Cardiovascular risk factors and alcohol consumption in women

In this cross-sectional study of stratified random sample of 1048 British women, aged 25 to 69 years, researchers investigated the relationship between habitual alcohol consumption and cardiovascular disease. Fasting plasma concentrations of insulin, total cholesterol, total triglycerides, and high-density lipoprotein (HDL) cholesterol, including HDL_2 and HDL_3, and body mass index were measured.

The authors compared these measurements of nondrinking women with those women who consumed a moderate amount of alcohol (one 20-g drink/day). Moderate drinkers had lower plasma concentrations of triglycerides by 0.19 mmol/L (95% confidence interval [CI], 0.07 to 0.35); a lower cholesterol level, by 0.4 mmol/L (95% CI, 0.19 to 0.61); a lower insulin level, by 1.4 mU/L (95% CI, .43 to 1.97); and a lower body mass index, by 1.2 kg/m^2 (95% CI, 0.43 to 1.97).

Compared with nondrinkers, moderate alcohol consumers had higher concentrations of HDL cholesterol, by 0.09 mmol/L (0.03 to 0.15), HDL_2 cholesterol by 0.05 mmol/L (-0.02 to 0.10) and HDL_3 cholesterol by 0.06 mmol/L (0.06 to 0.11). All of these measurements were independent of body mass index, smoking habits, and oral contraceptive use.

Based on these findings, the authors conclude that moderate alcohol consumption is associated with lower levels of cardiovascular risk factors in women in this age group; insulin may play a central role.

Razay G, Heaton KW, Bolton CH, et al: Alcohol consumption and its relation to cardiovascular risk factors in British women. *Br Med J* 1992;304:80-83.

Effect of hemophilia A, unilateral hemarthrosis of the knee on musculoskeletal function

A frequent complication of hemophilia A, acute hemarthrosis of the knee has been hypothesized to have an adverse effect on neuromuscular function. To test this hypothesis, researchers enrolled ten patients with hemophilia A in this study. All of the participants had a history of unilateral hemarthrosis of the knee. These same patients' unaffected knees (U) were used as controls.

Investigators averaged the time since diagnosis, factor level, and the number of bleeding episodes occurring in the affected knees (A). Their respective averages were 11.6 ± 6.6 years, $7.7 \pm 5.1\%$, and 7.0 ± 7.4. Neuromuscular function was evaluated on a Cybex 340 isokinetic dynamometer. Knee extensor strength measured at 60 degrees per second was significantly ($P < .05$) lower in the A side (mean, 58 Nm) than in the U side (mean, 85 Nm).

Similarly, lower total work ($P < .05$) and average power output values were obtained for the affected side than for the unaffected knees (A = 479 J vs U = 656 J), (A = 59 W vs U = 83 W), respectively. Adjusting for thigh circumference did not eliminate any of these differences. Testing the extensors at faster angular velocities (180 degrees per second and 240 degrees per second) and the flexor muscle groups at three speeds revealed no differences between the two groups of knees. X-ray films showed minimal changes.

These data show that patients with hemophilia A and a history of unilateral hemarthrosis of the knee have neuromuscular dysfunction in the affected knee. This dysfunction precedes the appearance of radiologic evidence of joint abnormality. The authors suggest starting strength training early in the rehabilitation period of hemophiliacs.

Pietri MM, Frontera WR, Pratts IS, et al: Skeletal muscle function in patients with hemophilia A and unilateral hemarthrosis of the knee. *Arch Phys Med Rehabil* 1992;73:22-28.

Predicting future serum total cholesterol levels in postmenopausal women with one measurement

Researchers studied the spontaneous fluctuation in serum total cholesterol levels in 169 healthy women in early postmenopause. The women were followed up for 12 years. Serum total cholesterol was measured enzymatically.

The initial measurement and the long-term serum total cholesterol level were highly related ($P < .0001$). The long-term level, calculated for each woman as the area under the curve of serum total cholesterol versus time, was not statistically different from the initial level (mean difference, 0.036 ± 0.046 mmol/L [mean ± SEM], not significant).

Researchers then used the initial serum total cholesterol level to classify each woman into a high- or low-cholesterol group, according to current recommendations. The predictive value of an initial total cholesterol value in the high level ($\geq$ 6.2 mmol/L) was 84%, compared with the long-term level. The predictive value of an initial total cholesterol level (< 6.2 mmol/L) was 80%. No improvement in these parameters was found when the average of the initial two (or three, when the difference exceeded 0.9 mmol/L) measurements were used as the baseline value. The fluctuations in serum total cholesterol levels were mainly due to short-term variations.

For screening purposes, one measurement of serum total cholesterol in a woman gives a good estimate of the long-term level. The current data indicate that repeated measurements of serum total cholesterol do not improve the predictability of future cholesterol levels. The data also suggest that, at least in this population, women with an elevated serum total cholesterol level should have lipoprotein analysis performed for further risk assessment.

Hetland ML, Haarbo J, Christiansen C: One measurement of serum total cholesterol is enough to predict future levels in healthy postmenopausal women. *Am J Med* 1992;92:25-28.

Reaction to long-term zidovudine treatment in children with HIV-1

In adults with the acquired immunodeficiency syndrome (AIDS), long-term monotherapy with zidovudine selects for the human immunodeficiency virus type 1 (HIV-1) strains with substantially reduced in vitro susceptibility to the drug. Researchers assessed the relationship between in vitro resistance to zidovudine and clinical outcome in children. (Progression is more rapid from HIV-1 infection to the onset of AIDS in children than in adults.)

Investigators studied 23 children with HIV-1 symptoms while they received extended monotherapy with zidovudine. An in vitro assay was used to determine the zidovudine concentration required to inhibit the replication of viral isolates (IC_{50}) by 50% after 9 to 39 months of treatment.

Viral stocks of high enough titer to yield reproducible results were obtained from 19 (82.6%) of the 23 children. During the following 6 months of therapy, 9 children were stable, 7 deteriorated, and 3 died. A highly significant relationship existed between decreased zidovudine susceptibility and poor clinical outcome ($P < .001$). However, no relationship was noted between IC_{50} and the age at the start of therapy or treatment length.

Age-adjusted CD4 lymphocyte counts were lower at the start of treatment ($P = .02$) and at the time of sampling ($P = .01$) among children with increased viral zidovudine IC_{50} viral isolates than those children with IC_{50} values less than 2 μmol/L.

Initial serum p24 antigen levels were not predictive of subsequent emergence of resistant virus, but at the time of sampling for viral sensitivity,

(continued on page 283)


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


FILTER CIGARETTES

New Habitrol™ nicotine

THE PATCH THAT BEATS THE PACK

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

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

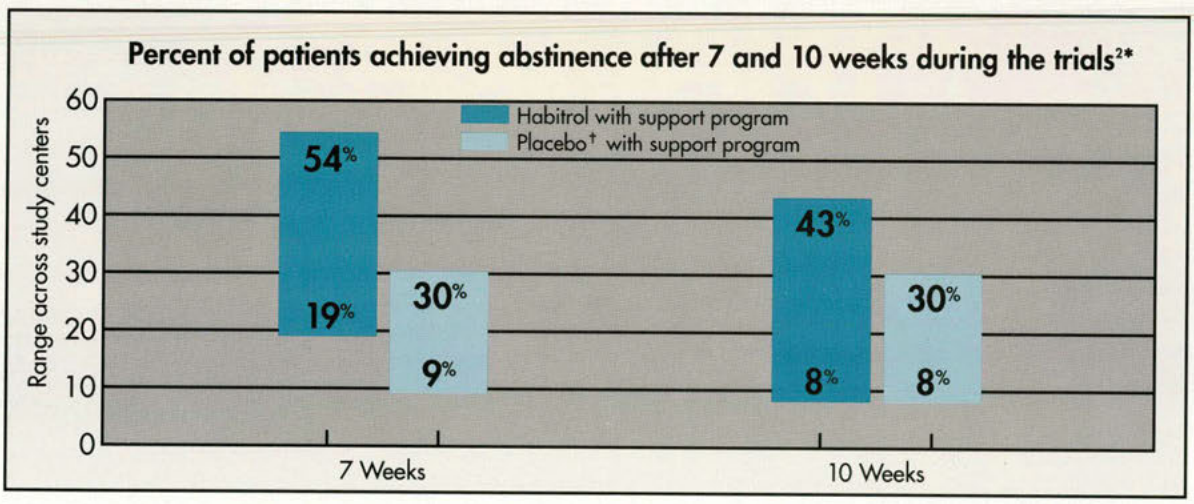
For the motivated patient...

New Habitrol™ nicotine

Significantly increases abstinence rates when used with support[2]

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

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



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

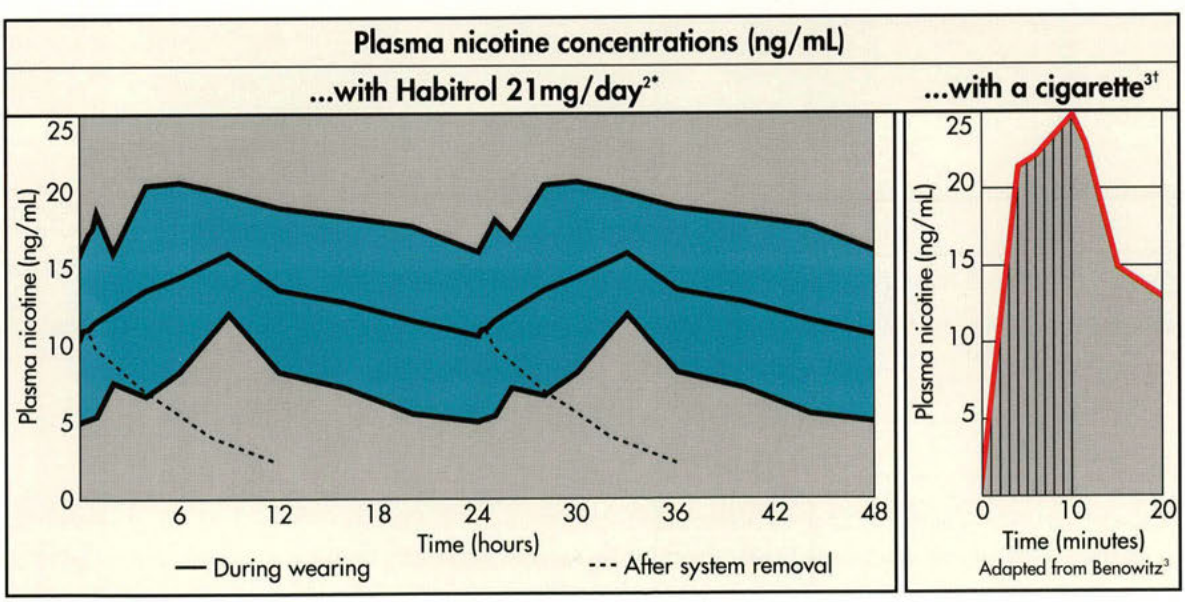
*Two trials with 9 study centers, number of patients per treatment ranged from 44 to 76.

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

THE PATCH THAT BEATS THE PACK

Significantly reduces cigarette craving through controlled nicotine release

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



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

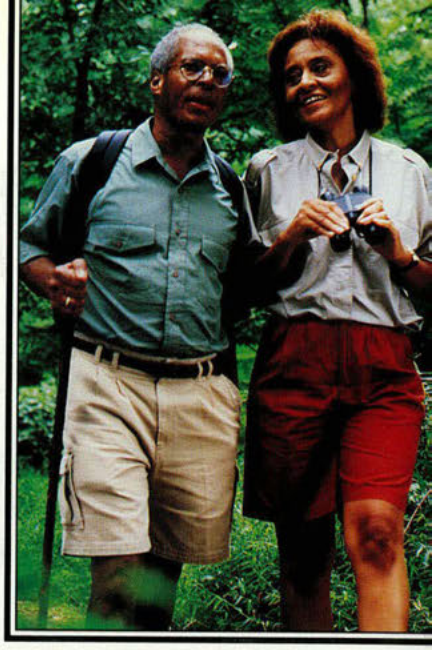
*Steady-state plasma nicotine concentrations for two consecutive applications of Habitrol 21mg/day (Mean ± 2SD).

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

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

For the motivated patient...

New Habitrol™ nicotine



A simple and convenient once-daily therapy for your patients

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

21 mg/day* ($30\ cm^2$)†

14 mg/day ($20\ cm^2$)†

7 mg/day ($10\ cm^2$)†

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

The most frequently observed adverse reaction is skin irritation.

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

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

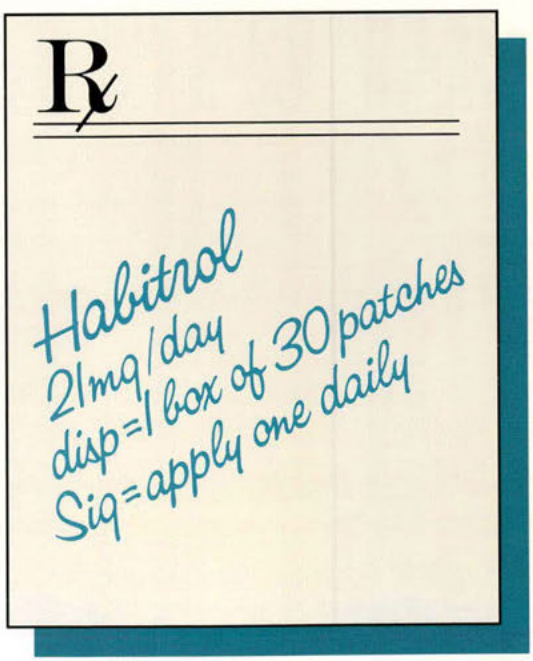
†Patches shown 50% of actual size.

THE PATCH THAT BEATS THE PACK

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

Comprehensive program includes...

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



BASEL Pharmaceuticals
Division of CIBA-GEIGY Corporation

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

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

273-12357-A

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

medi-notes

(continued)

higher p24 antigen levels were associated with increased IC_{50} levels ($P = .0004$).

Based on these findings, the authors suggest that most children who become unresponsive to zidovudine monotherapy, as determined by clinical criteria, will have changes in in vitro sensitivity to the drug. In these children, an alternative antiretroviral therapy should be considered.

Tudor-Williams G, St Clair MH, McKinney RE, et al: HIV-1 sensitivity to zidovudine and clinical outcome in children. *Lancet* 1992;339:15-19.

Retrospective review of the pituitary gland in hyperthyroidism

The authors retrospectively reviewed the pituitary glands of 33 patients (24 women and 9 men, aged 18 to 78 years) who died in thyrotoxicosis between 1925 and 1970. Eighteen of these patients had Graves' disease, and 15 patients had toxic multinodular goiter (Plummer's disease). These patients were examined by use of histologic and immunocytologic methods. Thirteen patients (39%) died in "thyroid storm." All but four of the deaths occurred before 1945.

The avidin-biotin-peroxidase complex immunostaining method was used to demonstrate the spectrum of pituitary hormones, including hor-

(continued on page 286)