A FRACTION of ingested ethanol is cleared by first-pass metabolism. At present, there is controversy concerning both the magnitude and site of this metabolism. It has been proposed that a major fraction of a sizable ethanol dose is removed by first-pass metabolism (2, 4, 7, 9) and that this metabolism occurs primarily in the gastric mucosa (2, 12, 18, 22). In contrast, work from our laboratory (13, 16, 23) suggests that first-pass metabolism probably accounts for only a small fraction of ethanol removal and occurs almost entirely in the liver.

Claims concerning first-pass gastric metabolism in humans have been based largely on the results of pharmacokinetic studies comparing areas under the curve (AUCs) for blood ethanol. However, the AUC is an accurate indicator of the quantity of a compound reaching the peripheral circulation only when the compound is cleared with first-order (nonsaturating) kinetics. Small doses of alcohol saturate hepatic metabolism, and, in this situation, increases in the amount of ethanol reaching the peripheral circulation produce disproportionate increases in AUC, and faster rates of delivery of identical doses also result in higher AUCs (see Fig. 1). The present lack of precise data on ethanol absorption rates in humans precludes accurate assessment of the site and magnitude of human first-pass metabolism.

The initial goal of the present study was to obtain quantitative data on the rate of ethanol absorption in humans by measuring the rates of gastric emptying and gastric absorption of ethanol administered to subjects with and without food. These absorption data were then used to assess the physiology of ethanol metabolism.

METHODS

Subjects and Meals

Five healthy, nonalcoholic males (21–45 yr of age) took part in this study. After an overnight fast, a nasogastric tube was inserted and one of two meals was instilled into the stomach through the tube. After an interval of 1–2 wk, the other meal was similarly administered. One meal consisted of a standard breakfast: two eggs (fried in butter), two slices of white bread (one tablespoon of butter per slice), two strips of bacon, 120 ml of orange juice, and 360 ml of coffee. This material was homogenized to form a suspension of 10% window. Sixty-second images were processed by an ADAC-PEGAsys computer system with a 256 by 10.220.33.2 on June 25, 2017 http://ajpgi.physiology.org/ Downloaded from http://ajpgi.physiology.org/ Downloaded from http://ajpgi.physiology.org/Downloaded from the site and magnitude of human first-pass metabolism.

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soluble radiopharmaceuticals, 99mTc-DTPA and [14C]PEG, were used to assess ethanol metabolism. The Michaelis constant (Km) for ethanol removal is very low, and metabolism, which is maximum velocity (Vmax) at any appreciable blood concentration, reduces blood concentration by 10 mM/h. Blood concentration curves are shown for bolus infusion of a dose that raises the blood ethanol to 30 mM (●; A), the same dose infused at a rate of 2/3 over the 1st h and 1/3 over the 2nd h (○; B), and 1/2 the dose infused as a bolus (□; C). Note that AUC in A is 2.2 times greater than in B despite administration of identical doses, and 4 times greater than in C although dose difference was only 2-fold. Because ethanol was infused intravenously in these examples, AUC differences are not attributable to first-pass metabolism. The fraction of the ethanol dose not emptied into the duodenum (FNE[Eth]0–t1) over the time period was calculated as

\[
FNE_{Eth0–t1} = 1 - FE_{Eth0–t1}
\]

The fraction of the ethanol dose actually remaining in the stomach at the end of the time period (FR[Eth]t1) was calculated from the fraction of [14C]PEG remaining in the stomach (FR[PEG]t1) and the decline in the concentration ratio of ethanol to [14C]PEG ([Eth/PEG]).

\[
FR_{Eth1} = FR_{PEG1}([Eth/PEG]_1/[Eth/PEG]_0)
\]

Finally, the fraction of the ethanol absorbed from the stomach over the time period (FA[Eth]0–t1) was calculated from the difference between the fraction that was not emptied into the duodenum and the fraction remaining in the gastric lumen.

\[
FA_{Eth0–t1} = FNE_{Eth1} - FR_{Eth1}
\]

Similar calculations were made for each time period utilizing the values obtained for the fraction of the initial dose of 99mTc-DTPA emptied during that time period and the [14C]PEG and ethanol concentrations of the gastric aspirates obtained at the beginning and end of the time period.

Estimation of gastric unstirred layer. The thickness of the unstirred fluid layer through which ethanol diffused to reach the gastric mucosa was estimated from the standard Fick diffusion equation.

Absorption rate = DA (C1 - Cm)/ unstirred layer thickness

where absorption rate (from the stomach) was measured, D, the diffusion constant for ethanol, is 1.0 x 10^-5 cm^2/s; A is the surface area of the gastric mucosa; and C1 and Cm are the ethanol concentrations in bulk luminal contents and the mucosa, respectively. A was assumed to be the surface area of a sphere with a volume equal to the volume of the gastric luminal contents. Only moderate alterations of area result from the stomach, which has a somewhat cylindrical, rather than spherical, shape. For example, if the stomach took the form of a cylinder with a length twice its width, the surface area of a 500-ml volume would be only 18% greater than that of a 500-ml sphere. C1 was measured directly, and Cm was calculated as described below.
Estimation of ethanol concentration and metabolism in gastric mucosa. Ethanol concentration in the gastric mucosa was calculated on the assumption that concentrations of ethanol in the mucosa and mucosal blood flow are in near-perfect equilibrium. In this situation, the concentration of ethanol in the mucosa can be estimated for each time period from the observed ethanol absorption from the stomach during that period and a gastric mucosal blood flow of 50 ml/min [estimated from a blood flow of 0.7 ml/min (11) and a gastric mucosal weight of 1 g/kg (12)].

\[ \text{Mucosal [Eth]} = \frac{\text{absorption rate/mucosal blood flow}}{} \]  

The above calculation assumed negligible ethanol metabolism in the gastric mucosa; appreciable mucosal metabolism would have reduced these concentrations.

The gastric metabolism of ethanol expected for a given mucosal concentration was calculated for three reported (8, 19, 24) sets of kinetic data for human gastric mucosal alcohol dehydrogenase (ADH). Thuluvath and co-workers (24) reported a Michaelis constant (\( K_m \)) of 7.8 mM and a maximum velocity (\( V_{\text{max}} \)) of -5 mmol·mg protein\(^{-1}\)·min\(^{-1}\). The weight of human gastric mucosa averages -1 g/kg body wt and tissue is \( \sim \)20% protein. Thus the entire gastric mucosa contains \( \sim \)14 g of protein and would have a \( V_{\text{max}} \) for ADH of \( \sim \)4.2 mmol/h. Frezza et al. (8) reported that human gastric ADH has a \( K_m \) of \( \sim \)500 mM and an activity of 2.6 μm·g mucosa\(^{-1}\)·min\(^{-1}\) at an ethanol concentration of 500 mM. Assuming Michaelis kinetics, the \( V_{\text{max}} \) would be \( \sim \)5.2 μm·g\(^{-1}\)·min\(^{-1}\) or 21 mmol·h\(^{-1}\)·70 g\(^{-1}\) of gastric mucosa. Moreno and Parés (19) reported that gastric ADH has a \( K_m \) for ethanol of 41 mM and that the entire human gastric mucosa would metabolize \( \sim \)20 μmol of ethanol/min at an ethanol concentration of 100 mM. This yields a \( V_{\text{max}} \) of 140 μmol/h for the entire mucosa. The predicted gastric mucosal metabolism for each of these three sets of kinetic data was then calculated for each time period from the predicted ethanol concentration in the gastric mucosa (\( \text{[Eth}_{\text{muc}] \)) and Michaelis-Menten kinetics.

Ethanol metabolism = \( V_{\text{max}} \cdot \text{[Eth}_{\text{muc}] / (K_m + \text{[Eth}_{\text{muc}]}) \)  

Predictions of blood ethanol concentrations and first-pass hepatic metabolism of ethanol using a model of human hepatic ethanol metabolism. We have previously described extensively (16) the model employed to predict the metabolism of ethanol by the human liver and the resulting peripheral blood ethanol curves. The model consists of a 1,000 g liver that receives ethanol via the portal vein and hepatic artery, which have blood flows of 1,000 and 500 ml/min, respectively. Hepatic ethanol metabolism is assumed to follow Michaelis-Menten kinetics with a \( V_{\text{max}} \) of 2.75 mmol·min\(^{-1}\)·80 kg\(^{-1}\) and a \( K_m \) of 0.1 mM, values that we (9) derived from the work of Wilkinson et al. (25). The overall rate of hepatic metabolism of ethanol at any moment is determined from the \( K_m \), the \( V_{\text{max}} \), and the concentration of ethanol that would exist at the hepatic cell, assuming the liver to be a well-mixed pool. To distinguish first-pass metabolism from total metabolism, alcohol arriving at the liver directly from the gastrointestinal tract must be distinguished from that derived from the recirculation of ethanol that previously escaped first-pass metabolism. First-pass metabolism is defined as the additional ethanol metabolism that occurs due to the higher hepatic ethanol concentration that results from delivery of ethanol directly to the liver from the gut as opposed to the concentration that would result from an intravenous infusion of ethanol. The total system is described by three first-order differential equations that were solved numerically using a fourth-order Runge-Kutta routine with adaptive step size control (21).

RESULTS

Figure 2 shows the data for gastric emptying of the radiopharmaceutical (\(^{99m}\)Tc-DTPA) and ethanol, gastric absorption of ethanol, and disappearance of ethanol from the stomach (gastric emptying plus absorption of ethanol) when the alcohol was administered with water. Ethanol disappearance from the stomach was extremely rapid in the fasting state with \( \sim \)47%, 85%, and 96% leaving the stomach by 3, 13, and 23 min, respectively. Of the total dose of ethanol, \( \sim \)89% left the stomach via emptying into the duodenum and \( \sim \)10% was absorbed across the gastric mucosa. Ethanol disappearance from the stomach was appreciably slower when the ethanol was administered with food (see Fig. 3). A sizable fraction (\( \sim \)23%) of the ethanol ingested with a meal was emptied into the duodenum during the \( \sim \)6-min period elapsing between the initiation of the
instillation of the meal and the first image. Subsequently, of the ethanol remaining in the stomach at any time point, ~10%/15 min was emptied into the duodenum and 6%/15 min was absorbed from the stomach. Ethanol removal from the stomach was nearly complete by 126 min with averages of 66% and 28% being emptied into the duodenum and absorbed from the stomach, respectively.

The blood ethanol curves obtained with the two meals are shown in Fig. 4. The blood ethanol concentration curves confirmed the very rapid gastric emptying of ethanol observed in the period immediately after ethanol administration (Figs. 2 and 3), with peak blood levels occurring within 20 min of the administration of the meals. When administered with water, the peak ethanol level and AUC were, respectively, ~2.5 and 2.8 times greater than when ethanol was administered with food. In addition, Fig. 4 also shows the blood ethanol curves predicted when the observed rates of disappearance of ethanol from the stomach (gastric disappearance assumed to equal absorption) were applied to the model of hepatic alcohol metabolism. The blood ethanol values predicted by the model were very close to the observed values when ethanol was administered with water. However, the blood levels predicted by the model for the first 45 min of the study with food were somewhat lower than the observed values.

Figure 5A shows hepatic ethanol concentration and first-pass and total ethanol metabolism predicted by the hepatic model for the observed rate of absorption of an ethanol dose of 0.15 g/kg. For the first hour of the study, hepatic ADH activity would have been nearly saturated and ethanol metabolism was near the $V_{\text{max}}$. Cumulative first-pass metabolism accounted for ~30% of the total dose. Figure 5B shows similar data for the 0.15 g/kg dose administered with water. The rapid early absorption causes a rapid rise in peripheral blood ethanol that saturates hepatic ADH and limits first-pass metabolism to a cumulative total of only 3.5% of the dose. Similarly, if twice the dose (i.e., 0.3 g/kg) were absorbed at the same rate as the 0.15 g/kg administered with food, first-pass metabolism would fall to only 2% of the dose, primarily due to inhibition of this metabolism by peripheral ethanol returning to the liver (see Fig. 5C). When the AUC of the time curve for predicted hepatic ethanol concentration is used as a measure of the exposure of the liver to ethanol, the hepatic exposure is four times greater for the 0.15 dose ingested with water (Fig. 5B) and 11 times greater for the 0.30 g/kg dose (Fig. 5C) for the 0.15 g/kg dose ingested with food.

Fig. 4. Observed vs. predicted blood ethanol concentrations when ethanol was administered with water or with a meal. Shown are blood ethanol concentrations observed (open symbols) and predicted (filled symbols) from model of hepatic ethanol metabolism when 0.15 g/kg in 360 ml of water (circles) or in 550 ml of homogenized breakfast (triangles) was instilled into the stomach. Data are means ± SE.

Fig. 5. Predictions of hepatic model of hepatic ethanol concentrations (A) and cumulative total (○) and first-pass (●) metabolism of ethanol. A: data for 0.15 g/kg of ethanol administered with food. B: data for 0.15 g/kg of ethanol administered with water. C: data for 0.30 g/kg of ethanol absorbed at fractional rate observed when 0.15 g/kg dose was administered with food. %Total metabolism that occurred during first-pass was estimated to be 27%, 3.6% and 2.2% for A, B, and C, respectively. AUCs for hepatic ethanol concentration for A, B, and C were 44, 163, and 487 mM/min, respectively.
The estimated unstirred layer thickness in the stomach was 410 µm for the time period of 3–9 min in the study carried out in fasting subjects and 444 and 414 µm for the periods of 6–21 min and 21–36 min, respectively, when ethanol was administered with food.

Figure 6 shows the predicted concentrations of ethanol in the gastric mucosa when ethanol was administered with food as well as the cumulative metabolism predicted for these concentrations using three published sets of kinetic data for gastric ADH activity. The total predicted gastric ethanol metabolism was 0.7, 0.9, and 5.3 mmol for the data of Moreno and Parés (19), Frezza et al. (8), and Thuluvath et al. (24), respectively. Predicted gastric metabolism was ~25% of these values for the studies employing an ethanol-water meal.

**DISCUSSION**

The initial goal of this study was to quantitate the rates of gastric emptying and gastric absorption of ethanol in healthy human volunteers. Because ethanol absorption from the small bowel is almost instantaneous (22), the sum of gastric emptying and absorption provides a measure of ethanol absorption rate. Knowledge of absorption rates made it possible to perform calculations concerning the site and magnitude of first-pass metabolism of alcohol.

The technique employed to quantitate gastric emptying and gastric absorption of ethanol has not been utilized previously. Ethanol, [14C]PEG, and 99mTc-DTPA were instilled into the stomach along with either 360 ml water or 550 ml of a homogenized breakfast. The rate that ethanol entered the duodenum was calculated from the emptying of 99mTc-DTPA (5) and the ethanol concentration in the aqueous phase of gastric contents. Gastric absorption of ethanol was determined from the quantity of ethanol not emptied into the duodenum minus the amount actually remaining in the stomach.

The accuracy of this technique is based on several assumptions. First, 99mTc-DTPA, [14C]PEG, and ethanol must be similarly distributed in the aqueous phase of gastric contents. This assumption was correct in that analysis of the water phase of the meal showed the expected concentration ratios of [14C]PEG, ethanol, and 99mTc-DTPA. It also was assumed that [14C]PEG and 99mTc-DTPA are nonabsorbable, an assumption supported by the wide use of PEG 3000 as a dilutional marker in perfusion studies and 99mTc-DTPA for gastric emptying measurements of water-soluble compounds (5). Finally, our sampling of gastric contents was assumed to be representative of total gastric contents. A large quantity of gastric material (150 ml, when possible) was withdrawn and mixed, and a small aliquot was saved for analysis. Presumably, the large quantity of withdrawn material provided a true representation of the total contents.

An average of 85% of the ethanol instilled with water was emptied into the duodenum by 23 min, whereas, when instilled with food, a mean of only ~30% was emptied over the this same time period (see Figs. 2 and 3). The roughly 50-min half-time of emptying of the liquid phase of our instilled, homogenized meal is similar to the half-time reported for the liquid phase of a meal ingested in physiological fashion (8). The percentage of the dose emptied into the duodenum averaged 69% and 89% for the food and water meals, respectively, and the respective fractions undergoing gastric absorption were 30% and 10%. These latter values represent the maximal fraction that could have undergone gastric mucosal metabolism. Claims that up to 90% of an ethanol dose undergoes gastric metabolism (2) can be excluded a priori.

When administered with food, ~6% of the ethanol in the stomach was absorbed per 15-min interval. This value is slightly less than the gastric clearance of 4.7 ml/min reported by Cooke (5), who used a gastric aspiration technique to assess ethanol absorption from a 350-ml meal.

Our gastric absorption measurements permitted several apparently novel calculations concerning the gastric handling of ethanol. First, it was possible to estimate the diffusion barrier separating bulk luminal contents and the gastric mucosa. This barrier appeared to have a resistance equivalent to that of an unstirred layer ~400 µm thick, a value ~16 times greater than the 25-µm thickness reported for the human small intestine (15). This difference presumably reflects more efficient luminal stirring in the small bowel, although the thick mucus layer in the stomach may have accounted for some of the difference. The very thin intestinal unstirred layer plus a greater surface-to-volume ratio explains the virtually instantaneous intestinal absorption of ethanol vs. the slower gastric absorption rate.

Knowledge of gastric absorption rates of ethanol also made possible the estimation of in vivo metabolism of ethanol in the gastric mucosa. Although several in vitro determinations of the $V_{max}$ and $K_m$ of ADH have been performed, extrapolation of these data to the in vivo situation requires knowledge of gastric mucosal ethanol concentrations. The high diffusivity of ethanol...
should result in a near-perfect equilibrium between the ethanol concentrations of mucosal tissue and blood perfusing the mucosa. Thus the mucosal concentration equals gastric ethanol absorption divided by gastric mucosal blood flow. Resting gastric mucosal blood flow in adult males is \( \sim 0.6 \text{ ml \cdot g}^{-1} \cdot \text{min}^{-1} \) (20), and both food and ethanol ingestion should enhance this flow rate. Utilizing a value of 0.7 ml \cdot g mucosa\(^{-1}\) \cdot \text{min}^{-1} and a mucosal weight of 70 g (11), the flow for the entire stomach would be \( \sim 50 \text{ ml/min} \). At this flow rate, the maximal gastric mucosal concentration after ingestion of the ethanol with food was \( \sim 19 \text{ mM} \), and this value declined to \(< 5 \text{ mM} \) by 2 h (Fig. 6). Previous estimations of gastric ethanol metabolism assumed, without evidence, gastric mucosal ethanol concentrations of 200–500 mM for a 3-h period (9, 10). Given the high \( K_m \) of gastric ADH, such inflated concentrations resulted in marked overestimations of gastric ethanol metabolism.

Utilizing three recently published (8, 19, 24) sets of gastric ADH kinetic data with our calculated concentrations of mucosal ethanol, we estimated gastric mucosal ethanol metabolism from the Michaelis-Menten equation. When administered with food, total ethanol metabolism in the gastric mucosa was 0.7, 0.9, and 5.3 mmol for the kinetic data of Moreno and Parés (19), Frezza et al. (8), and Thuluvath et al. (24), respectively. This metabolism accounted for only 0.3%, 0.4%, and 2% of the 250-mmol dose. Thus the stomach appeared to metabolize a negligible fraction of a very low dose of ethanol (0.15 g/kg) ingested with food, the situation in which first-pass metabolism is maximal.

The more rapid absorption of ethanol administered with water vs. food was associated with higher blood ethanol levels and a 70% greater AUC (see Fig. 4). These higher blood concentrations could reflect either a reduction in the efficiency of first-pass hepatic metabolism and/or simply the increased AUC observed with more rapid and/or greater delivery of ethanol to the peripheral circulation when clearance is saturated (see Fig. 1).

Determination of hepatic first-pass metabolism vs. metabolism of recirculating ethanol requires knowledge of ethanol absorption and the kinetics of hepatic ethanol metabolism. We have employed a model of hepatic ethanol metabolism in which total metabolism at any moment is determined from the ethanol concentration at the hepatocyte, the \( K_m \) of the hepatocyte, and \( V_{max} \) (16). Many studies (10, 18, 22) assessed hepatic ethanol metabolism utilizing the apparent \( K_m \), the peripheral blood ethanol concentration that yields the half-maximal metabolic rate. However, at nonsaturating concentrations liver metabolism may reduce the liver ethanol concentration to only a small fraction of that of peripheral blood. Thus sizable errors occur when estimates of first-pass metabolism are based on calculations employing peripheral blood concentrations and apparent \( K_m \) (16).

In our modeling, first-pass ethanol metabolism was defined as the extra metabolism that results when newly absorbed ethanol is delivered to the liver via the portal vein as opposed to the delivery at the same rate via an intravenous infusion. First-pass metabolism occurs to the extent that the higher hepatic concentrations resulting from portal delivery allow more rapid hepatic metabolism of ethanol. This model also permits prediction of blood ethanol levels, and in studies using a rat hepatic model (analogous to that employed for humans), predicted blood ethanol concentrations were similar to observed values (17).

The model accurately predicted the observed blood ethanol levels for the studies in which ethanol was administered with water (see Fig. 4). However, when administered with food, observed blood ethanol concentrations were \(< 0.7 \text{ mM} \) greater than that predicted during the first 45 min of the study (see Fig. 4). To account for this discrepancy, we first examined our hepatic modeling. The sizable alterations in \( K_m \) or \( V_{max} \) required to appropriately increase predicted values caused marked discrepancies between predicted and observed values during the latter phase of the study. Alterations in liver blood flow did not appreciably influence predicted results. Additional evidence that factors other than our modeling played a role in this discrepancy was as follows. When distributed in body water (60% of body wt), the blood ethanol concentration (1.7 mM) at 10 min represents 34% of the dose. During this 10-min period, ethanol was metabolized at near the \( V_{max} \) rate. Thus the liver would have cleared an additional 10% of the dose. The sum of ethanol in body water plus hepatic metabolism at 10 min equals 44% of the dose in contrast to the observed 30% absorption (see Fig. 3). Thus the major cause of the discrepancy between the observed and predicted blood ethanol values appeared to have been an \(< 15\% \) underestimation of ethanol absorption early in the study, although incomplete distribution cannot be excluded.

When the absorption of 0.15 g/kg of ethanol was applied to the hepatic model, 30% of the dose was predicted to undergo first-pass metabolism. Because this small dose nearly saturated hepatic removal (Fig. 5), increments in ethanol absorption would escape first-pass metabolism and, on returning to the liver, compete for metabolism with newly absorbed ethanol. Thus ethanol dosages \( > 0.15 \text{ g/kg} \) (absorbed at the fractional rate of our study with food) or increases in the rate of absorption of the 0.15 g/kg dose are associated with precipitous falls in first-pass metabolism. For example, the more rapid absorption observed when ethanol was administered with water reduced predicted first-pass metabolism from 30% to only 3%. If twice the ethanol dosage (i.e., 0.3 g/kg) were absorbed at the same fractional rate as in our food study, only \(< 2\% \) would have undergone first-pass metabolism (see Fig. 5). Thus appreciable first-pass metabolism is limited to the situation where there is slow absorption of a very small dose of ethanol (0.15 g/kg). The accuracy of this theoretical concept is supported by studies showing that the apparent inhibition of first-pass metabolism by \( H_2 \) antagonists is demonstrable only when the ethanol dosage is limited to 0.15 g/kg and absorption is slowed via meal ingestion (14).
The model of hepatic metabolism indicates that the peak and total hepatic exposure to ethanol increases dramatically with more rapid absorption of identical alcohol dosages (see Fig. 5). Using the AUC of hepatic ethanol concentration as an indicator of liver exposure, we found that the predicted exposure was fourfold greater for the 0.15 g dose administered with water vs. food. Furthermore, similar fractional absorption rates of modestly greater doses of ethanol dosage can cause markedly disproportionate increases in hepatic ethanol exposure (see Fig. 5). Thus, to the extent that liver damage is a function of hepatic ethanol concentration (as opposed to hepatic ethanol metabolism), subtle factors other than total daily intake could influence ethanol toxicity.

It should be axiomatic that the AUC provides an inaccurate assessment of first-pass metabolism of a compound such as ethanol, which is removed largely with saturation kinetics. For example, the difference in AUC of the two meals used in the present study was 70%, whereas the true difference in first-pass metabolism, calculated from the hepatic model, was only ~26%. Nevertheless, multiple recent reports (1, 2, 9) continue to use the difference between the AUCs of ingested vs. a rapid intravenous infusion of ethanol to assess first-pass metabolism. As a result, first-pass metabolism of ethanol appears to have been repeatedly overstated. Similar misapplication of the difference between AUCs obtained when ethanol was administered via the stomach vs. an intraduodenal or intraportal infusion initially led to the proposal that the stomach was the major site of first-pass metabolism of ethanol (3, 12). The present study indicates that this first-pass metabolism occurs almost entirely in the liver and this metabolism removes only a minor fraction of potentially inebriating doses of ethanol.

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