a study of hospitals in California and Massachusetts.

Shorter hospital stays also may help contain skyrocketing healthcare costs, according to Paul Cleary, Ph.D., of Harvard Medical School in Boston, author of the study which appeared in a recent issue of the Journal of the American Medical Association.

Researchers from six teaching hospitals in Boston and San Francisco studied 2,484 people hospitalized for acute myocardial infarction, coronary artery bypass graft surgery, total hip replacement, cholecystectomy or transurethral prostatectomy.

They reviewed patients' medical records and surveyed patients between 3 and 12 months after being discharged.

Despite significant differences in length of hospital stay for almost all conditions, the patients' recovery or probability of being readmitted did not improve or worsen, regardless of the time spent in the hospital, Cleary said.

Lengths of stay were similar only among severe heart-attack patients, Cleary reported.

For coronary bypass and gallbladder removals, longer hospital stays actually were linked to less improvement in health, he said.

A separate study, reported in the same issue of the journal, found that the majority of people with chronic lung disease were kept in the hospital for a longer period of time than was medically necessary.

Researchers found that after six days in the hospital, 90% of patients were free of complications or the need for doctors' supervision, yet 16 days passed before the patients were discharged.

Hypertension drug aimed at elderly

WASHINGTON—The antihypertensive drug Lotensin recently approved by the Food and Drug Administration, will be targeted for use in elderly patients when it is launched later this month, manufacturer Ciba-Geigy Pharmaceuticals said.

The drug, a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor, effectively lowers both diastolic and systolic blood pressure, Ciba-Geigy said.

The drug's package insert, which includes information on the product's safety and efficacy in elderly patients, is one of the first to reflect some of the FDA's new geriatric labeling requirements.

Lotensin was evaluated for interactions with many medications often prescribed to older hypertensives.

The drug showed no evidence of clinically important interactions with digoxin, warfarin, naproxen, cimetidine and hydrochlorothiazide, the company said.

The recommended initial dose for patients not receiving a diuretic is 10mg a day.

In addition, data from Lotensin clinical trials showed no correlation between a patient's age and the incidence of side effects commonly associated with antihypertensive agents, Ciba-Geigy said.

Franz Messerli, M.D., a physician at the Ochsner Clinic in New Orleans and a former FDA advisory committee member, said the drug doesn't really offer distinct advantages over other ACE inhibitors currently on the market.

He said Ciba-Geigy is simply the first drug company to conduct safety and efficacy studies specifically on groups of older patients. "All ACE inhibitors are excellent drugs for use in the elderly," Dr. Messerli said.

The other ACE inhibitors approved for use in hypertension are captopril (Capoten, Squibb) and Enalapril (Vasotec, Merck Sharp & Dohme).

Zantac® 150 Tablets (ranitidine hydrochloride)

Zantac® 300 Tablets (ranitidine hydrochloride)

Zantac® Syrup (ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated:

1. Short-term treatment of active duodenal ulcer. Most patients heal within four weeks.
2. Short-term therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer. Most heal within four weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of gastroesophageal reflux disease (GERD). Symptomatic relief commonly occurs within one or two weeks after starting therapy and is maintained throughout a six-week course of therapy.

Inactive duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to be hypersensitive to the drug.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy. 2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.) Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein

Multistix® may occur during Zantac therapy, and therefore testing for albumin and glucose should be repeated.

Drug Interactions: Although recommended doses of Zantac do not inhibit the action of cytochrome P-450 enzymes in the liver, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism yet to be determined (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of harm to the fetus due to Zantac. 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: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.

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

ADVERSE REACTIONS: Headache, sometimes severe, seems to be related to Zantac® administration. Diarrhea, nausea, vomiting, abdominal discomfort, and, rarely, pancreatitis have been reported. There have been rare reports of malaise, dizziness, somnolence, insomnia, vertigo, tachycardia, bradycardia, atrioventricular block, premature ventricular beats, and fibrillations. Rare cases of peripheral neuropathy, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

In normal volunteers, SGOT values were increased to at least twice the normal range in 1 of 12 patients receiving 150 mg oral Zantac® intravenously for seven days, and in 4 of 24 subjects receiving 50 mg orally for five days. There have been occasional reports of hepatitis, hepatocellular or hepatocarcinomatous or mixed, with or without cirrhosis. In such circumstances, ranitidine should be immediately discontinued. (See CONTRAINDICATIONS.)

Incidents of rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia, have been reported, as well as rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small bowel obstruction.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)

Causes of Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage for patients with a creatinine clearance less than 50 ml/min is 150 mg or 10 ml (2 teaspoonsfuls equivalent to 150 mg of ranitidine) orally once daily. Dosage may be increased to 300 mg (30 ml) orally once daily if necessary. The frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of the next dose coincides with the end of hemodialysis.

HOW SUPPLIED: Zantac® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-30) tablets and unit dose packages of 100 (NDC 0173-0393-47) tablets.

Zantac® 300 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packages of 100 (NDC 0173-0344-47) tablets.

Storage: Store at 15° and 30° C (59° and 86° F) in a dry place.

Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 ml. bottle of 16 fluid ounces (one-half liter) (NDC 0173-0344-54).

Storage: Store at 25° C (77° F). Dispense in light,

light-resistant containers as defined in the USP/NF.

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Glaxo Pharmaceuticals™
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

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One Of A Kind



Zantac®
ranitidine HCl/Glaxo 150 mg and
300 mg tablets

Please see Brief Summary of Prescribing Information on adjacent page.

Glaxo/ROCHE

Semi-synthesis technique shows promise Taxol ready in 2 years

Continued from page 1

School of Medicine in Baltimore, Md., also has sobering longer-term survival data.

In 1989, Dr. McGuire reported that 12 of 48 patients with refractory ovarian cancer (30%) responded to taxol (at least 50% tumor shrinkage) for periods of from three to 15 months.

To date, all but two of the patients are dead, a Johns Hopkins spokesperson said.

Taxol, currently in stage III clinical trials, will prove most effective when it can be combined with other anti-cancer drugs, according to Saul Shepartz, Ph.D., of the National Cancer Institute in Bethesda, Md.

Earlier, Dr. Shepartz said taxol "is probably the best drug for cancer that we've seen in the last 10 to 15 years."

However, obtaining enough taxol to complete Phase III trials has proven difficult.

Using ordinary extraction methods, it takes the bark from six 100-year-old Pacific yew trees to supply enough taxol to treat just one patient.

Commercial quantities are anticipated by ESCAgenetics Corp., of San Carlos, Calif., which is pursuing a cell-culture technique.

Cuttings from the Pacific yew are stimulated to form cells, which in turn are cultured in a fermentation process.

But fermentation tanks the size of small buildings are required. Moreover, ESCAgenetics may be infringing on a cell-culture patent recently awarded to the U.S. Department of Agriculture, which also



Robert Holton has been granted a patent for his synthesis technique.

anticipates the commercial production of taxol.

Donna Gibson, a USDA biologist and joint holder of the patent, said the ESCAgenetics process sounded "very familiar." But the West Coast biotechnology company maintains its work is unique.

In any case, USDA patent attorney Howard Silverstein said that even if ESCAgenetics is in violation, the government might blink at it to expedite taxol production.

The taxol production patent may mark the first time the government has tried to balance a public health concern against potential profit, said Silverstein.

USDA has licensed its patent to Phytoncatalytic of Ithaca, N.Y. Florida State University chemistry professor Robert Holton also received a patent—for a semi-synthetic method of producing taxol.

One is aimed at scaling up for commercial production of taxol and the other is a 5-year \$1.5 million research grant to Holton to produce taxol through semi-synthesis.

A Bristol-Meyers spokesperson said the company believed it would take two years to make the Holton method commercially viable.

MDs irked by fee plan

By Jane Anderson

WASHINGTON—Physicians outraged with the Health Care Financing Administration proposed plan for the new Medicare fee schedule are flooding HCFA with letters protesting the deep cuts planned.

HCFA has received more than 1,000 letters so far from doctors protesting the proposal, which would increase fees for general and family practitioners by about 15% while cutting reimbursement for every other specialty.

HCFA will accept comments on the plan until Aug. 5, and expects to issue the final implementation plan in late October to take effect Jan. 1, 1992.

Many physicians say the government has broken its agreement with medicine to implement the fee schedule fairly; others maintain they'll have to stop treating Medicare patients if the proposal takes effect.

Grattan Woodson, III, M.D., a general internist in Decatur, Ill., protested HCFA's assumption that physicians will make up 50 cents of every dollar they lose under the fee schedule.

"It is ludicrous to assume that physicians are going to increase their volume of intensity of services they provide to Medicare patients when they are already at maximum production," said Dr. Woodson.



The new Jarvik 2000 is monitored in a calf by Dr. Jarvik (left).

Jarvik device may cut hemolysis, clotting risk

Continued from page 1

a small amount of blood in between the rotary blade and its bearing wire to act as a natural lubricant. "This blood wash reduces the joint friction and coagulation usually seen with rotary devices," he said.

An artificial lubricant is used in both the Novacor LVAD, made by the Novacor Co., Oakland, Calif., and the HeartMate LVAD, produced by Thermo Cardiosystems Inc., Woburn, Mass.

Another advantage of the Jarvik 2000 is a coupling from the power pack that is pasted to the surface of a "skin button" on the sternum. The coupling completes a circuit with coils underneath, powering the pump without piercing the skin and guarding against infection, according to Dr. Jarvik.

"That's just a copy of our design," said Victor Poirier, president of Thermo Cardiosystems.

"They may show feasibility for a week with their device, but they are liable to run into trouble long-term."

Thermo Cardiosystems' HeartMate models have been used as "bridges" in 41 patients awaiting heart transplants. Thirty have survived more than two months. The longest duration is 300 days.

Eighty-four patients have received Novacor devices, one for 370 days before transplantation, according to Leslie Miller, M.D., director of heart transplantation at St. Louis (Mo.) University Medical Center.

In January 1990, the FDA barred the Jarvik 7 from further study, citing poor quality control and research deficiencies.

Of five patients put on the Jarvik 7 as a sole survival device, the longest duration was 620 days. Of 118 patients supported by it as a "bridge," 10 suffered strokes; 66 lived at least a year.



High-definition TV allows better view of surgical procedures.

HDTV aids surgery with finer detail

Continued from page 1 during a coronary angiography procedure enough to make immediate therapeutic decisions possible, according to Robert Levine, M.D., of the Mount Sinai School of Medicine in New York.

"As a foundation technology it has applications in all areas of medicine as it does in other industries," said the cardiologist.

Angioscopy, for example, could benefit from high-definition technology, said Dr. Levine, a consultant for REBO.

Dr. Smith admits he doesn't know what role high-definition television will play in the operating room. "It doesn't allow me to do anything that I couldn't do before," he said. "I'm speaking within my specialty. I don't know if that kind of a picture is absolutely necessary for endoscopy."

High-definition television may be more useful in teaching open surgical methods, Dr. Smith said. "I think it has a lot of potential, but its full potential has not been evaluated at the present time."

He cited difficulty suspending the 29-pound camera as a limitation.

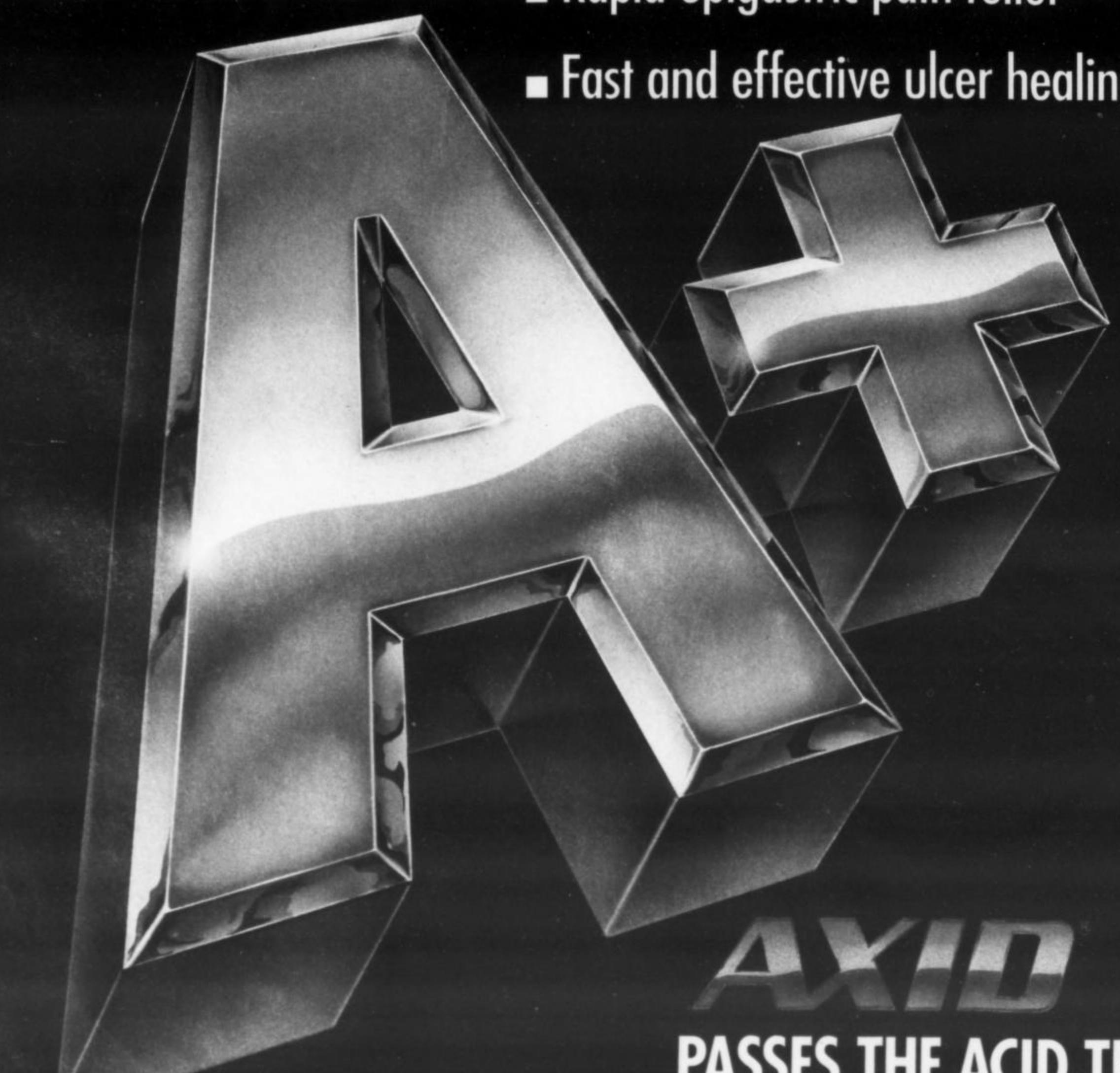
Researchers were slated to show high-definition television pictures of the endoscopic surgery at the Third World Congress of Videourology in Hakone, Japan.

Sony Advanced Systems in Teaneck, N.J., made the camera, videotape recorder and the tape that was used in surgery. Sony Medical Electronics Division in Montvale, N.J., and TTI Medical in Pleasanton, Calif. made the adaptor that connects the camera to the telescope.

For excellent response in the treatment of duodenal ulcers...

AXID nizatidine
has the right answers

- Rapid epigastric pain relief^{1,2*}
- Fast and effective ulcer healing^{2,3,4}



PASSES THE ACID TEST

*Most patients experience pain relief with the first dose.
See adjacent page for references and brief summary of prescribing information.

NZ 2930-T-049351

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AXID® (nizatidine capsules)

Brief Summary. Consult the package literature for complete information.

Indications and Usage: 1. Active duodenal ulcer—for up to 8 weeks of treatment. Most patients within 2 weeks.

2. Maintenance therapy—for treated duodenal ulcer patients at a reduced dosage of 150 mg b.i.d. The consequences of therapy with Axid for longer than 1 year are not known.

Contraindications: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: General: 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with hepatic dysfunction and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests: False-positive tests for urolinol with Multistix® may occur during therapy.

Drug Interactions: No interactions have been observed with theophylline, chloramphenicol, ibuprofen, lidocaine, phenytoin, and warfarin. And does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of axid, increased serum lactate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of heterochromatin-like (ECL) cells in the gastric oxytic mucosa. At a 2-year dose, however, there was no evidence of evidence of mild liver injury (transaminase elevations). The occurrence of a marginally significant effect in the rat liver may be due to a negative mutagenicity battery. It is not known whether nizatidine can cause a carcinogenic effect in rats, mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and female mice (given up to 360 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other tissues. The maximum dose tested in the rat liver was within the historical control limits seen for the strain of mice used. The female mice given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginally significant effect in the rat liver may be due to a negative mutagenicity battery. It is not known whether nizatidine can cause a carcinogenic effect in rats, mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and female mice (given up to 360 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other tissues. The maximum dose tested in the rat liver was within the historical control limits seen for the strain of mice used. The female mice given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginally significant effect in the rat liver may be due to a negative mutagenicity battery.

Pregnancy: In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 150 mg/kg/day provided no adverse effects on the reproductive performance of parental animals.

Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect.

At a dose equivalent to 20 mg/kg/day, nizatidine was no teratogenic in rats, rabbits, and mice. All abnormal developmental findings in rats and mice were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other tissues. The maximum dose tested in the rat liver was within the historical control limits seen for the strain of mice used. The female mice given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginally significant effect in the rat liver may be due to a negative mutagenicity battery.

Nursing Mothers: Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups noted by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

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

Use in Elderly Patients: Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities.

Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of varying durations included almost 5,000 patients.

Among the more common adverse events in domestic placebo-controlled trials of over 1,900 nizatidine patients and over 1,300 on placebo, sweating (1% vs 0.2%), urticaria (0.5% vs 0.1%), and somnolence (2.4% vs 1.3%) were significantly more common with nizatidine. It was not possible to determine if sweating and somnolence were associated with a pregnant woman or if the potential benefit justifies the potential risk to the fetus.

Hepatic— Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) of SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The upper limit of normal was not significantly different from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholangitis with jaundice have been reported with nizatidine.

Gastrointestinal— In clinical pharmacology studies, short episodes of asymptomatic tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS— Rare cases of reversible mental confusion have been reported.

Endocrine— In clinical pharmacology studies and in clinical trials, no evidence of antidiabetic activity due to nizatidine occurred in some patients. Impotence and decreased libido were reported with equal frequency by patients on nizatidine and those on placebo.

Genitourinary— Axid was reported in a patient treated with nizatidine.

Respiratory— Bronchospasm, laryngeal edema, rash, and eosinophilia have been reported.

Integumental— Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity— As with other H₂-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (e.g., bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other— Hyperemia unassociated with peptic ulcer disease was reported.

Overdosage: Overdoses of Axid have been reported rarely. If over dosage occurs, activated charcoal, emesis, or laxatives should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine from its large volume of distribution.

References: 1. Data on file. Lilly Research Laboratories.

2. Scand J Gastroenterol 1987;22(suppl 136):61-70.

3. Scand J Gastroenterol 1987;22(suppl 136):47-53.

4. Am J Gastroenterol 1989;84:769-774.

PV 2991 AMP

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