INTERRUPTION OF THE ENTEROHEPATIC CIRCULATION OF BILE SALTS IN PATIENTS WITH INCOMPETENT ILIO-CAECAL VALVE

THESIS

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BY

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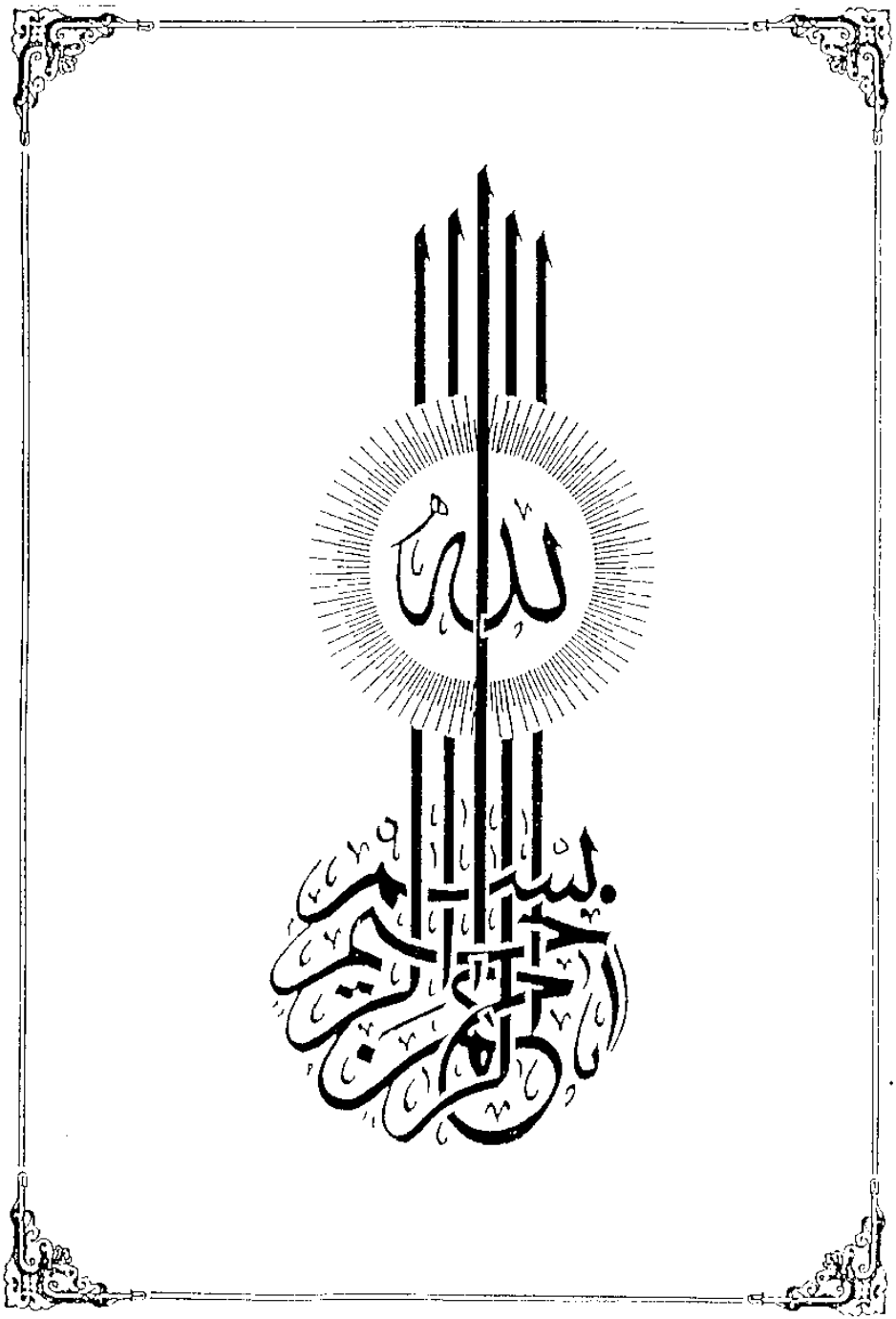
1986

TO
MY PARENTS
AND
MY WIFE



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INTRODUCTION AND AIM OF THE WORK

AIM OF THE WORK

Irritable bowel syndrome (IBS) accounts for half of the gastrointestinal complaints brought to the attention of physicians. Despite numerous investigations, no organic cause for this syndrome has been discovered. Disturbed motility seems the basic abnormality underlying the syndrome of irritable bowel due to abnormal gut brain axis.

One of these disturbances is the incompetent ileo-cecal valve. when the ileo-cecal valve becomes incompetent, retrograde contamination of the ileum and jejunum by colonic flora occurs.

Also, rapid delivery of ileal contents to the cecum is also a possibility with a smaller chance of bile salts absorption interrupting their enterohepatic circulation.

The aim of this work is to study the effect of incompetent ileocaecal valve on enterohepatic circulation of bile salts. This was done indirectly by estimation of fasting serum cholesterol, triglycerides and total lipids in twenty five patients with incompentent ileocaecal valve which was proved by double contrast barium compared with twenty five individuals without incompetent ileo-caecal valve.

REVIEW OF LITERATURE

BILE ACID METABOLISM IN HEALTH

Bile acids are a group of acidic steroids which are synthesized in the liver from cholesterol by several intermediate steps (Hofmann A.F., et al., 1984; Danielsson and Sjovall, 1975).

Cholic acid and chendeoxy cholic acid are known as primary bile acids.

Before there secretion into bile, bile acids are conjugated with either glycine or taurine. Conjugated bile acids exist as their Na^+ and K^+ salts and are called bile salts (Hanson et al., 1977).

90-95% of bile salts are absorted from terminal ileum (Hofmann A.F., 1971) by active transport prosses 100-150 cm proximal to ileocecal valve. A test meal containing radioactive bile salt was fed, and the extent of absorption of bile salts are recorded. The results of this experiment was in agreement that net bile salt absorption occur in the distal small intestine, in the distal jejenum or at a more distal site (Hofmann A.F., et al., 1971).

The remaining 5% of bile salts enters the colon where cholic acid is converted to deoxy-cholic acid by the action of bacteria. Also, chenodeoxy-cholic acid is converted to lithocholic acid which is relatively insoluble and is mostly excreted in stools. Both deoxy cholic and litho-cholic acids are known as secondary bile acids.

The absorbed bile salts are transported back to the liver via the portal vein and excreted in bile. This is known as "Entero-hepatic circulation" (Mayes, 1978).

A small fraction of the bile salts about 500 mg/day escapes absorption and is eleminated in faeces.

The total bile acid pool is about 3-5 grams. The entero-hepatic circulation of bile acid is so efficient that each day bile acid pool can be cycled through the intestine 6-10 times with only a small amount lost in faeces (Dowling, 1972).

Regulation of bile acid bio synthesis:

Each day an amount of bile acids equivalent to that lost in faeces is produced from cholesterol by the liver in order to maintain the bile acid pool size constant.

Bile acids regulate their own synthesis by a negative feed back mechanism. The rate of bile acid synthesis by the liver appears to be controlled by the magnitude, circulation of the bile acid pool (Shefer et al., 1970).

The rate of bile acid synthesis from cholesterol is regulated by the enzyme cholesterol 7 ∝ hydrolase. This enzyme is a hepatic microsomal enzyme catalyzes the 1st step of bile acid synthesis from cholesterol and it is a rate limiting enzyme (Einarson et al., 1973).

HMg-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase), the rate limiting enzyme for cholesterol synthesis (Wilson, 1972) may play an important role in the regulation of bile acid synthesis by controlling the quantity of newly synthesised cholesterol available for bile acid production (Shefer et al., 1972).

Cholesterol 7∝ hydroxylase activity exhibit a diurnal rhythm which parallels that of hepatic and intestinal HMG-CoA reductorse (maximum activity at night).

The hepatic microsomal enzyme 7 ∝ hydroxy-cholesterol 4 en -3-one-12 ∝ hydroxylase may play a role in determining the relative proportion of lry bile acids (cholic acid to chendeoxcholic acid ratio) (Einarsson, 1968).

IMPORTANCE OF BILE ACID BIOSYNTHESIS

Bile acids are the major route of elemination of cholesterol from the body. Hepatic synthesis of cholesterol, in addition to being subject to feed back regulation by dietary intake of cholesterol, is also under profound regulation by the bile acids in the enterohepatic circulation.

A number of experiments support this fact:

First, external diversion of bile flow leads to striking increase in the rate of cholesterol synthesis both in the liver and intestine.

Second, the oral administration of a variety of free and conjugated bile acids in unphysiologically high amounts causes an inhibition of cholesterol synthesis.

Finally, interference with the enterohepatic circulation of bile acids as aresult of ileal bypass operations also results in striking increase in cholesterol synthesis by the liver. These findings show that the bile acids are responsible for the feed back effect on cholesterol synthesis (Mayes, 1978).

The enterohepatic circulation of bile salts: (Fig. I)

In man two primary bile acids cholic acid (CA) and chenodeoxy cholic acid (CDCA) are synthesized from cholesterol. The rate of (CA) synthesis is about twice chenodeoxycholic acid (Vlahcevic Z.R., Miller, et al., 1971). The primary bile acids are conjugated with glycine and taurine, The conjugates of (CDCA) are conserved to a greater extent than those of (CA) (Fig. 2). Therefore bile becomes enriched in (CDCA) conjugates (in human bile the proportion of the two primary bile acids is about equal despite the synthesis rate of (CDCA) being only half that of (CA) (Fig. 3) the bile salts are efficiently reabsorbed from the terminal ileum by an active transport mechanism. Diseases of the distal part of small intestine causes bile salts malabsorbed (Dietschy J.M., 1968).

The small amounts of parts of glycine conjugates are absorped passively from the jejunum (Fig. 4) bile salts which escape ileal absorption are degraded by bacteria and absorbed by passive non ionic diffusion in the colon (Samuel, P. et al., 1968).

After intestinal absorption bile salts are transported to the liver via the portal vein. This cyclical movement of bile salts from liver into the intestine back to the liver and back into the intestine is termed the enterohepatic circulation.

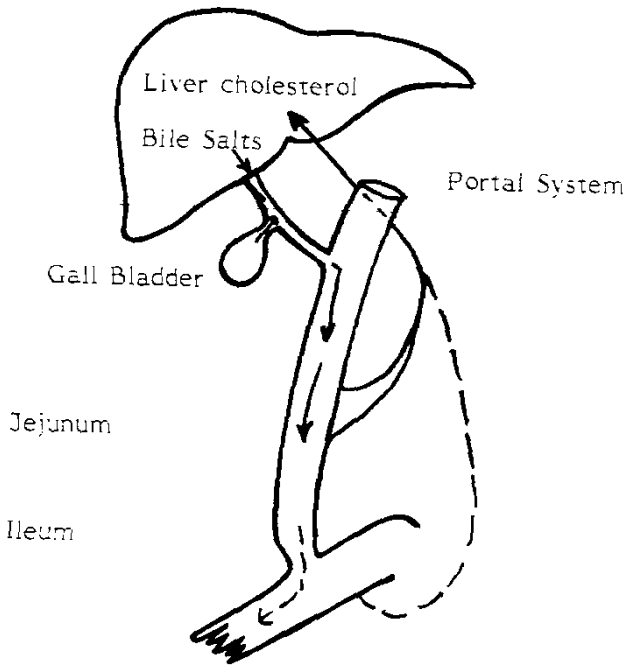

Fig. (1)

Schematic representation of the enterohepatic circulation of bile salts. The solid lines entering the portal system represent conjugated bile salt absorbed via ileal transport. The broken lines represent unconjugated bile salts resulting from bacterial action
(Garbutt J.T. et al., 1971)

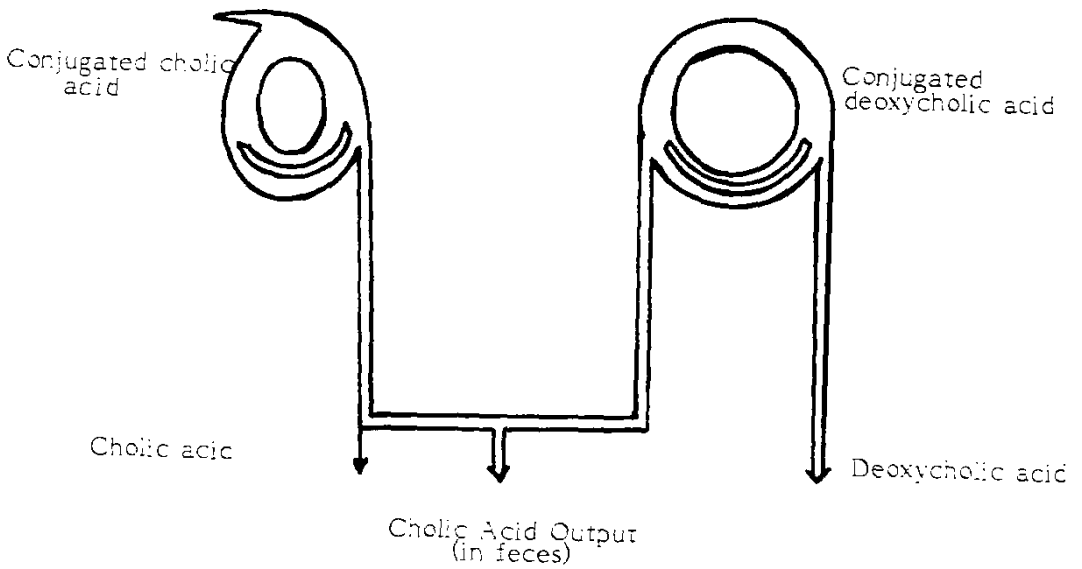

Fig. (2)

Exterohepatic circulation of cholic acid (left) and deoxycholic acid (right).
(After Hofmann A.F., 1977)