Enterohepatic recirculation (EHRC) is a multistaged process with the following sequence: liver metabolism, bile secretion, gut metabolism, and reabsorption from the gut back to the systemic circulation. Enterohepatic recirculation prolongs drug half-lives and may be associated with the generation of 1 or more secondary plasma peaks. For EHRC to occur, there is substantial dependence on the flora residing in the gastrointestinal (GI) tract. The role of gut microflora is so essential to our overall homeostasis that it is referred to by some authorities as an endocrine organ or “a second brain.” Hepatic metabolism plays the dominant role in the fate of drugs and other xenobiotics that we encounter. The liver is rich in a host of chemical manipulators that can hydrolyze, reduce, oxidize, and conjugate xenobiotics. Many drugs, morphine being a good example, are inactivated by glucuronide or sulfate conjugation, with subsequent movement into the bile and eventual emptying into the GI tract. Once in the GI tract, enzymes produced by gut flora can hydrolyze conjugated drugs in the small and large intestine, resulting in the active form reemerging, with reabsorption likely. The clinical relevance of EHRC is discussed with its major implications for efficacy and safety.

Keywords: Bile, enterohepatic recirculation, hepatic metabolism.

Introduction
You and a friend are out for a Saturday hike in the woods. Your friend, somewhat more adventuresome than you, decides to harvest some mushrooms abundant on the forest floor. You start collecting some yourself and, after your friend mentions how tasty they are, you abandon your initial reservations and begin eating your trove. Both of you have collected Hericium erinaceus, with its iciclelike spines and soft white tissue giving it its popular “lion’s mane” label, and Laetiporus sulphureus, its vernacular the “chicken of the woods,” with its knobby, shelflike architecture. Unlike your friend, you have also managed to collect 2 Amanita phalloides, whose appearance is quite ordinary, like those mushrooms you find in the supermarket—certainly nothing suggesting a warning of any kind.

Chatting all the way back to the car, you both are in good spirits and make plans to have lunch the next day before returning to work on Monday. That evening your favorite TV program is interrupted by a wave of nausea, which you attribute to the flu. You head for bed only to be roused within minutes, then repeatedly throughout the night, with propulsive vomiting, diarrhea, and a sense of absolute malaise.

The following morning you feel better, and you manage to drink some juice and that pink stuff your mother always gave you for gastrointestinal (GI) distress. You wonder if perhaps the cause was the mushrooms. You phone your friend and find her enthused, inquiring where you should meet for lunch. You reason that it can’t be the mushrooms, because after all you both indulged. Rather than have her learn of your night in the bathroom, you manage an excuse about needing to deal with a family issue. “See you at work tomorrow,” and with that you’ve canceled lunch.

Good thing because within 45 minutes you are in the bathroom again with violent, propulsive vomiting and diarrhea, although this time you cannot even manage to get back to bed. You simply lie on the bathroom floor, drifting...
intermittently in and out of consciousness over 14 hours. At work the next day you are missed, and your co-worker attributes this to your dealing with the “family issue,” assuring the boss she’ll follow up later. There is no reply to a text message, and a phone call goes unanswered. Little does anyone suspect that you’ve succumbed to those 2 *Amanita phalloides* you consumed. How could this have happened?

*Amanita phalloides* is a reservoir of amatoxin, a family of octapeptides, formed by 9 (or more) different compounds; α-amanitin and β-amanitin are the primary toxins. The mortal dose is quite small; as little as 0.1 mg/kg body weight is lethal to a fit adult, an amount easily achieved by eating a single mushroom, raw or cooked.

The amatoxins are rapidly absorbed in the gastrointestinal (GI) tract. When they encounter the liver, they are moved into the hepatocytes by an active transport system, with resultant rapid hepatic necrosis due to inhibition of RNA polymerase. In a classic example of enterohepatic circulation, as much as 60% of the absorbed amanitin is excreted into the bile and returned to the liver via the portal circulation, providing a second bolus of the hepatotoxin to an already damaged liver. An additional blow, for good measure, is the hit that it delivers to the kidneys causing acute tubular necrosis.

**Enterohepatic Recirculation Defined**

Enterohepatic recirculation (EHRC) is a multistaged process with the following sequence: liver metabolism, bile secretion, gut metabolism, and reabsorption from the gut back to the systemic circulation. By its nature, EHRC prolongs drug half-lives and may be associated with the generation of 1 or more secondary plasma peaks. I choose to use the designation recirculation rather than the traditional circulation because the predominant concern for the clinician is that there is a return of the solute (or its metabolites) to the systemic circulation.

A drug (or toxin) enters the systemic circulation through oral, rectal, parenteral, inhalational, dermal, or intravenous administration. Once in the systemic circulation, it is transported to the liver. Any agent undergoing EHRC is most often metabolized into constituents, some of which enter the bile, although some primary agents may not be metabolized at all and enter the bile in their original form. Once in the bile, they are stored in the gallbladder, which drains directly into the duodenum. Adults produce 400 to 800 mL of bile daily, with secretion occurring in 2 stages. First, hepatocytes secrete bile into canaliculi, from which it flows into bile ducts, containing bile acids, cholesterol, and other organic molecules. Second, the bile flowing through the ducts is modified by the addition of watery, bicarbonate-rich secretions from ductal epithelial cells.

Given the movement of bile, with any additional drug and chemical additives into the duodenum, the potential for their reabsorption into the portal circulation exists. Drug or metabolite reabsorption can occur at any point along the length of the GI tract. Those drugs or metabolites not reabsorbed are eliminated in the feces. If the drugs and metabolites are not reabsorbed into the systemic circulation, this is simply termed biliary excretion and is not EHRC. (See the Rocuronium section at the end of this course.)

**Role of Gastrointestinal Tract Microflora**

For EHRC to occur, there is substantial dependence on the flora residing in the GI tract. The role of gut microflora is so essential to our overall homeostasis that it is referred to by some authorities as an endocrine organ or “a second brain.” A host of specific enzymes secreted by gut bacteria such as cysteine conjugate β-lyase act to metabolize cysteine conjugates. Gut bacteria deconjugate and transform bile acids through a number of biochemical pathways, including oxidation-reduction of hydroxyl groups, resulting in dehydrogenation activity. The species list is long but includes *Escherichia coli* and *Pseudomonas, Clostridium, Bacillus, Eubacterium, Proteus, Lactobacillus*, and *Bacteroides* organisms. The range of actions of these different bacteria (and their associated unique chemistries) is such that some break apart only one bond, whereas others lyse numerous bonds.

The bottom line is that gut flora is vital in the deconjugation and other transformations involving metabolic activity in the bile. The activity of the diverse species residing in the gut is such that considerable work is under way involving the use of probiotic interventions in an attempt to optimize the theoretical and already established actions on the pharmacokinetics of administered drugs.

**A Look at the Liver and Bile**

The liver is a densely vascular organ with oxygenated blood arriving via the hepatic artery and the portal vein, playing the role of mobilizing nutrients from the digestive tract. Because of this double blood supply, the liver functions to remove constituents from both arterial and venous blood in an elegant physiologic arrangement that removes unwanted materials before widespread systemic distribution occurs; this constitutes the “first-pass effect.”

Liver sinusoids receive both arterial and venous blood from the hepatic artery and the portal vein, respectively. With the abundant hepatocyte lining of the hepatic artery and portal vein, bile is actively produced and enters the biliary canaliculi; this secreted product goes on to drain into ductules and then canals, which become extrahepatic ducts and ultimately the common hepatic duct (Figure 1). The complex architecture finds the common hepatic duct dividing into the common bile duct, which empties directly into the duodenum (the sphincter of Oddi is the ultimate spigot control), and the cystic duct, which leads to the gallbladder for bile storage (Figure 2).
The greenish-yellow hepatocyte secretion we term bile is an essential component to our GI tract’s processing of nutrients. Stored in the gallbladder and released into the duodenum, its most notable role is to aid the efficient absorption of lipids by the intestine, with a secondary role of protecting the mucosal lining of the digestive tract from gastric acid.3

The liver is luxuriously perfused with both the hepatic artery and portal vein intermesh, ultimately draining in the central vein, then on to the systemic circulation. The nature of the hepatic vascular architecture is such that the liver encounters (and purifies/detoxifies) blood from both arterial and venous input.

Bile contributes to liver purification by acting as a medium for holding bilirubin (from hemoglobin metabolism), cholesterol, many heavy metals, exogenous chemicals, and drugs that are presented to the liver. The biliary system is intimately involved in the first-pass effect that the liver plays by helping to remove materials before they can reach the blood system.

Certain substances (eg, drugs, toxins), once sequestered into bile, may be reabsorbed through the intestinal mucosa and reenter the systemic circulation. These chemicals can be broadly termed xenobiotics, that is, a substance that is foreign to the human body. This is the very essence of EHRC (see Figure 2).

A recent article, summarizing the quantification of bile in the forensic analysis of more than 200 cases of death involving 133 different xenobiotics, revealed the value of sampling bile as a forensic tool based on EHRC.8 There is good science for using bile analysis to support or refute hypotheses related to toxins as a cause of death even when results of plasma sampling prove unhelpful.

Drug Elimination and the Liver

One way to characterize drug elimination is the removal of a drug in an unchanged form (eg, exhaling isoflurane on its discontinuance at the end of surgery) or by metabolism, where it has been chemically modified (eg, the rapid hydrolysis of remifentanil by nonspecific plasma and tissue esterases). The actual excretion of a drug occurs via 1 or more of 3 primary mechanisms: in bile via the liver, in urine via the kidneys, or exhaled via the lungs. In select cases there may be other routes, such as through saliva, sweat, breast milk, or tears.

Polar, hydrophilic drugs have an electrical charge allowing their exit from the body via the kidneys through ion trapping and are excreted out of the body in the urine. Drugs that are insoluble in water, the lipophilic drugs, generally require some type of biotransformation that converts them to water-soluble metabolites.

Hepatic metabolism plays the dominant role in the fate of drugs and other xenobiotics that we encounter. The liver is rich in a host of biotransformational manipulators that can hydrolyze, reduce, oxidize, and conjugate xenobiotics. These reactions can be termed either phase 1 or phase 2 metabolism. The latter are concerned with conjugation-type modifications because a major task of the liver is to convert water-insoluble xenobiotics into water-soluble forms that can be excreted into urine or bile. There are many factors that can influence hepatic metabolism, as follows:

- Enzyme inducers (eg, phenytoin, long-term alcohol use)
- Enzyme inhibitors (eg, cimetidine, erythromycin)
- Hepatic blood flow (how much drug is delivered per unit time)
- Amount of free drug in the blood
- Efficiency of the metabolic process
Overall health and function of the liver
• Age of the individual
• Unique genomic factors

The hepatocyte is a remarkable physiologic entity with a diverse and impressive resume (Figure 3). It absorbs exogenous substrates from the blood and secretes metabolites into the bile, also producing bile acids from cholesterol. Hepatocytes excrete a variety of endogenous metabolites and degrade a number of hormones. These cells perform diverse and highly variable metabolic actions, often in a landscape best described as changing on a day-to-day (if not hourly) basis, which is greatly dependent on what the host human is experiencing. This adaptability to xenobiotic challenges reveals a plasticity in function that is unrivaled given the structural uniformity of these cells.

Relevancy of Enterohepatic Recirculation
We know the liver is remarkably diverse in inactivating xenobiotics employing several different phase 1 and phase 2 mechanisms. Many drugs, morphine being a good example, are inactivated by glucuronide or sulfate conjugation with subsequent movement into the bile and eventual emptying into the GI tract. Once in the GI tract, enzymes produced by gut flora can hydrolyze conjugated drugs in the small and large intestine, resulting in the active form reemerging, with reabsorption likely. This process of deconjugation may result in the parent drug or its metabolites becoming available for reabsorption. The Table lists common compounds that undergo some degree of EHRC.

Conservation of Essential Substrates?
From an evolutionary perspective, one can argue that beyond the management of xenobiotics, EHRC plays an important role regarding a number of essential endogenous substrates. Enterohepatic recirculation permits conservation of bile acids, vitamin D₃, vitamin B₁₂, folic acid, and estrogen, minimizing their inefficient loss when such substrates can continue to play a role in homeostasis by giving the body a second (or third) opportunity to utilize them.

Scientific work performed in the 1980s was the first to provide evidence that a single dose of oral morphine demonstrated relatively poor analgesic effect, whereas its relative potency seemed to increase when used in repeated dosing, a phenomenon that could not be explained by accumulation of the parent drug alone. The explanations provided included a dose-dependent presystemic metabolism of the drug; a contribution of a metabolite, namely morphine-6-glucuronide (M₆G); and EHRC of morphine and its metabolites. Morphine-6-glucuronide is a strong μ-receptor agonist. The principal metabolite of morphine (along with morpine-3-glucuronide), M₆G is produced in abundance after either intravenous or oral administration of morphine. In this study, the M₆G
levels were very high, with plasma levels exceeding that of the parent drug. A prolongation of the clinical and terminal elimination half-lives was observed with both conjugates. The authors of the study noted that because of EHRC, the high plasma concentration of the conjugates was not due to rapid metabolism of the parent molecule, but rather to continued production of the 2 glucuronides.

Reconsidering the unfortunate outcome of the Amanita phalloides ingestion presented earlier, it is obvious that the hepatocytes are at highest risk for exposure to the effect of toxicants and their associated metabolites, analogous to the vulnerability of the “tip of the sword” of an infantry patrol unit. Furthermore, blood directed to the liver from the GI tract containing reabsorbed toxic materials has the opportunity to deliver a second hit to the hepatocytes, increasing the potential for greater cell and organ damage. In cases such as poisoning due to Amanita phalloides, the second confrontation of the toxin with the hepatocytes, due to EHRC, may leave the affected individual with little hope for survival outside rapid plasmapheresis or, in some cases, liver transplantation, because there is no specific antidote.14

The salient message for clinicians is that if a drug’s pharmacokinetics involves EHRC, then drug secreted in the bile may serve as a secondary source for drug absorption, prolonging elimination and possibly causing additional elevations in drug plasma concentration (see Figure 2).

**Rocuronium: Biliary Excretion Versus EHRC**

Initially, kinetic elimination studies of rocuronium, currently the most common nondepolarizing muscle relaxant used in surgical anesthesia, were based on animal models. The now definitive article by Proost et al15 clearly defined the metabolic fate of this drug in humans. The elegant and methodologically sound work of Proost and colleagues also demonstrates the logistical complexities of performing pharmacokinetic studies that involve bile, because sampling must occur both before and after its entry into the small intestine, along with periodic plasma assays.

Thirty-eight adult patients, ASA classes 1 to 3, undergoing general anesthesia for procedures where a T-drain remained in place for bile sampling, were studied.15 Using sound pharmacokinetic methods (including bile, urine, fecal, and plasma assays over about a week), Proost et al found that rocuronium is taken up by the liver and excreted into bile in high concentrations. Fecal and urinary excretion are the primary pathways of rocuronium elimination, with only very small amounts of the metabolite 17-desacetyl-rocuronium recovered.

The case of rocuronium provides the opportunity to differentiate between EHRC and biliary excretion, because there is some confusion in many practitioners’ minds and in the literature. Although EHRC does involve biliary excretion, it does so with a return of the drug or its metabolites to the systemic circulation. Biliary excretion as a unique and independent pharmacokinetic process is the fecal loss of the drug or its metabolites without their return to the systemic circulation. Biliary excretion then should be thought of as an elimination pathway all to itself, as is the case with rocuronium. This is quite different from EHRC, which has an important distributive component in addition to an elimination component that encompasses its uniqueness.16

**Conclusion**

Enterohepatic recirculation can be viewed as an elimination pathway of xenobiotics (drugs, toxins, and other solutes) with a distributive component. Patients exposed to drugs that undergo a high percentage of EHRC will have longer clinical half-lives of those drugs; metabolites of some of the compounds may have greater potency or toxicity than the parent form. Considering the variability among patients in their actual EHRC activity, some drugs will experience longer apparent half-lives, whereas some may generate more toxic metabolites. In any event, all will require longer interdosing intervals and careful monitoring for drug effect, to achieve safe and effective administration.

Given the methodologic challenges of studying EHRC and the many factors that can influence a given patient's

---

**Table. Partial List of Compounds and Their Metabolites Found in Bile and Involved in Enterohepatic Circulation**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Digitoxin</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Indocyanine</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Rifamycin</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Warfarin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clorazepate</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
</tr>
<tr>
<td></td>
<td>Cephazolin</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
</tr>
<tr>
<td></td>
<td>Gentaminex</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
</tr>
<tr>
<td></td>
<td>Mornaphine</td>
</tr>
<tr>
<td></td>
<td>Nortriptyne</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
</tr>
<tr>
<td></td>
<td>Testosterone</td>
</tr>
</tbody>
</table>

|                | Ampicillin          |
|                | Cefixime            |
|                | Clindamycin         |
|                | Doxycycline         |
|                | Imipramine          |
|                | Methadone           |
|                | Norfloxin           |
|                | Rifampic           |

---

**Adriamycin** | **Amiodarone** | **Amphetamine** | **Ampicillin**

**Benzylpenicillin** | **Bilirubin** | **Clorazepate** | **Cefixime**

**Ceftazidime** | **Chloramphenicol** | **Cephazolin** | **Clindamycin**

**Diazepam** | **Digitoxin** | **Digoxin** | **Doxycycline**

**Erythromycin** | **Estradiol** | **Gentaminex** | **Imipramine**

**Indocyanine** | **Indomethacin** | **Lorazepam** | **Methadone**

**Methotrexate** | **Metronidazole** | **Mornaphine** | **Norfloxin**

**Meperidine** | **Penicillin** | **Phenytoin** | **Rifampic**

**Rifamycin** | **Spironolactone** | **Testosterone** | **Tetracycline**

**Valproic acid** | **Warfarin** |
hepatic function, not the least of which is his or her unique pharmacokinetic profile, much work still needs to be accomplished in this domain. For example, with many drugs currently in use and complimentary remedies such as herbal medicines available, the role of EHRC likely has not been quantified. The worst-case scenario would be a drug that undergoes a high degree of EHRC and has a narrow therapeutic window. Be careful of what mushrooms you indulge in, especially if self-foraged!

REFERENCES


AUTHOR

Chuck Biddle, PhD, CRNA, is a professor and staff anesthetist at Virginia Commonwealth University, Richmond, Virginia. He is the editor-in-chief of AANA Journal and had no oversight role in the peer review of this manuscript, which was handled by other members of the editorial board. Email: cjbiddle@vcu.edu.

DISCLOSURES

The author has declared no financial relationships with any commercial entity related to the content of this article. The author did not discuss off-label use within the article. Disclosure statements are available for viewing upon request.

ACKNOWLEDGMENT

The author would like to thank Taylor Simson, MS, a medical illustrator, for preparing Figure 1.