BSP-GSH binding to TR¯ CMV was similar to that observed in normal CMV would suggest the latter hypothesis. Clearly the combined effect of the findings from these two studies is more than just a better description of canalicular non-bile-acid organic anion secretion. Because the transport defect has been characterized in a mutant animal model, it is only a matter of time before the membrane protein involved in the canalicular secretion of non-bile-acid organic anions will be identified. Radioactive photoaffinity labels are available for the detection of glutathione S-conjugate-binding membrane proteins (12). Once isolated, further studies including molecular cloning of this protein will follow.

REFERENCES

EDITOR’S ABSTRACT
Diaz and colleagues have carefully studied the effects of omeprazole on the expression of cytochrome P-450 in primary cultures of human hepatocytes. When omeprazole was added to the culture medium in varying concentrations, there was an increase in P-450IA2 protein and mRNA concentrations, an increase in de novo synthesis of P-450IA2 protein, and an increase in microsomal catalytic activities characteristic of P-450IA2 (phenacetin deethylase and acetanilide hydroxylase). Omeprazole treatment also resulted in an increase in both enzymatic activity characteristic of P-450IA1 (ethoxyresorufin deethylase and benzpyrene hydroxylase) and concentration of P-450IA1 mRNA. In contrast, omeprazole appeared to have no significant effect on expression of other P-450s within the P-450II or P-450III families in the hepatocytes. To validate these in vitro observations, liver biopsy specimens were obtained from five patients before and after a 4-day course of pharmacological doses of omeprazole. In each patient, omeprazole treatment appeared to result in a two- to eightfold increase in P-450IA2 immunoreactive protein and P-450IA1 and P-450IA2 enzymatic activities. The authors conclude that omeprazole is an inducer of P-450IA2 and probably P-450IA1 in human liver. Induction of these enzymes could potentiate the bioactivation of carcinogens or the hepatotoxicity of some drugs such as acetaminophen.

COMMENTS
This is an important article likely to spark considerable controversy. The data presented and the accompanying editorial (1) appear to raise new concerns about the safety of omeprazole (Losec; Merck, Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA). This drug is the latest addition to the peptic ulcer disease therapeutic arsenal, which accounts for sales well in excess of $1 billion annually. As the most potent inhibitor of gastric acid secretion clinically available, omeprazole is already used widely in the treatment of severe esophagitis, Zollinger-Ellison syndrome and refractory peptic ulcer disease.

Diaz et al. investigated the effects of omeprazole on the regulation of phase I drug metabolizing enzymes termed cytochromes P-450 (P-450s). P-450s often play critical roles in the metabolism of drugs and other xenobiotics found in the environment (2, 3). The P-450 literature has recently been simplified by the adoption of nomenclature that classifies individual P-450 enzymes by gene family (designated by roman numerals) (4). Three major P-450 families appear to be involved in xenobiotic metabolism, each consisting of proteins that share >40% amino acid sequence homology. Each family contains subfamilies of proteins (designated by capital letters) that share >60% amino acid sequence homology. This nomenclature replaces other classifications that often designated P-450s by substrate specificity or by response to known inducers. The enzymes demonstrated to be induced in the hepatocytes by Diaz et al. (P-450IA1 and P-450IA2) are “aryl hydrocarbon hydroxylases” and correspond to what has also been termed “P-448.”
The safety concern raised by the findings of Diaz et al. is new and not at all related to previous concerns about omeprazole directly causing mutagenesis (5) or predisposing rats to carcinoid tumors. Rather, concern stems from the fact that P-450IA enzymes are responsible for the bioactivation of some aryl hydrocarbons to carcinogens. “Aryl” or “aromatic” refers to a broad class of hydrocarbons that contain benzenelike carbon rings in their structures. These chemicals are found in cigarette smoke, charbroiled food and industrial solvents. If omeprazole is an inducer of P-450IA enzymes, treatment with the drug might theoretically predispose individuals to bioactivate otherwise harmless procarcinogens in the environment, possibly resulting in malignancies many years after starting therapy. The studies performed by Diaz et al. are complete and very carefully executed. However, we believe that the data presented and the current state of knowledge about the role of P-450s in disease are insufficient to make conclusions regarding the safety of omeprazole in patients. We would like to make several points in this regard.

First, although there can be no doubt that omeprazole-induced P-450IA2 and probably P-450IA1 in the hepatocytes, the relevance of these findings to patients treated with omeprazole is less clear. P-450IA1 appears to be primarily an extrahepatic enzyme in man and is usually present in the liver at concentrations below limits of detection by most assays (2, 3). The apparent prominence of P-450IA1 mRNA and catalytic activity observed by Diaz et al. in the omeprazole-treated hepatocytes may therefore indicate nonphysiological regulation of P-450IA enzymes in the culture system.

Second, although the results of the in vivo biopsy studies appear to validate the authors’ in vitro findings, they run contrary to at least one clinical observation. Omeprazole treatment does not appear to significantly accelerate clearance of theophylline (6), although P-450IA2 catalyzes a major metabolic pathway (N-demethylation [7]) for this drug. The in vivo changes in P-450IA protein and catalytic activity observed by Diaz et al. were generally small compared with that observed in culture and may not have resulted from the omeprazole treatment. It seems likely that patient medications and diets changed significantly between the first and second biopsies. Moreover, variations in P-450IA2 protein concentration of less than twofold (observed in three of the 5 patients studied) could merely reflect differences in biopsy site because the distributions of these enzymes do not appear to be uniform in the livers of rats or man (8).

Third, the relationship between P-450IA enzymatic activity and aryl hydrocarbon–associated carcinogenesis is indirect and best associated with P-450IA1 activity in extrahepatic tissues (9). In vitro assays for mutagenesis or DNA adduct formation indicate that aryl hydrocarbon procarcinogens are bioactivated by P-450IA enzymes. In animals, administration of very large doses of aryl hydrocarbons is associated with the development of lung, brain and lymphoreticular tumors. In some studies, patients with lung cancer have had higher levels of lymphocyte aryl hydrocarbon hydroxylase activity compared with patients without lung cancer. Collectively, these studies suggest a relationship between P-450IA levels and chemical-induced carcinogenesis; however, a true causal relationship remains to be defined. As the authors point out, there is reason to believe that induction of P-450IA enzymes may in fact be protective against some induced malignancies.

Fourth, it is probably not appropriate to single out inducers of P-450IA enzymes as a safety concern. Activation of procarcinogens is also catalyzed by P-450IIIE1 (nitrosamines), P-450IIIA (mycotoxins) and probably many other P-450s (2, 3). Moreover, modification in the “profile” of liver P-450 activity is an expected part of many and perhaps most medication regimens. Although omeprazole is the first drug identified as a potential inducer of P-450IA, medications that induce P-450IIIE1 (ethanol and isoniazid) and P-450IIIA (rifampicin, antiseizure medications, glucocorticoids) are widely used (2, 3). In addition, any drug that is metabolized by—and hence binds to—a P-450 (which appears to be most drugs) will likely inhibit the activity of that P-450 toward other substrates (2). Inhibiting a pathway involved in detoxification could theoretically “shunt” xenobiotics through bioactivation pathways, resulting in the same net health consequences as a P-450 inducer.

Finally, even if omeprazole treatment does result in a two- to eightfold induction of hepatic P-450IA enzymes in patients, this would intuitively seem to be unimportant in most patients. There appears to be great heterogeneity in the expression of P-450IA enzymes in man; several studies suggest a 30- to 60-fold interpatient variation in the liver content and catalytic activity of hepatic P-450IA enzymes (2, 3). After a two- to eightfold induction, most patients would probably still remain within 2 S.D. of the mean in this broad distribution.

We eagerly await studies that document the health risks or benefits associated with the wide interpatient variations in activities of the P-450s that appear to exist independent of the influence of medications. The continued development of noninvasive assays capable of determining activities of individual P-450s (2) will allow such prospective long-term studies. In the meantime, it would seem inappropriate to deny omeprazole to patients whose symptoms have been refractory to other available medications, even if omeprazole is confirmed to induce P-450IA1 and P-450IA2 in patients.

J.C. Kolars, D.K. Turgeon, P.B. Watkins
University of Michigan Medical Center
Ann Arbor, Michigan 48109
REFERENCES

6. Gugler R, Jensen JC. Drugs other than H2-receptor antagonists as agents, including propylthiouracil, anabolic steroids and corticosteroids. The latter has been the most intensively studied, starting with a report in 1971 of a randomized controlled study terminated early by the investigators because of the overwhelming protective effect found for corticosteroid use in encephalopathic patients with alcoholic hepatitis (2). A succession of randomized controlled trials followed, two of which showed significant improvement in survival with steroids and seven of which did not. In 1989 a multicenter trial found a substantial benefit from steroid treatment in a population of patients selected for encephalopathy or high prothrombin times and bilirubin levels (3).

Combining results from multiple trials allows a metaanalysis to achieve large sample sizes and statistically significant results where individual trials have failed to do so. Accumulating a large sample size in this manner is easy relative to the difficulty of conducting a large clinical trial. However, to prevent the sample size from giving the reader false confidence in the results of the analysis, the methodology of the metaanalysis assumes an even greater significance for both authors and readers. Imperiale and McCullough carefully follow the emerging standards for the performance of a metaanalysis by specifying the literature-search methods, supplying a list of rejected trials, describing the criteria for the quality review of the articles and describing standards for deciding if the trials may be appropriately aggregated.

Although the authors adhere to many of the standards of metaanalysis methodology, in a few areas their methodology could be more rigorously described. It is very important for a metaanalysis to use all available studies done on the research question. Imperiale and McCullough describe their use of a computerized database, textbook references and references from the articles retrieved by the first two methods. A more complete search would have specified the use of a professional librarian to perform the computer search, as skill in using these databases varies widely. Other sources for finding references recommended in the literature on metaanalysis include Current Contents, databases of unpublished material and polls of senior researchers in the field (4). The latter two sources are important for addressing the issue of publication bias or the selective appearance in the published literature of trials with positive results. The authors' case for the lack of publication bias, on the grounds that a large proportion of the studies found no significant difference in the study groups, is not compelling. Although the question of how to include unpublished studies in a pooled analysis is complicated, a simple sensitivity analysis can be done to determine how many unpublished negative trials (of good quality) would be required to render the result of the pooled analysis statistically insignificant.

EDITOR'S ABSTRACT

The purpose of the study was to determine whether corticosteroids affect short-term mortality from alcoholic hepatitis. A metaanalysis was conducted using studies identified through a MEDLINE computer search from 1966 to 1989 and extensive manual searches of associated bibliographies. Eleven randomized studies that assessed mortality in hospitalized patients diagnosed with alcoholic hepatitis and treated with corticosteroids were evaluated. Overall, the protective efficacy of corticosteroids was 37% (95% confidence interval 20% to 50%). Protective efficacy was higher among those trials with higher quality scores and in trials that excluded subjects with active gastrointestinal bleeding in patients with hepatic encephalopathy, protective efficacy was 34% overall (confidence interval 15% to 48%). In subjects without hepatic encephalopathy, corticosteroids were not believed to have a protective effect; this lack of efficacy was noted across all trial subgroups. Results of the metaanalysis suggest that corticosteroids reduce short-term mortality in patients with acute alcoholic hepatitis who have hepatic encephalopathy. The protective effect is dependent on exclusion of patients with acute gastrointestinal bleeding.

CORTICOSTEROIDS AND ALCOHOLIC HEPATITIS