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Clearing of Metabolic Waste via Enterohepatic Recirculation

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Introduction

Thesis statement: The nature of bile lends itself to the recycling of metabolic waste, causing these waste products to reenter the blood stream through the process known as enterohepatic recirculation. This recycling could possibly become a concern as exposure to potentially harmful waste products is increased.

A thorough literature research using Science Citation Index was conducted, covering the years from 1971 until present (182 articles were studied). Search criteria included all references to enterohepatic recirculation. This resulted in many references including the filtering from the bloodstream of hormones that the human body produces on a consistent basis; pharmaceuticals; environmental synthetic contaminants; vitamin, anti-oxidant compounds and other non-pharmaceutical compounds; enterohepatic recirculation in the metabolism of cholesterol; the role of dietary fiber in interrupting the enterohepatic recirculation; and the use of bile sequestrant medications that interrupt the enterohepatic recirculation. Additionally, there were a number of studies that noted various factors and compounds that affected the enterohepatic recirculation.

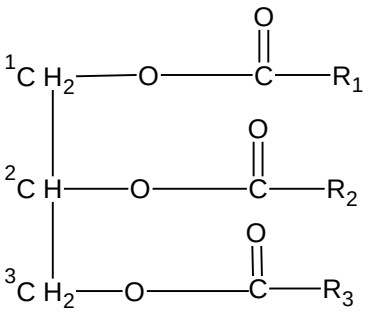
A General Description of Enterohepatic Recirculation

Due to the physiology of the gastro-intestinal tract, bile salts and acids emulsify nonpolar compounds which can then be absorbed in the small colon. This recycling of bile and the nonpolar compounds it contains is labeled the enterohepatic recirculation. The enterohepatic recirculation is an efficient system that allows the bile acids to reenter the bloodstream and return to the liver for reuse several times each day. Bile is amphipathic (both polar and nonpolar) with the large majority of the bile acids confined within the enterohepatic recirculation system. (Crosignani et al. 1996) The recycling of nonpolar compounds that are returned to the bloodstream may have significant impact on various

health conditions. The reabsorption of metabolic wastes into the bloodstream through the enterohepatic recirculation may contribute to adverse health events as exposure to potentially harmful substances increase.

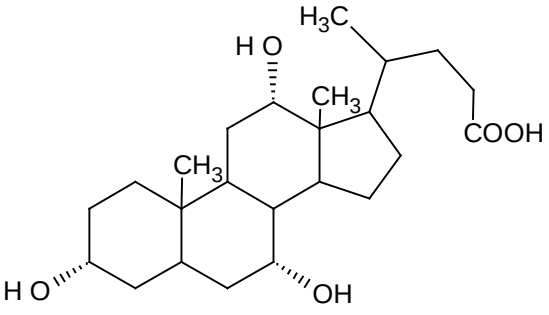
The Nature of Bile Acids and Bile Salts and Their Role in Enterohepatic Recirculation

Besides water, bile is composed of several substances including triacylglycerols, also known as triglycerides or fats. Triacylglycerols are nonpolar, water-insoluble substances that are fatty acid triesters of glycerol (Figure 1, where R_1, R_2, and R_3 are long hydrocarbon chains containing 14 to 22 carbons).

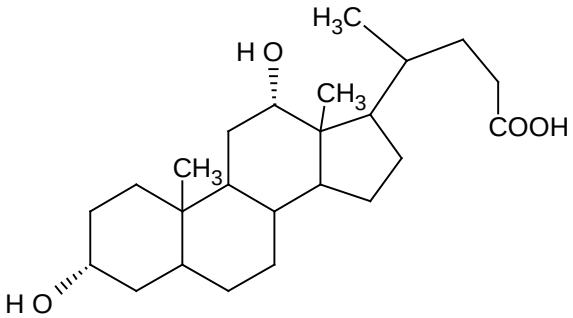


Triacylglycerol Figure 1

Bile acids are constituents of bile and include cholic and deoxycholic acid (Figure 2). These detergent molecules assist in the absorption of dietary lipids in the intestine.



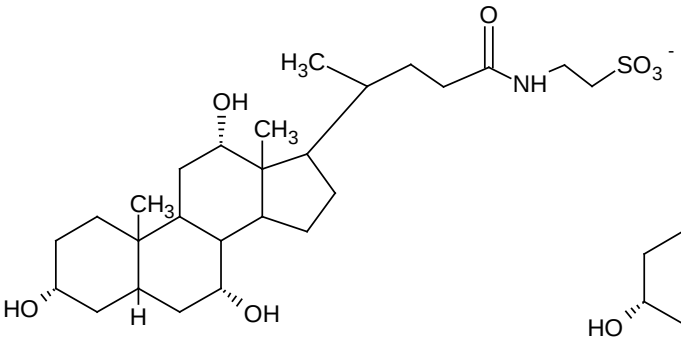
Cholic acid



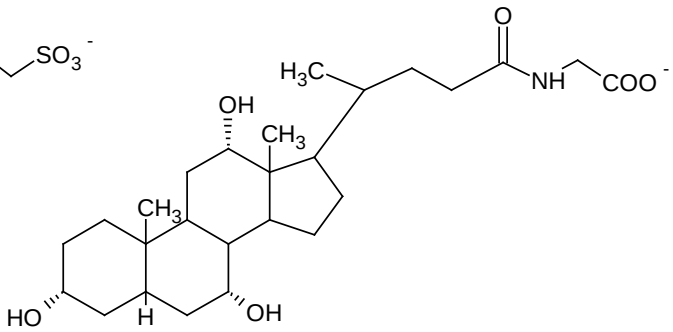
Deoxycholic acid

Figure 2

The bile acids are mostly composed of bile salts, a family of carboxylic acid salts with steroid backbones that act as detergents to emulsify the triacylglycerols. The Na^+ and K^+ salts of taurocholic acid and glycocholic acid are the principal bile salts (Figure 3). Bile salt anions have a hydrophilic side and a hydrophobic side. They tend to aggregate around droplets of fat (triacylglycerols) to form micelles. The hydrophobic side is towards the fat and the hydrophilic side towards the outside. The hydrophilic sides are positively charged which prevent fat droplets coated with bile from re-aggregating into larger fat particles. Without bile salts most lipids would be passed out of the body through the feces. Bile increases the absorption of fats and therefore is important in the absorption of fat-soluble substances, including vitamins A, D, E, and K.



Taurocholic acid



Glycocholic acid

Figure 3

Specific Examples of Wastes that Are Recirculated

As the enterohepatic recirculation deposits nonpolar substances back into the bloodstream, it becomes important to study the compounds that may be subject to this recycling. Repeated exposure to some nonpolar compounds may not be beneficial to the human body.

Hormones

Hormones are one such set of recycled substances. These endogenous (internally derived) signal molecules are secreted by endocrine glands. Hormones are filtered from the bloodstream by the liver and placed in the bile. That hormones are recycled through the enterohepatic recirculation is clear from the studies that have been thus far conducted. In fact, the intestine may be considered as an "endocrine" active site or organ (Groh et al. 1993).

Steroid Hormones

Estrogen, a steroid hormone, was noted to recycle through the enterohepatic recirculation at a much higher degree than androgen. (Barone et al. 2001) Animal studies with four lynx species reveal that estrogen metabolism had a large proportion (50%) excreted through the bile. (Dehnhard et al. 2010) The bile with the estrogen was recycled via the enterohepatic recirculation thus reintroducing the estrogen into the bloodstream and increasing the animal's exposure to this hormone.

In a study to investigate the pharmacokinetics of oestriol in plasma in the dog, it was found that the concentration-time curve strongly suggested the existence of enterohepatic recirculation. The average relative contribution of the enterohepatic recirculation to the oestriol in the plasma was estimated to be 22%, 38%, and 44% on days 1, 3 and 7. The oestrial was administered to the dogs daily for seven consecutive days, showing that the consistent daily exposure to this hormone showed increased amounts of the hormone being recycled back into the bloodstream via the enterohepatic recirculation.(Hoeijmakers et al. 2003)

An interesting study involving the intravenous injection of progesterone in non-pregnant monkeys resulted in total disappearance of the labeled hormone from the circulation within three hours. However, .5 to 1.75 hours after the progesterone disappeared from circulation it reappeared, reaching 20% of the initial maximal concentration. The conclusion of the study was that the unexpected

reappearance of the progesterone wasn't explained by enterohepatic recirculation as "progesterone does not undergo enterohepatic recirculation" and a suggested explanation was that a delayed release from tissue stores was the cause for this unexpected reappearance of the progesterone in the bloodstream. (Kowalski et al. 1996) That progesterone is not recycled is echoed by G.N. Shenfield "The progestogens are only metabolized in the liver and have no significant enterohepatic recirculation." (Shenfield 1993)

Eighteen healthy postmenopausal women were given oral doses of three equimolar doses of oestradiol (Figure 4); oestradiol plus desogestrel, a synthetic progestational hormone used in combined oral contraceptives (Figure 5), and oestradiol valerate, a synthetic estrogen. (Figure 6). The conclusion of the study was that the exogenously added oestradiol and its metabolites follow the recirculation pathway of the endogenous oestrogen pool. (Vree and Timmer 1998) This is a significant finding if both endogenous (internally- derived) and exogenous (externally-derived) estrogens are treated the same by the enterohepatic recirculation. It raises the possibility of increased susceptibility to estrogen-fed cancers through the administration of hormonal replacement therapy as these exogenous hormones reenter the bloodstream.

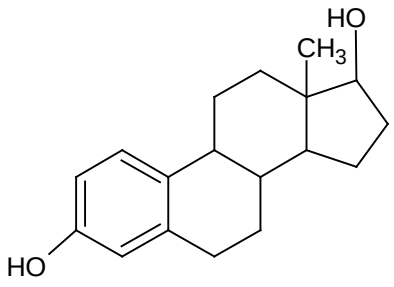
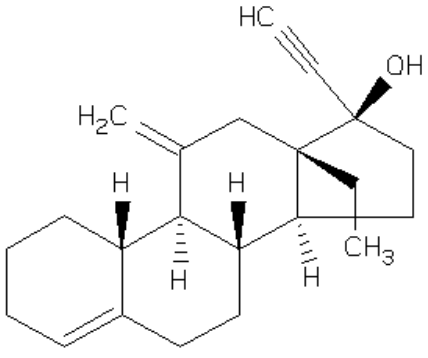
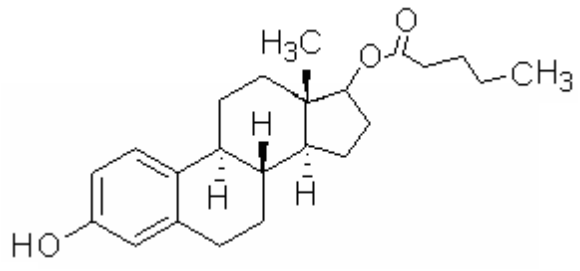


Figure 4 Oestradiol



Desogestrel Figure 5



Oestradiol Valerate Figure 6

In contrast, effective enterohepatic recirculation can interfere with the plasma concentrations of estrogens as the estrogen levels could be higher than expected. In a study evaluating the effectiveness of an oral contraceptive (ethinylestradiol) a small percentage of women had impaired plasma concentrations due to the interference with the enterohepatic recirculation resulting in contraceptive failure. (Weisberg 1999)

In a study examining the use of racemic phyto-oestrogen 8-prenylnaringenin (8-PN) as a possible alternative to classical hormone replacement therapy, the enterohepatic recirculation was significant. A serum concentration second peak indicated pronounced enterohepatic recirculation. (Rad et al. 2006)

In a study of the biological activity of steroid hormones, it was found that liver metabolism and enterohepatic recirculation were important considerations in the use of halogenated estrogen radiopharmaceuticals. (Holt et al. 1992) These halogenated estrogens are used in imaging and site-directed radiocytotoxicity of receptor-rich cancers. As the efficacy of the enterohepatic recirculation increases the possibility of higher levels of recirculated halogenated estrogen radiopharmaceuticals is a consideration.

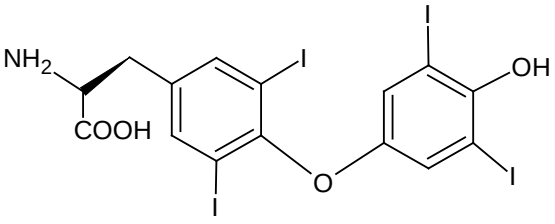
Selective estrogen receptor modulators used in metastatic breast cancer also undergo enterohepatic recirculation. In a study examining the safety, tolerability, pharmacokinetics, and

pharmacodynamics of the oral selective estrogen receptor modulator ERA-923 it was noted that the ERA-923 underwent extensive metabolism and enterohepatic recirculation. In addition, pharmacokinetic analysis showed that a high fat breakfast increased the extent of absorption. (Cotreau et al. 2002) The consequence that is implied is a more thorough exposure to the ERA-923.

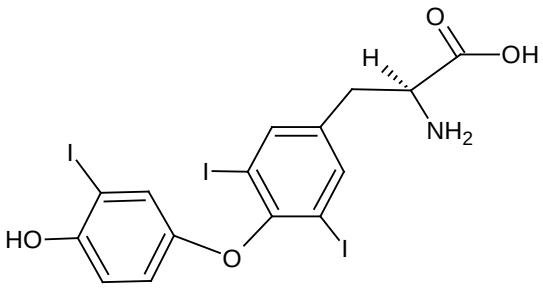
Estrogens are not the only hormone to undergo enterohepatic recirculation. A study of the fecal steroid content in golden eagles and peregrine falcons showed enterohepatic recirculation of the administered non-estrogenic steroids as demonstrated by biphasic and triphasic excretion patterns. (Staley et al. 2007)

Thyroid Hormones

Not only do the fat-derived hormones undergo enterohepatic recirculation, but also the amino acid-derived hormones such as the thyroid hormones. It is noted that thyroxine (T4) and triiodothyronine (T3) (Figure 7) undergo increased enterohepatic circulation in thyrotoxicosis, a condition known as Graves disease or hyperthyroidism. (Azezli et al. 2007)



Thyroxine



Triiodothyronine

Figure 7

In a study on rats, the role of the intestines and enterohepatic pathways in the regulation of whole-body thyroid hormone in both the intact hypothyroid and euthyroid rat was studied. It was concluded that the hypothyroid rats compensated for the low T3 levels by fecally excreting a much

smaller fraction of the total T3 production (correlating to an increase in enterohepatic recirculation). (Distefano et al. 1993)

As noted before that the enterohepatic recirculation of thyroid hormones is increased in Graves disease, a study was conducted to determine if a pharmaceutical bile sequestrant, cholestyramine, could be used as an adjunctive therapy in the management of hyperthyroidism. In the randomized, double-blind, placebo-controlled trial, 45 patients were treated. It was concluded that an interruption in the enterohepatic recirculation by the low dose of cholestyramine was an effective adjunctive agent in the treatment of Graves disease. (Kaykhaei et al. 2008)

Insulin Growth Factors

Other hormones that are subject to enterohepatic recirculation are insulin-like growth factors that control the growth and development during the perinatal period. These hormones are also present in biologically significant quantities in mammalian milks. In a study involving suckling rats it was concluded that the insulin-like growth factors were circulated back to the blood stream via enterohepatic recirculation. (Philipps et al. 2000)

Vitamins - Folate

Various vitamins and anti-oxidants undergo enterohepatic recirculation. Serum folate concentration increased in a study done with nine healthy female volunteers in a fasting state. The rise in serum levels of folate was hypothesized to be due to the enterohepatic recirculation. (Cahill et al. 1998) In animals, the liver controls the supply of folate through first pass metabolism, biliary secretion, enterohepatic recirculation, as well as through senescent erythrocyte recycling. (Donnelly 2001)

Vitamin D_3 and Resveratrol

Vitamin D_3 undergoes an enterohepatic recirculation in both man and experimental animals. (Kumar 1990) Resveratrol, a plant phoalexin, prevents or delays carcinogenesis by inhibiting the three phases of the cancer process: initiation, promotion, progression and invasion phases. It is not toxic in animal models even at high dosages. The enterohepatic recirculation contributes to a delayed elimination of the molecule from the body which can also show a prolonged effect enhanced by its binding to plasmatic proteins. (Latruffe et al. 2006) In this case, the enterohepatic recirculation would be beneficial in preventing or delaying cancer growth as repeated exposure to the resveratrol is affected.

Flavonoids

Luteolin is a flavonoid. It is thought to play an important role in the human body as an antioxidant, free radical scavenger, and immune system modulator. In a study evaluating plasma concentration of luteolin, double peaks were found after intravenous and oral administration, suggesting enterohepatic recirculation. (Sarawek et al. 2008)

Flavopiridol, a flavone derivative under clinical development for the treatment of chronic lymphocytic leukemia , exhibited a postinfusional peak which appears to be related to enterohepatic recirculation.(Rudek et al. 2003)

Enterohepatic Recirculation and Cholesterol

The enterohepatic recirculation plays a major role in the excretion of cholesterol. Bile acids are synthesized from cholesterol. "The quantitatively most important pathway for the excretion of cholesterol in mammals is the formation of bile acids (also called bile salts). This is the body's only route for cholesterol excretion." (Voet et al. 1995)

Enterohepatic Recirculation and Pharmaceuticals

The literature extensively reports the effects of enterohepatic recirculation on pharmaceuticals. Of all the references researched for this paper, 40% involved the recycling of pharmaceuticals. In

general, enterohepatic recirculation may prolong the pharmacological effect of certain drugs and drug metabolites. (Roberts et al. 2002) Models have been developed to estimate the impact of serum level concentrations of medications affected by the enterohepatic recirculation. A general treatment of enterohepatic recirculation of drugs has been developed based on the fraction of drug in systemic circulation that is excreted in the bile and the fraction of drug reabsorbed from the gut that reaches systemic circulation in each enterohepatic cycle. The deduced equations make it possible to establish mathematical relationships between the areas under the blood level curves. (Shou et al. 2005; Perisribera et al. 1992). Drugs undergoing enterohepatic circulation are associated with typical pharmacokinetic characteristics such as multiple-peak phenomenon in the plasma concentration-time profile and prolongation of the apparent elimination half-life. (Lehr et al. 2009) (Plusquellec and Houin 1995) In general, enterohepatic recirculation may prolong the pharmacological effect of certain drugs and drug metabolites. (Roberts et al. 2002)

Cholesterol-Lowering Medications

Medications to control cholesterol levels are also affected by the enterohepatic recirculation. HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase of HMGCR) is the rate-controlling enzyme of the metabolic pathway that produces cholesterol. This enzyme is thus the target of the widely available cholesterol-lowering drugs known collectively as the statins. In a study investigating the effects of cholesterol and cholestyramine (a medication used to inhibit the reabsorption of bile acids), it was shown that the interruption of the enterohepatic circulation of bile acids (cholestyramine feeding) increased HMG-CoA reductase activity five-fold. (Shefer et al. 1992)

The drug ezetimibe acts through inhibition of enterohepatic circulation. In a study of hypercholesterolemia (high cholesterol level) liver transplant recipients, the reduction in cholesterol by the use of this bile sequestrant pharmaceutical was effectively used. This provided an alternative to the

use of statins that are not recommended for patients with chronic liver disease. (Almutairi et al. 2009) Ezetimibe (also known as Zetia) reduces the small intestinal enterocyte uptake and absorption of cholesterol. (Davis and Veltri 2007) Ezetimibe itself is excreted into bile and undergoes extensive enterohepatic recirculation. (Yamamoto et al. 2007)

Enterohepatic recirculation occurs via biliary excretion and intestinal reabsorption of a drug. Drug recycling through enterohepatic recirculation can lead to a change in pharmacokinetic properties, such as reduced clearance, extended half-life and increased plasma exposure. As a result, enterohepatic recirculation may prolong the pharmacological effect of drugs. (Shou et al. 2005)

Antihypertensive Drugs

The pharmacokinetic actions, bioequivalence (two products that are expected to be the same for all intents and purposes), and cardiovascular effects of two verapamil products (high blood pressure medications) were studied in a randomized, double-blind, crossover study in eight elderly hypertensive patients. Multiple concentration peaks after absorption were observed in all patients with both verapamil products and were perhaps related to enterohepatic recirculation. (Saseen et al. 1997)

Following a single dose of a new antihypertensive drug, UP 269-6 to 12 healthy volunteers, the plasma levels showed at least two secondary peaks. To explain this observation, the data were fitted to a new compartmental model of enterohepatic recirculation, without using a numerical method. Most subjects exhibited two cycles of recirculation. The amount of drug involved in each recirculation was calculated and the AUCs compared. The drug showed high biliary excretion and reabsorption. (Plusquellec et al. 1998)

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the pharmaceuticals that are known to be affected by the enterohepatic recirculation. Nonsteroidal anti-inflammatory drugs are effective

antipyretic, analgesic, and anti-inflammatory agents. One of the major concerns regarding the use of these compounds is the incidence of gastrointestinal adverse effects, ranging from dyspepsia to the serious and potentially life-threatening complications of ulcers, hemorrhages, and perforations.

The effect of exogenously added bile acids upon the bioavailability of indomethacin (a NSAID) was investigated in healthy human volunteers. In vitro dissolution studies were performed on formulations containing indomethacin and bile acids and the effects of enteric coating determined. Pharmacokinetic evaluation of the results of the human volunteer study suggests that bile acids increase the bioavailability of indomethacin by prolonging its enterohepatic circulation. (Cole et al. 1992)

Mechanisms underlying the gastric toxicity of nonsteroidal anti-inflammatory drugs have been extensively investigated, whereas those leading to intestinal damage are not completely understood. Several hypotheses have been put forward on the pathophysiology of intestinal damage by NSAIDs including enterohepatic recirculation. (Cipolla et al. 2002) It is postulated that decreased enterohepatic recirculation contributes to decreased APAP (acetaminophen) hepatotoxicity by reducing liver exposure. (Ghanem et al. 2005)

The small intestine is a more common site for nonsteroidal anti-inflammatory drug toxicity than the well-recognized effects on the stomach and duodenum. Although NSAID strictures and perforation are rare, two-thirds of regular-NSAID users may be prone to small bowel enteropathy. NSAID toxicity to the small intestine is common. (Fortun and Hawkey 2005) The recycling of NSAIDs could possibility be a contributing factor to small intestine toxicity as the exposure to the NSAID in the gastro-intestinal tract would be increased through enterohepatic recirculation.

Development of resistance to toxic effects of acetaminophen (APAP) was reported in rodents and humans, though the mechanism is only partially understood. A study examined the effect in rats of administration with subtoxic daily doses of APAP on enterohepatic recirculation and liver toxicity. The

beneficial effect of interfering with the enterohepatic recirculation was alternatively tested in animals receiving activated charcoal by gavage to absorb APAP of biliary origin. The data indicated decreased liver APAP content and glutathione consumption. The conclusion was that selective up-regulation of Mrp3 (multidrug resistance protein-3) expression by APAP pre-treatment may contribute to development of resistance to APAP hepatotoxicity, at least in part by decreasing its enterohepatic recirculation. (Ghanem et al. 2009)

The pathogenesis of NSAID-induced small intestinal damage remains poorly understood. The aim of one study was to examine the relative importance of enterohepatic recirculation, using an NSAID derivative (nitrofenac) that does not cause small intestinal damage. The conclusion of the study was that the enterohepatic recirculation of NSAIDs is of paramount importance in the pathogenesis of enteropathy. (Reuter et al. 1997) The pharmacokinetics of diclofenac, a NSAID, was evaluated and found to be "definitely subject to enterohepatic circulation." (Fukuyama et al. 1994) This could increase the possibility of intestinal injury by the gut exposure to increased amounts of the NSAID. Enterohepatic recirculation of nonsteroidal anti-inflammatory drugs is a critical factor in the pathogenesis of intestinal injury; however, the underlying mechanism of toxicity has not been confirmed. (Seitz and Boelsterli 1998)

Other Pharmaceuticals

Morphine elimination is characterized by a prolonged terminal elimination phase, at least in part because of enterohepatic recirculation. (Ouellet and Pollack 1995) The plasmatic profiles of twelve healthy volunteers after oral administration of ranitidine (Zantac), a histamine H2-receptor antagonist that inhibits stomach acid production were studied. The presence of two peaks was observed. The proposed mechanism responsible for the existence of secondary peaks includes enterohepatic recirculation and the existence of multiple sites of absorption along the gastrointestinal tract.

(Schaiquevich et al. 2002) Secondary peaks in oral concentration-time profiles following ranitidine administration may be due to discontinuous absorption along the gastrointestinal tract, postabsorptive storage and release, and/ or enterohepatic recirculation. (Suttle and Brouwer 1994)

The absorption and disposition of roquinimex, a quinoline derivative immunostimulant which increases natural killer cell activity were studied in four male and two female healthy volunteers. A secondary peak was observed between 6 and 8 hours, indicating enterohepatic circulation of roquinimex. (Strandgarden et al. 2000)

Enterohepatic recirculation of a chemotherapy drug, irinotecan and one of its metabolites, SN-38, used to treat colon and rectal cancer, has been observed in pharmacokinetic data sets from previous studies. Rebound in the plasma concentration suggestive of enterohepatic recirculation at approximately 0.5-1 hour post-infusion was observed in most irinotecan plasma concentration profiles, and in some plasma profiles of the SN-38 metabolite. (Younis et al. 2009)

Enterohepatic Recirculation and Exposure to Environmental Contaminants

Bisphenol A (BPA)

Environmental contaminants are affected by the enterohepatic recirculation. Bisphenol A (BPA) is an important industrial chemical used in the manufacture of polycarbonate plastic products and epoxy resin-based food can liners. BPA is thought to be an endocrine disruptor, mimicking the body's own hormones. Early development years appears to be the period of time that a person may have the greatest sensitivity to its effects. BPA has received much attention in the last several years due to the possibility of toxic effects. In a study of 660 Americans it was apparent that more than 90% had ubiquitous and frequent exposure found by the presence of BPA in urine. Evidence for enterohepatic recirculation of the conjugated BPA was observed in adult rats. (Doerge et al. 2010) Bisphenol A, a weak xenestrogen that has estrogenic effects that differ chemically from naturally occurring estrogenic

substances was shown to be excreted with the feces as free BPA. However, a second peak in the time-course of plasma radioactivity suggested enterohepatic recirculation of BPA glucuronide. (Kurebayashi et al. 2005)

Despite its low oestrogenic potency there is concern that, as a consequence of slow clearance, BPA might reach biologically significant levels in humans and animals exposed to environmental levels. This could result in an increase of disease such as estrogen-related cancers. As a result a study assessed the kinetic behavior of BPA in female rats was conducted. Fluctuations in BPA plasma levels were potentially explained by the enterohepatic recirculation. (Upmeier et al. 2000)

Perfluorinated Compounds (PFCs)

There has been no proven method thus far to accelerate the clearance of potentially toxic perfluorinated compounds (PFCs) in humans. PFCs are a family of commonly used synthetic compounds with many applications, including repelling oil and stains on furniture, clothing, carpets and food packaging, as well as in the manufacturing of polytetrafluoroethylene-a nonstick surfacing often used in cookware (e.g. Teflon). Some PFCs remain persistent within the environment due to their chemical stability, and are very slowly eliminated from the human body due, in part, to enterohepatic recirculation. Exposure to PFCs is widespread and some subpopulations, living in proximity to or working in fluorochemical manufacturing plants, are highly contaminated. PFC bioaccumulation has become an increasing public health concern as emerging evidence suggests reproductive toxicity, neurotoxicity and hepatotoxicity, and some PFCs are considered to be likely human carcinogens. Further recirculation study is required but this report suggests that cholestyramine therapy may facilitate gastrointestinal elimination of some PFCs from the human body. (Genuis et al. 2010)

Factors that Inhibit or Increase Enterohepatic Recirculation

Dietary Fiber

Dietary fiber has long been studied largely focusing on its beneficial effects on colon cancer and disorders of the gastric intestinal tract. In the 1980's it was suggested that dietary fiber may have a beneficial effect on breast cancer due to its ability to interrupt the enterohepatic recirculation thereby reducing the amount of recycling estrogens. Through evidence from epidemiology, clinical interventions, and animal model studies, this hypothesis is supported in chemically-induced mammary tumorigenesis, but interestingly enough, some studies do not support an estrogen-based mechanism. (Cohen 1999)

Circulating bile acid concentrations were significantly lower in soluble-fiber fed rats versus rats that were fed insoluble fibers. Additionally, the soluble-fiber fed rats fecal bile acid output was significantly higher than that of the insoluble fiber fed rats. These results point to a mechanism involving the disruption of the enterohepatic recirculation. (Overton et al. 1994)

Dietary Restriction (Fasting)

There are other factors affecting the enterohepatic recirculation. Dietary restriction (fasting) was shown to be a factor in the concentration of 17-beta-estradiol (E-2) in sheep. The concentration of E-2 was two times greater in bile in the fasted ewes compared to the fed ewes, yet the rate of clearance of E-2 was decreased during nutritional restriction indicating that the enterohepatic recirculation was involved in the decreased E-2 clearance during dietary restriction. (Renquist et al. 2008)

Gastric Bypass Surgery

Another factor that may affect the enterohepatic recirculation is gastric bypass surgery. The altered gastrointestinal anatomy was hypothesized in a study done to assess circulating bile acid concentrations in patients who previously underwent gastric bypass. (Lewis and Heaton 1999) Demand for bariatric surgery has risen exponentially and bariatric patients often have multiple indications for post-operative pharmacotherapy. The purpose of this study was to systematically review the published

literature examining the effect of bariatric surgery on drug absorption. The effect of bariatric surgery on drug absorption appears drug-specific. Drugs that are intrinsically poorly absorbed, highly lipophilic and/or undergo enterohepatic recirculation exhibited the greatest potential for malabsorption. Rigorously conducted controlled studies are needed to evaluate the effect of modern bariatric procedures on drug absorption. (Padwal et al. 2010)

Intestinal Transit

A substantial influence on the enterohepatic recirculation of bile acids is intestinal transit. Slow transit is likely to favor disease processes that are related to over-efficient enterohepatic recirculation. These include gallstones, large bowel cancer, and possibly breast cancer. (Lewis and Heaton 1999)

Ezetimibe and Cholestyramine

Medications that are used to inhibit the enterohepatic recirculation are ezetimibe, also known as Zetia and cholestyramine. Ezetimibe is commonly prescribed for reducing blood cholesterol; however, the mechanism of action is inhibition of the enterohepatic recirculation versus the mechanism of statins (which is HMB-CoA reductase inhibition). Cholestyramine had been shown to inhibit the recycling thyroid hormones by interrupting the enterohepatic recirculation. (Kaykhaei 2008)

Conclusion

The enterohepatic recirculation appears to play a major role in absorption of fat-soluble substances including beneficial compounds such as fat soluble vitamins. However, it appears that the enterohepatic recirculation also can play a detrimental role as compounds that can cause harm are allowed to recycle. This additional exposure to potentially dangerous substances may increase the risk of disease (i.e. hormonally receptive cancers). The use of inhibitory agents such as dietary fiber would be prudent to employ in order to block the possible negative effects of the enterohepatic recirculation.

References

Almutairi, F., T. C. Peterson, M. Molinari, M. J. Walsh, I. Alwayn, and K. M. Peltekian. 2009. Safety and Effectiveness of Ezetimibe in Liver Transplant Recipients with Hypercholesterolemia. *Liver Transplantation* 15 (5):504-508.

*Azezli, A. D., T. Bayraktaroglu, and Y. Orhan. 2007. The use of konjac glucomannan to lower serum thyroid hormones in hyperthyroidism. *Journal of the American College of Nutrition* 26 (6):663-668.

Barone, D., F. Peroglio, E. Toso, and T. Bruzzese. 2001. Binding of mepartricin to sex hormones, a key factor of its activity on benign prostatic hyperplasia. *Arzneimittel-Forschung-Drug Research* 51 (12):984-990.

Cahill, E., J. McPartlin, and M. J. Gibney. 1998. The effects of fasting and refeeding healthy volunteers on serum folate levels. *International Journal for Vitamin and Nutrition Research* 68 (2):142-145.

Cipolla, G., F. Crema, S. Sacco, E. Moro, F. De Ponti, and G. Frigo. 2002. Nonsteroidal anti-inflammatory drugs and inflammatory bowel disease: Current perspectives. *Pharmacological Research* 46 (1):1-6.

*Cohen, L. A. 1999. Dietary fiber and breast cancer. *Anticancer Research* 19 (5A):3685-3688.

Cole, S. K., M. J. Story, T. Laudanski, M. Dwyer, D. Attwood, J. Robertson, and S. G. Barnwell. 1992. TARGETING DRUGS TO THE ENTEROHEPATIC CIRCULATION - A POTENTIAL-DRUG DELIVERY SYSTEM DESIGNED TO ENHANCE THE BIOAVAILABILITY OF INDOMETHACIN. *International Journal of Pharmaceutics* 80 (1):63-73.

Cotreau, M. M., L. Stonis, K. H. Dykstra, T. Gandhi, M. Gutierrez, J. Xu, Y. Park, P. H. Burghart, and U. S. Schwertschlag. 2002. Multiple-dose, safety, pharmacokinetics, and pharmacodynamics of a new selective estrogen receptor modulator, ERA-923, in healthy postmenopausal women. *Journal of Clinical Pharmacology* 42 (2):157-165.

Crosignani, A., K. D. R. Setchell, P. Invernizzi, A. Larghi, C. M. P. Rodrigues, and M. Podda. 1996. Clinical pharmacokinetics of therapeutic bile acids. *Clinical Pharmacokinetics* 30 (5):333-358.

Davis, H. R., and E. R. Veltri. 2007. Zetia: Inhibition of Niemann-Pick C1 like 1 (NPC1L1) to reduce intestinal cholesterol absorption and treat hyperlipidemia. *Journal of Atherosclerosis and Thrombosis* 14 (3):99-108.

Dehnhard, M., K. Fanson, A. Frank, S. V. Naidenko, A. Vargas, and K. Jewgenow. 2010. Comparative metabolism of gestagens and estrogens in the four lynx species, the Eurasian (Lynx lynx), the Iberian (L. pardinus), the Canada lynx (L. canadensis) and the bobcat (L. rufus). *General and Comparative Endocrinology* 167 (2):287-296.

Distefano, J. J., W. L. Morris, T. T. Nguyen, A. J. Vanherle, and W. Florsheim. 1993. ENTEROHEPATIC REGULATION AND METABOLISM OF 3,5,3'-TRIIODOTHYRONINE IN HYPOTHYROID RATS. *Endocrinology* 132 (4):1665-1670.

Doerge, D. R., N. C. Twaddle, M. Vanlandingham, and J. W. Fisher. 2010. Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. *Toxicology and Applied Pharmacology* 247 (2):158-165.

Donnelly, J. G. 2001. Folic acid. *Critical Reviews in Clinical Laboratory Sciences* 38 (3):183-223.

Fortun, P. J., and C. J. Hawkey. 2005. Nonsteroidal antiinflammatory drugs and the small intestine. *Current Opinion in Gastroenterology* 21 (2):169-175.

Fukuyama, T., K. Yamaoka, Y. Ohata, and T. Nakagawa. 1994. A NEW ANALYSIS METHOD FOR DISPOSITION KINETICS OF ENTEROHEPATIC CIRCULATION OF DICLOFENAC IN RATS. *Drug Metabolism and Disposition* 22 (3):479-485.

Garrett, R.H., C.M. Grisham. 2002. Principles of Biochemistry with a Human Focus, Harcourt College Publishers, Fort Worth.

Genuis, S. J., D. Birkholz, M. Ralitsch, and N. Thibault. 2010. Human detoxification of perfluorinated compounds. *Public Health* 124 (7):367-375.

Ghanem, C. I., M. L. Ruiz, S. S. M. Villanueva, M. Luquita, S. Llesuy, V. A. Catania, L. A. Bengochea, and A. D. Mottino. 2009. Effect of repeated administration with subtoxic doses of acetaminophen to rats on enterohepatic recirculation of a subsequent toxic dose. *Biochemical Pharmacology* 77 (10):1621-1628.

Ghanem, C. I., M. L. Ruiz, S. S. M. Villanueva, M. G. Luquita, V. A. Catania, B. Jones, L. A. Bengochea, M. Vore, and A. D. Mottino. 2005. Shift from biliary to urinary elimination of acetaminophen-glucuronide in acetaminophen-pretreated rats. *Journal of Pharmacology and Experimental Therapeutics* 315 (3):987-995.

Groh, H., K. Schade, and C. Horholdschubert. 1993. STEROID-METABOLISM WITH INTESTINAL MICROORGANISMS. *Journal of Basic Microbiology* 33 (1):59-72.

Hoeijmakers, M., B. Janszen, A. Coert, and L. Horspool. 2003. Pharmacokinetics of oestriol after repeated oral administration to dogs. *Research in Veterinary Science* 75 (1):55-59.

Holt, J. A., A. Scharl, S. Kullander, and M. W. Beckmann. 1992. INTRACELLULAR ACTIONS OF STEROID-HORMONES AND THEIR THERAPEUTIC VALUE, INCLUDING THE POTENTIAL OF RADIOHALOSTEROIDS AGAINST OVARIAN-CANCER. *Acta Obstetricia Et Gynecologica Scandinavica* 71:39-54.

Kaykhaei, M. A., M. Shams, A. Sadegholvad, M. H. Dabbaghmanesh, and G. R. Omrani. 2008. Low doses of cholestyramine in the treatment of hyperthyroidism. *Endocrine* 34 (1-3):52-55.

Kowalski, W. B., R. T. Chatterton, R. R. Kazer, and T. A. Severini. 1996. Disappearance and unexpected reappearance of progesterone in the circulation of the monkey: Novel hormone kinetics. *Journal of Physiology-London* 493 (3):877-884.

Kumar, R. 1990. VITAMIN-D METABOLISM AND MECHANISMS OF CALCIUM-TRANSPORT. *Journal of the American Society of Nephrology* 1 (1):30-42.

Kurebayashi, H., S. I. Nagatsuka, H. Nemoto, H. Noguchi, and Y. Ohno. 2005. Disposition of low doses of C-14-bisphenol A in male, female, pregnant, fetal, and neonatal rats. *Archives of Toxicology* 79 (5):243-252.

Latruffe, N., D. Delmas, D. Colin, A. Lancon, B. Jannin, and P. Dutartre. 2006. Nutritional prevention by dietary resveratrol as chemopreventive agent: application to colorectal cancers. *Agro Food Industry Hi-Tech* 17 (6):18-21.

Lehr, T., A. Staab, C. Tillmann, D. Trommeshauser, H. G. Schaefer, and C. Kloft. 2009. A Quantitative Enterohepatic Circulation Model Development and Evaluation with Tesofensine and Meloxicam. *Clinical Pharmacokinetics* 48 (8):529-542.

Lewis, S. J., and K. W. Heaton. 1999. The metabolic consequences of slow colonic transit. *American Journal of Gastroenterology* 94 (8):2010-2016.

Ouellet, D. M. C., and G. M. Pollack. 1995. BILIARY-EXCRETION AND ENTEROHEPATIC RECIRCULATION OF MORPHINE-3-GLUCURONIDE IN RATS. *Drug Metabolism and Disposition* 23 (4):478-484.

Overton, P. D., N. Furlonger, J. M. Beety, J. Chakraborty, J. A. Tredger, and L. M. Morgan. 1994. THE EFFECTS OF DIETARY SUGAR-BEET FIBER AND GUAR GUM ON LIPID-METABOLISM IN WISTAR RATS. *British Journal of Nutrition* 72 (3):385-395.

Padwal, R., D. Brocks, and A. M. Sharma. 2010. A systematic review of drug absorption following bariatric surgery and its theoretical implications. *Obesity Reviews* 11 (1):41-50.

Perisribera, J. E., F. Torresmolina, M. C. Garciacarbonell, J. C. Aristorena, and L. Granero. 1992. GENERAL TREATMENT OF THE ENTEROHEPATIC RECIRCULATION OF DRUGS AND ITS INFLUENCE ON THE AREA UNDER THE PLASMA-LEVEL CURVES, BIOAVAILABILITY, AND CLEARANCE. *Pharmaceutical Research* 9 (10):1306-1313.

Pharmacogenomics Knowledge Base. 2001. Department of Health and Human Services, USA, http://www.pharmgkb.org/do/serve?objCls=Drug&objId=PA449238

Philipps, A. F., B. Dvorak, P. J. Kling, J. G. Grille, and O. Koldovsky. 2000. Absorption of milk-borne insulin-like growth factor-I into portal blood of suckling rats. *Journal of Pediatric Gastroenterology and Nutrition* 31 (2):128-135.

Plusquellec, Y., R. Arnaud, S. Saivin, T. A. Shepard, I. Carrie, P. Hermann, J. Souhait, and G. Houin. 1998. Enterohepatic recirculation of the new antihypertensive drug UP 269-6 in humans - A possible model to account for multiple plasma peaks. *Arzneimittel-Forschung-Drug Research* 48 (2):138-144.

Plusquellec, Y., and G. Houin. 1995. ESTIMATION OF THE EFFECTIVE AMOUNT ENTERING THE BODY FOR DRUGS SUBJECT TO ENTEROHEPATIC RECIRCULATIONS. *Medical Engineering & Physics* 17 (3):172-176.

Rad, M., M. Humpel, O. Schaefer, R. C. Schoemaker, W. D. Schleuning, A. F. Cohen, and J. Burggraaf. 2006. Pharmacokinetics and systemic endocrine effects of the phyto-oestrogen 8-prenylnaringenin after single oral doses to postmenopausal women. *British Journal of Clinical Pharmacology* 62 (3):288-296.

Renquist, B. J., T. E. Adams, B. M. Adams, and C. C. Calvert. 2008. Dietary restriction reduces the rate of estradiol clearance in sheep (Ovis aries). *Journal of Animal Science* 86 (5):1124-1131.

Reuter, B. K., N. M. Davies, and J. L. Wallace. 1997. Nonsteroidal anti-inflammatory drug enteropathy in rats: Role of permeability, bacteria, and enterohepatic circulation. *Gastroenterology* 112 (1):109-117.

Roberts, M. S., B. M. Magnusson, F. J. Burczynski, and M. Weiss. 2002. Enterohepatic circulation - Physiological, pharmacokinetic and clinical implications. *Clinical Pharmacokinetics* 41 (10):751-790.

Rudek, M. A., K. S. Bauer, R. M. Lush, S. F. Stinson, A. M. Senderowicz, D. J. Headlee, S. G. Arbuck, M. C. Cox, A. J. Murgo, E. A. Sausville, and W. D. Figg. 2003. Clinical pharmacology of flavopiridol following a 72-hour continuous infusion. *Annals of Pharmacotherapy* 37 (10):1369-1374.

Sarawek, S., H. Derendorf, and V. Butterweck. 2008. Pharmacokinetics of Luteolin and Metabolites in Rats. *Natural Product Communications* 3 (12):2029-2036.

Saseen, J. J., J. A. Porter, D. J. Barnette, J. L. Bauman, E. J. Zajac, and B. L. Carter. 1997. Postabsorption concentration peaks with brand-name and generic verapamil: A double-blind, crossover study in elderly hypertensive patients. *Journal of Clinical Pharmacology* 37 (6):526-534.

Schaiquevich, P., A. Niselman, and M. Rubio. 2002. Comparison of two compartmental models for describing ranitidine's plasmatic profiles. *Pharmacological Research* 45 (5):399-405.

Seitz, S., and U. A. Boelsterli. 1998. Diclofenac acyl glucuronide, a major biliary metabolite, is directly involved in small intestinal injury in rats. *Gastroenterology* 115 (6):1476-1482.

Shefer, S., L. B. Nguyen, G. Salen, G. C. Ness, I. R. Chowdhary, S. Lerner, A. K. Batta, and G. S. Tint. 1992. DIFFERING EFFECTS OF CHOLESTEROL AND TAUROCHOLATE ON STEADY-STATE HEPATIC HMG-COA REDUCTASE AND CHOLESTEROL 7-ALPHA-HYDROXYLASE ACTIVITIES AND MESSENGER-RNA LEVELS IN THE RAT. *Journal of Lipid Research* 33 (8):1193-1200.

Shenfield, G. M. 1993. ORAL-CONTRACEPTIVES - ARE DRUG-INTERACTIONS OF CLINICAL-SIGNIFICANCE. *Drug Safety* 9 (1):21-37.

Shou, M. G., W. Lu, P. H. Kari, C. Xiang, Y. X. Liang, P. Lu, D. Cui, W. B. Emary, K. B. Michel, J. K. Adelsberger, J. E. Brunner, and A. D. Rodrigues. 2005. Population pharmacokinetic modeling for enterohepatic recirculation in Rhesus monkey. *European Journal of Pharmaceutical Sciences* 26 (2):151-161.

Staley, A. M., J. M. Blanco, A. M. Dufty, D. E. Wildt, and S. L. Monfort. 2007. Fecal steroid monitoring for assessing gonadal and adrenal activity in the golden eagle and peregrine falcon. *Journal of Comparative Physiology B-Biochemical Systemic and Environmental Physiology* 177 (6):609-622.

Strandgarden, K., P. Hoglund, L. Gronquist, L. Svensson, and P. O. Gunnarsson. 2000. Absorption and disposition including enterohepatic circulation of (C-14) roquinimex after oral administration to healthy volunteers. *Biopharmaceutics & Drug Disposition* 21 (2):53-67.

Suttle, A. B., and K. L. R. Brouwer. 1994. BILE-FLOW BUT NOT ENTEROHEPATIC RECIRCULATION INFLUENCES THE PHARMACOKINETICS OF RANITIDINE IN THE RAT. *Drug Metabolism and Disposition* 22 (2):224-232.

Upmeier, A., G. H. Degen, P. Diel, H. Michna, and H. M. Bolt. 2000. Toxicokinetics of bisphenol A in female DA/Han rats after a single i.v. and oral administration. *Archives of Toxicology* 74 (8):431-436.

Voet, D., J. G. Voet. 1995. Biochemistry, 2nd ed., John Wiley & Sons, Inc., New York.

*Vree, T. B., and C. J. Timmer. 1998. Enterohepatic cycling and pharmacokinetics of oestradiol in postmenopausal women. *Journal of Pharmacy and Pharmacology* 50 (8):857-864.

Weisberg, E. 1999. Interactions between oral contraceptives and antifungals antibacterials - Is contraceptive failure the result? *Clinical Pharmacokinetics* 36 (5):309-313.

Yamamoto, T., K. Ito, M. Honma, T. Takada, and H. Suzuki. 2007. Cholesterol-lowering effect of Ezetimibe in uridine diphosphate glucuronosyltransferase 1A-deficient (Gunn) rats. *Drug Metabolism and Disposition* 35 (9):1455-1458.

Yilmaz, B. 2010. Determination of estradiol valerate in pharmaceutical preparations by zero- and first-order derivative spectrophotometric methods. International Journal of Pharmaceutical Sciences Review and Research Vol I, Issue 2, Article 021.

Younis, I. R., S. Malone, H. S. Friedman, L. J. Schaaf, and W. P. Petros. 2009. Enterohepatic recirculation model of irinotecan (CPT-11) and metabolite pharmacokinetics in patients with glioma. *Cancer Chemotherapy and Pharmacology* 63 (3):517-524.

* of special interest