Do recommended textbooks contain adequate information about bile salt transporters for medical students?

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Azer, Samy A. Do recommended textbooks contain adequate information about bile salt transporters for medical students? Adv Physiol Educ 28: 36–43, 2004; 10.1152/advan.00027.2003.—Several studies have recently highlighted a number of limitations in medical textbooks. The aims of this study were to 1) to assess whether available medical textbooks provided students with adequate information about bile salt transporters, 2) compare the level of detail and the amount of information provided in current textbooks on hepatic transport mechanisms with those available in the literature, and 3) compare the amount of information provided in medical textbooks on hepatocyte transport mechanisms with those involving other transporters e.g., those found in the nephron. Seventy medical textbooks from disciplines including physiology, pathology, cell biology, medicine, pediatrics, pharmacology, pathophysiology, and histology published during the past six years were examined. The literature on bile salt transport has been searched mainly from the Internet (MEDLINE and PubMed). Most textbooks failed to provide any information on transporters found in the basolateral and canalicular membranes of hepatocytes. There are also deficiencies in information on bile salt transporters in the terminal ileum. However, up to the end of 2002, 3,610 articles and reviews had been published on hepatobiliary and enterocyte transport of bile salts. During the same period (from 1965), 10,757 articles had been published on renal transport. Thus the contents of textbooks may reflect the overall volume of research knowledge on renal transport. However, despite our current understanding of hepatic and intestinal transport of bile salts and extensive research, particularly over the past 12 years, there are major deficiencies in textbooks in this area. These findings indicate that there is an imbalance in the contents of current textbooks and a lack of information about hepatobiliary physiology, bile salt transporters, bile formation, and mechanisms underlying cholestasis and drug-induced injury. Authors, editors, and publishers of medical textbooks should consider the need to update the information provided on bile salt transporters.

ONE OF THE MAIN OBJECTIVES of an integrated, problem-based curriculum is to promote self-directed learning. To prepare their weekly learning issues, students enrolled in such courses usually rely on a wide range of resources, including journal articles, the Internet, and computer-aided learning (CAL) programs. However, textbooks remain the main resource for their learning and the authoritative reference for study of topics. Textbooks are central to medical training at both the undergraduate and postgraduate levels, not only to provide students with detailed information but also to help them identify underlying key principles, enhance deep understanding of concepts, and emphasize their significance in clinical care. However, most medical textbooks are still discipline based and do not exactly reflect the needs of students enrolled in an integrated problem-based learning curriculum.

Recently, several studies have highlighted a number of limitations in medical textbooks. For example, the internal medicine, pediatrics, and nursing clinical care textbooks failed to adequately address the end-of-life contents (18, 46, 52); medical textbooks failed to provide adequate information about musculoskeletal examination skills (32); surgical textbooks did not provide enough information with regard to breaking bad news/advanced care planning, mode of death, treatment decision making, effect on family/surgeon and symptom management (16); and standard textbooks were less useful to postgraduate students preparing for the professional anaesthetic examination (36). Recently, Waldum et al. (62) found that physiology textbooks lacked information on the enterochromaffin-like (ECL) cells. These authors suggested that use of the Internet may fill the gaps between the textbooks and the literature in physiology education. Furthermore, neuroscience textbooks were not up to date in their contents and failed to provide students with recent findings in neuroscience (11). The overall results suggest that most recommended medical textbooks are not up to date with their contents, particularly in areas where there is rapid development and changes in our understanding of new concepts.

Identification, molecular cloning, and understanding of the functions of bile salt transporters at the sinusoidal and canalicular domains of hepatocytes and the terminal ileum, together with our recent understanding of the enterohepatic circulation of bile salts, means that the exact mechanisms underlying cholestasis and a number of hepatic disorders have been achieved after a long journey of research for over 50 years (8). The current knowledge has added new insight to our understanding of the mechanisms by which drugs induce hepatic injury and improved our understanding of the pathogenesis of hepatic disorders and their management.

The present study was designed with the following aims: 1) to assess whether available medical textbooks provided students with adequate information about bile salt transporters, 2) to compare the level of detail and amount of information provided in current textbooks about hepatic transport mechanisms with those available in the literature, and 3) to compare the amount of information provided in medical textbooks on hepatocyte transport mechanisms with those involving other transporters, e.g., those found in the nephron, proximal convoluted tubule, thick ascending limb, distal convoluted tubule, and collecting duct.

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Background. Bile is a complex, watery secretion that originates from hepatocytes and is concentrated in the gallbladder. The bile secreted by the liver is modified by bile duct cells and the gallbladder epithelium before entering the duodenum. Formation of bile is an important hepatic function because bile is essential for intestinal digestion and absorption of fat. Bile is also an important source of elimination for environmental toxins, carcinogens, and drugs and their metabolites. Bile is also the major route of excretion for endogenous compounds and metabolic products such as bilirubin, cholesterol, and steroidal hormones. The main constituents of bile are 1) water, which makes up ~82% of bile; 2) bile salts, the main ones being chenodeoxycholic acid and cholic acid; 3) lecithin and other phospholipids (the lecithin phosphatidylcholine is predominantly present in the bile); 4) unesterified cholesterol; 5) other compounds being proteins such as biliary glycoprotein (mucins), serum immunoglobulins, electrolytes, bilirubin, steroid hormones, metabolites, drugs, amino acids, peptides, vitamins, heavy metals, and toxins.

Cholesterol is an extremely water-insoluble (hydrophobic) molecule. The presence of amphipathic molecules containing both hydrophilic and hydrophobic ends, such as bile acids and phospholipids, allows cholesterol to remain in solution. Normal ratios of bile salts, lecithin, and cholesterol favor the formation of solubilizing mixed micelles. Any abnormalities in this ratio promotes the precipitation of cholesterol crystals and the formation of gallbladder stones.

Bile salts have a number of functions including:

- Induction of bile flow
- Induction of biliary lipid secretion
- Solubilization of cholesterol in bile and of dietary fats and cholesterol in the intestinal fluid
- Facilitation of absorption of lipid-soluble vitamins (vitamins A, D, E, and K)
- Regulation of pancreatic secretions and the release of gastrointestinal peptides
- Negative feedback regulation of bile salt synthesis in hepatocytes from cholesterol.

With food ingestion and the presence of breakdown products in the small intestine (i.e., peptones, amino acids, and lipids), cholecystokinin (CCK) is released from neuroendocrine cells present in the duodenum into the blood. CCK causes contraction of the gallbladder and the release of bile stored in the gallbladder into the duodenum along the biliary system. In the small intestine, conjugated bile salts become deconjugated via the action of bacteria. In the large intestine, the secondary bile salts deoxycholic and lithocholic acids are formed by 7-dehydroxylase of deconjugated primary bile salts with cholanic acid and chenodeoxycholic acids, respectively. This reaction is mediated through the action of bacterial enzymes present in the large intestine. In the terminal ileum, more than 90% of bile salts in the intestine are reabsorbed by an active transport system into the portal circulation. Bile salts are taken up by the liver, reconjugated with glycine or taurine at a ratio of 3:1, and then released into bile. The cyclic transport of bile salts from intestine to liver and back to the intestine is called the enterohepatic circulation of bile salts. The enterohepatic circulation aims at the preservation of bile salts by recycling them and also controlling primary bile salt synthesis (cholic acid and chenodeoxycholic acid) from cholesterol in the liver hepatocytes by a negative feedback mechanism.

Milestones in the area of bile salt transporters. As early as 1959, a Sweden physiologist, Ivar Sperber, discussed in a paper published in Pharmacologic Reviews titled “Secretion of organic anions in the formation of urine and bile” the significance of osmotic filtration phenomenon in bile formation. This concept became the cornerstone that guided research into bile formation and possible mechanisms underlying bile salt transport for the next four decades (8, 56). During the 1950s, the pioneering work of Ralph Brauer, using isolated perfused rat liver, demonstrated that bile flow was not influenced by hydrostatic filtration pressures and could be secreted against pressure that exceeded the vascular perfusion pressure (9). The work of Brauer formulated the concept that the formation of bile is an active process rather than simple filtration or secretion. It was later realized that clearance of solutes into bile involved three main processes, namely hepatocellular uptake, transcellular transport, and canalicular excretion. This last process was found to be the rate-limiting process in hepatocellular transport. During the 1960s and 1970s, a number of pioneering works demonstrated major differences between bile formation by hepatocytes and urine production by nephrons. Most research focused on characterization of the transport system responsible for bile formation and the driving forces for its secretion. In 1978, Blitzer and Boyer (6) identified the presence of the sodium pump Na"^-K"^-ATPase in the basolateral membrane of hepatocytes and highlighted its role in canalicular secretion of bile salts. The development of molecular techniques and cloning studies have allowed us to identify the molecular properties of the hepatocellular transport system responsible for the sinusoidal uptake and canalicular secretion of bile salts, organic compounds, and other xenobiotics (Table 1). These studies have added new dimensions to our understanding of the molecular mechanisms underlying bile formation, bile salt transport in the liver, the enterohepatic circulation as well as the molecular regulation of hepatocellular systems in impaired bile flow (cholestasis) (35, 61) and drug-induced liver dysfunction (57).

MATERIALS AND METHODS

Medical textbooks. In this study, reviews of 70 recommended medical textbooks in a number of disciplines, physiology (n = 28), pathology (n = 8), cell biology (n = 5), medicine (n = 5), paediatrics (n = 5), pharmacology (n = 8), pathophysiology (n = 5), and histology (n = 6), were undertaken. These textbooks were selected from websites of international publishers and were recommended by several universities in Australia and worldwide for preclinical courses in medicine. The textbooks included in this study were published during the past six years (1996–2002). A copy of each of these textbooks was supplied by the publisher to the author for review or borrowed from two medical libraries in Melbourne, Victoria, The Brownless Medical Library at the University of Melbourne, and the Hargrave-Andrew Library at Monash University.

Assessment of contents of textbooks for bile salt transporters. In each book, chapters that pertained to liver, physiology of liver, bile, bile salt/bile acid, gallbladder, gallstones, fat metabolism, epithelial transport system, bile formation, functions of the liver, hepatobiliary system, enterohepatic circulation, bile salt transporters at the sinusoidal and canalicular domains of hepatocytes, and bile salt transporters at the apical surface of entocytes in the terminal ileum were examined. The table of contents of each textbook was also reviewed to identify chapters specifically covering topics related to the liver and bile salt transporters. Also, the index of each textbook was searched.
for the following keywords concerning bile salts/bile acids and the bile transport system: bile acids, bile salts, bile biosynthesis, bile secretion, uptake of bile salts, sinusoidal domain, canalculus, canalicul secretion, canalicul efflux, bile salt transporters, enterohepatic secretion, epithelial cells, hepatocytes, liver, bile recirculation, biliary obstruction, biliary calculi, gallstones, fat metabolism, fat-soluble vitamins, cholesterol metabolism, terminal ileum, hepatobiliary dysfunction, cotransporters, active transport, and the Na\(^+\)-K\(^+\)-ATPase transporters and multidrug resistance P glycoprotein (MDR). These keywords were selected because they are commonly used in the literature and related to the area of this research.

Assessment of literature for bile salt transport. The literature, MEDLINE and PubMed, was searched using the keywords bile transport, liver transporters, and enterohepatic circulation. Research articles and review papers related to bile salt transport and dating back to 1965 and up to the end of 2002 were collected, evaluated, and categorized by year of publication. Only articles in English and directly related to this topic were included in the study.

Assessment of medical textbooks for renal transporters. To assess whether textbooks included in the study have provided information on transporters other than those involved in bile salt transport, it was decided to assess the number of research papers on the renal transport system published during the same period, from 1965 through 2002. The key phrase used in the search was renal transport. By use of MEDLINE and PubMed, data were collected, evaluated, and categorized by year of publication. Only articles in English and directly related to the topic searched were included in the study.

**RESULTS**

*Textbooks and bile salt transporters*. Only 13 of 70 textbooks contained information on bile salt transporters at the sinusoidal and canalicul domains of hepatocytes and at the sinusoidal and canalicul domains of hepatocytes and at the

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**Table 1. Main bile salt transporters: nomenclature, location, function, and clinical significance**

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Location</th>
<th>Function</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium taurocholate cotransporting polypeptide</td>
<td>NTCP</td>
<td>Hepatocyte: basolateral membrane (BM)</td>
<td>Uptake of conjugated bile salts such as taurocholate (TC)</td>
<td>Decreased expression of NTCP in cholestasis and animal models for cholestasis (22)</td>
</tr>
<tr>
<td>Organic anion-transporting proteins</td>
<td>OATPs</td>
<td>Hepatocyte: basolateral membrane (BM)</td>
<td>Uptake of compounds including unconjugated and conjugated bile salts, anions, and uncharged compounds</td>
<td>Unknown</td>
</tr>
<tr>
<td>Multidrug resistance-associated protein-3</td>
<td>MRP3</td>
<td>Hepatocyte: BM</td>
<td>Multispecific organic solute transporter</td>
<td>Highly upregulated on BM of hepatocytes in cholestasis and primary biliary cirrhosis (33)</td>
</tr>
<tr>
<td>Bile salt export pump</td>
<td>BSEP</td>
<td>Hepatocyte: canalicul membrane (CM)</td>
<td>ATP-dependent transport of monovalent bile salts (such as TC) into bile</td>
<td>Obstructive cholestasis and progressive familial intrahepatic cholestasis type 2 may be related to mutations in BSEP transporter (28)</td>
</tr>
<tr>
<td>Multidrug resistance-1 P-glycoprotein</td>
<td>MDR1</td>
<td>Hepatocyte: CM</td>
<td>ATP-dependent excretion of various organic cations, and xenobiotics into bile</td>
<td>MRP3 is absent or mutated in progressive familial intrahepatic cholestasis type 3 (14)</td>
</tr>
<tr>
<td>Multidrug resistance-3 P-glycoprotein</td>
<td>MDR3</td>
<td>Hepatocyte: CM</td>
<td>Specifically involved in transport of phosphatidylcholine</td>
<td>MRP2 is absent from patients with Dubin-Johnson syndrome (43)</td>
</tr>
<tr>
<td>Multidrug resistance-associated protein-2</td>
<td>MRP2</td>
<td>Hepatocyte: CM</td>
<td>Mediates ATP-dependent multispecific organic-anion transport (e.g., bilirubin diglucuronide, glutathione) into bile</td>
<td>Unknown</td>
</tr>
<tr>
<td>Organic anion-transporting polypeptide 3</td>
<td>OATP-A</td>
<td>Small intestine: ileal enterocytes</td>
<td>Sodium-independent uptake of bile salts from small intestinal lumen</td>
<td>Significance of this transporter in man awaits confirmation</td>
</tr>
<tr>
<td>Apical sodium-dependent bile salt transporter</td>
<td>ASBT</td>
<td>Small intestine: apical surface of enterocytes</td>
<td>Electrogenic bile salt transporter, coupled with sodium in a 2:1 Na(^+)-bile salt stoichiometry (sodium-dependent bile salt uptake from intestine)</td>
<td>Mutation in cDNA of ASBT results in primary bile salt malabsorption: diarrhea, malabsorption of fat, and malnutrition (41)</td>
</tr>
<tr>
<td>Multidrug resistance-associated protein-3</td>
<td>MRP3</td>
<td>Small intestine: BM ileal enterocytes</td>
<td>Major transporter for bile salts returning to portal circulation</td>
<td>MRP3 may be involved in cholesterol/bile salt homeostasis</td>
</tr>
</tbody>
</table>

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Bile salt transporters in medical textbooks. Only 13 of 70 textbooks contained information on bile salt transporters at the sinusoidal and canalicul domains of hepatocytes and at

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Available in the literature and the contents provided in textbooks, it was decided to assess the number of research papers on the renal transport system published during the same period, from 1965 through 2002. The key phrase used in the search was renal transport. By use of MEDLINE and PubMed, data were collected, evaluated, and categorized by year of publication. Only articles in English and directly related to the topic searched were included in the study.

**Data analysis.** Given the descriptive nature of the study, analysis of data was limited to a descriptive approach. Information provided in textbooks about bile salt transporters or other transporters in the renal tubules were evaluated under three categories: “adequate,” “minimal,” or “absent.” Information was described as adequate when it included the names of transporters, their functions, specificity for substrates transported, and significance of these transporters in the enterohepatic circulation of bile salts. Information was described as minimal when only the names of the transporters were mentioned. Information was described as absent when there was no information about the transporter or the process at all. Microsoft Excel (Excel Mac 2001) was used for data management and analysis of findings.

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**RESULTS**

*Textbooks and bile salt transporters*. Only 13 of 70 textbooks contained information on bile salt transporters at the sinusoidal and canalicul domains of hepatocytes and at the sinusoidal and canalicul domains of hepatocytes and at the
apical membrane of enterocytes in the terminal ileum (Table 2). The information provided on bile salt transporters was mainly at the minimal level. One physiology textbook mentioned briefly the Na\(^{+}\)-K\(^{+}\)-ATPase transporters at the sinusoidal domain (29); another physiology textbook described a number of mechanisms for bile salt transport including Na\(^{+}\)-cotransporters, Na\(^{+}\)-independent bile acid anion exchanger, ATP-dependent bile acid transporter at canalicular domain (5); and five physiology textbooks mentioned the Na\(^{+}\)-bile salt cotransport system at the terminal ileum (4, 12, 20, 29, 37). Two physiology textbooks did not state the transporters but mentioned active transport of bile acids at the terminal ileum (25, 48). Only one textbook in each of the disciplines pathology (n = 8), medicine (n = 5), pathophysiology (n = 5), and histology (n = 6) mentioned briefly the Na\(^{+}\)-K\(^{+}\)-ATPase transporters at the sinusoidal and/or canalicular domains, but none of these texts mentioned the Na\(^{+}\)-bile salt cotransport system at the apical membrane of the enterocytes in the terminal ileum. One of the cell biology textbooks (n = 5) mentioned MDR2 at the apical membrane (44). None of the pharmacology texts (n = 8) included any information on bile salt transporters.

### Table 2. Textbooks referring to bile salt transporters at hepatocytes and enterocytes of terminal ileum

<table>
<thead>
<tr>
<th>Textbook Subject</th>
<th>Number of Books Examined</th>
<th>Sinusoidal and Canalicular Bile Salt Transporters (Reference)</th>
<th>Terminal Ileum Bile Salt Transporters (Reference)</th>
<th>Number of Textbooks Mentioning Bile Salt Transporters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiology</td>
<td>28</td>
<td>Na(^{+})-K(^{+})-ATPase transporters at the sinusoidal domain (29)</td>
<td>Na(^{+})-bile salt cotransport system at the terminal ileum (4, 12, 20, 29, 37)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Na(^{+})-cotransporter, Na(^{+})-independent bile acid anion exchanger, ATP-dependent bile acid transporter at canalicular domain (5)</td>
<td>Active transport of bile salts at the terminal ileum (25, 48)</td>
<td>8</td>
</tr>
<tr>
<td>Pathology</td>
<td>8</td>
<td>Na(^{+})-K(^{+})-ATPase transporters at the canalicular domain (50)</td>
<td>Not mentioned</td>
<td>1</td>
</tr>
<tr>
<td>Cell Biology</td>
<td>5</td>
<td>MDR2 at the apical membrane (44)</td>
<td>Not mentioned</td>
<td>1</td>
</tr>
<tr>
<td>Medicine</td>
<td>5</td>
<td>Sinusoidal and canalicular bile salt transport is Na(^{+})-K(^{+})-ATPase dependent (17)</td>
<td>Not mentioned</td>
<td>1</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>5</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>0</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>8</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>0</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>5</td>
<td>Sinusoidal and canalicular bile salt transport is Na(^{+})-K(^{+})-ATPase dependent (54)</td>
<td>Not mentioned</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other canalicular transporters e.g., sister of P-glycoprotein (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>6</td>
<td>Na(^{+})-K(^{+})-ATPase transporters at the canalicular domain (21)</td>
<td>Not mentioned</td>
<td>1</td>
</tr>
</tbody>
</table>

**Number of Publications in the Area of BileSalt Transport since 1965 to 2002**

![Graph showing the number of publications on bile salt transport from 1965 through 2002](http://advan.physiology.org/)

**Fig. 1.** Number of publications on bile salt transport from 1965 through 2002.
Medical textbooks and renal transporters. Table 3 shows the transporters at the different segments of the nephron. Most textbooks included in this study contained adequate information on renal transporters (e.g., Refs. 1, 3–5, 10, 12, 13, 15, 17, 19, 20, 23–27, 29–31, 34, 37–40, 42, 45, 47–49, 51, 53, 55, 59, 60, 63). The physiology textbooks included in this study that did not provide information on bile salt transporters contained minimal to adequate information on renal transporters at the proximal tubules, thick ascending limb, distal convoluted tubules, and collecting duct. Thus the content of the current textbooks may reflect the overall amount of research knowledge in the area of renal transporters. The figures yielded from the literature are consistent with those found in medical textbooks.

Renal transport system in the literature. Searching the literature (MEDLINE and PubMed) showed that 11,523 research and review articles were published between 1965 and the end of 2002. Only 10,757 articles were found to be directly related to the renal transport system and in English (Fig. 2). The data show that 5,445 (51%) of these articles were published from 1990 through 2002, whereas 3,437 (31%) of these articles were published in the 1980s.

**DISCUSSION AND CONCLUSIONS**

This study demonstrates the lack of information in medical textbooks at the sinusoidal

### Table 3. Summary of renal transporters at the basolateral and apical (luminal) membranes

<table>
<thead>
<tr>
<th>Site of Nephron</th>
<th>Basolateral Membrane Function</th>
<th>Apical (Luminal) Membrane Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal convoluted tubule</td>
<td>Maintain a low intracellular sodium concentration and negative electrical potential in the cell</td>
<td>Na⁺/glucose cotransporter Na⁺/inorganic phosphate cotransporter Na⁺ &amp; glucose uptake by cell Na⁺ &amp; inorganic phosphate uptake by cell</td>
</tr>
<tr>
<td>GLUT2 (early proximal tubule cells)</td>
<td>Glucose is transported to the interstitium by GLUT2</td>
<td>Na⁺/amino acid cotransporter Na⁺/H⁺ exchanger Cl⁻/base exchanger Na⁺ &amp; amino acid uptake by cell Na⁺ &amp; H⁺ extrusion Cl⁻/K⁺ cotransporter Na⁺, Cl⁻, &amp; K⁺ uptake by cell</td>
</tr>
<tr>
<td>Thick ascending limb</td>
<td>Maintain a low intracellular sodium concentration and negative electrical potential in the cell</td>
<td>Na⁺/2Cl⁻/K⁺ cotransporter Na⁺/H⁺ exchanger K⁺ channels Na⁺ &amp; H⁺ extrusion K⁺ extrusion</td>
</tr>
<tr>
<td>Cl⁻ channels</td>
<td>Cl⁻ extrusion to renal interstitial fluid</td>
<td>Na⁺/H⁺ exchanger K⁺ channels</td>
</tr>
<tr>
<td>K⁺ channels</td>
<td>K⁺ extrusion to renal interstitial fluid</td>
<td>Cl⁻ &amp; K⁺ leave cell to renal interstitial fluid</td>
</tr>
<tr>
<td>Cl⁻/K⁺ cotransporter</td>
<td>Cl⁻ &amp; K⁺ leave cell to renal interstitial fluid</td>
<td>Na⁺/H⁺ exchanger Na⁺ &amp; Cl⁻ uptake by cell</td>
</tr>
<tr>
<td>Distal convoluted tubule</td>
<td>Pumps Na⁺ to the interstitial fluid</td>
<td>Na⁺Cl⁻ cotransporter Na⁺ &amp; Cl⁻ uptake by cell</td>
</tr>
<tr>
<td>Cl⁻ channels</td>
<td>Cl⁻ extrusion to renal interstitial fluid</td>
<td>Na⁺/H⁺ exchanger Na⁺ &amp; H⁺ extrusion</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>Pumps Na⁺ to the interstitial fluid</td>
<td>Na⁺ channel (ENaC) Na⁺ uptake</td>
</tr>
<tr>
<td>Cl⁻ channels</td>
<td>Cl⁻ extrusion to renal interstitial fluid</td>
<td>K⁺ channels</td>
</tr>
</tbody>
</table>

**Fig. 2. Number of publications on renal transport from 1965 through 2002.**
and canalicular domains of hepatocytes and in the enterocytes in the terminal ileum, the latter transporters being important for the enterohepatic circulation of bile salts. Only 13 of 70 textbooks examined provided information on bile salt transport. With the exception of one textbook (5), the level of information about bile salt transporters in these texts was minimal, and there was no indication about the significance of these transporters. Five physiology textbooks mentioned the Na\(^+\)-bile salt cotransporter system at the terminal ileum (4, 12, 20, 29, 37), and two merely stated active transport of bile salts in the terminal ileum (25, 48). The Na\(^+\)-K\(^+\)-ATPase transporter at the sinusoidal and/or canalicular domains is mentioned briefly in only one textbook of the disciplines pathology (n = 8), medicine (n = 5), pathophysiology (n = 5), and histology (n = 6), and none of these textbooks mentioned Na\(^+\)-bile salt cotransport system at the terminal ileum. One of the cell biology textbooks (n = 5) mentioned the MDR2 transporter located in the apical membrane of hepatocytes (44) but did not mention other transporters involved in bile salt transport. None of the pharmacology texts (n = 8) included any information on bile salt transporters.

Even the 10th edition of the encyclopedic textbook Goodman & Gilman’s (26), the pharmacological basis of therapeutics in its one volume of 2,148 pages, failed to mention any information on the physiology of the liver and provided the reader with about one-half a page on bile acids and the use of ursodeoxycholic acid in the management of cholestatic liver disorders. On the other hand, the renal physiology and renal transporters at the proximal tubules, ascending thick limb, distal convoluted tubules, and collecting ducts are covered with diuretics in a chapter of over 30 pages.

Because of the lack of information about bile salt transporters, the mechanisms behind several physiological, pathological, and pharmacological concepts were not clear. For example, bile formation, the dynamics of the enterohepatic circulation, the pathogenesis of liver conditions such as cholestasis, and the mechanisms underlying drug-induced hepatic injury were not well structured or explained on the basis of common foundations.

The facts that there are 3,610 research and review articles in the literature on bile salt transport since 1965 and that more than 53% of these papers were published in the period 1990–2002 indicate that there is rapid progress in this area, particularly with the introduction of cloning and the ability to define the specificity of these transporters to transport-specific substrates. A similar pattern of research publications on renal transporters has been found, with 51% of the research papers published during the past 12 years. However, medical textbooks failed to include up-to-date information on bile salt transporters. This failure cannot be justified by the assumption that textbooks are out of date because of the time needed for preparing and publishing them. In fact, most of these textbooks have provided the reader with extensive information about other transporters, such as those in the proximal tubule, thick ascending limb, distal convoluted tubules, and collecting duct, indicating a lack of balance in the design of these textbooks and the failure of authors, editors, and publishers to keep information up to date in these textbooks.

Scientific errors in the information provided in this area have also been noted in some textbooks. For example, one textbook states, “Between the endothelial cells that make up the walls of the portal capillary system are spaces termed fenestrations that allow plasma and its proteins, but not red blood cells, free and direct access to the surface of the hepatocytes” (37). In fact, according to a number of authoritative resources, “The endothelial cells have an attenuated cytoplasm that is highly fenestrated. Most of the fenestrae are 100 to 150 nm in diameter and tend to be clustered together to form sieve plates” (58).

At the University of Melbourne, we believe that it is important to encourage students to explore the transport systems of different epithelial cells and study the big picture as well as the molecular basis of mechanisms underlying common disorders. Because of deficiencies in medical textbooks and the lack of integration and application of knowledge across disciplines, a number of integrated computer-aided learning (CAL) programs covering these deficiencies and enhancing self-directed learning have been created. This author has created an interactive CAL program covering the liver, bilirubin, and bile salts (2). The program was used by the first-year medical students during 2002 and 2003 and a study evaluating the program has been prepared for publication.

Why is it important to include information on bile salt transporters in medical textbooks? Understanding the current physiology of bile salts, molecular mechanisms underlying their hepatocellular uptake and secretion, and the pathogenesis of chronic cholestatic hepatic disorders has not been adequately discussed in current medical textbooks. These principles are essential for medical students in preclinical years and will enhance students’ understanding of the scientific basis underlying hepatobiliary disorders. The rationales for including this information in medical textbooks may be summarized as follows:

- To enhance understanding of the hepatobiliary physiology, expression, and function of bile salt transporters.
- To understand the molecular mechanisms underlying hepatic disorders such as cholestasis.
- To understand the mechanisms by which drugs may cause hepatic injury and the role of impaired hepatic uptake and secretion of bile salts on the development of hepatic injury.
- To understand the role of bile salts in the pathogenesis of gallstones and the use of bile salts such as chenodeoxycholic acid and ursodeoxycholic acid in their management.
- To understand the possible mechanisms by which UDCA improves the liver function of patients with chronic cholestatic hepatic disorders.
- To understand the metabolism of cholesterol and bile salts and the scientific basis of treatment of hypercholesterolemia.
- To understand the scientific basis of genetic defects in hepatobiliary transport, e.g., progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis, and the Dubin-Johnson syndrome (see Table 1).
- To better understand the enterohepatic circulation of bile salts and the molecular mechanisms controlling bile salt absorption into the portal circulation.
- To understand the possible mechanisms underlying raised serum bile acids e.g., decreased expression of NTCP in some drug-induced liver dysfunction, chronic cholestatic liver disorders, and primary biliary cirrhosis.
- To understand the broad scientific concepts about the structure and function of epithelial cells and how transporters are designed to fulfill the function of an epithelial cell, which
might provide them with the opportunity to compare and contrast the function and structure of a number of epithelial cells in regard to the transporters, their locations, and the substrates transported into and out of these cells.

The contents of textbooks are not the basis for the construction of a curriculum. This is particularly important with the introduction of problem-based learning (PBL) in most medical schools and the enforcement of self-directed learning. However, textbooks should be comprehensive, be up to date, and provide the learner with their needs regardless of the structure and design of the curriculum or the geographic location of the university in which they enrolled. The aim is not to load students with information but to provide them with the main principles and enhance their self-directed learning to comprehend these details as needed. Adding new information to textbooks needs to be well planned and should aim at enhancing integration of knowledge. Editors and authors need to write their books from a new perspective. Rather than expand the content of medical textbooks by adding these new details, authors need to restructure the design of contents of textbooks, focus on the educational principles, encourage the discussion of pathophysiological mechanisms, and highlight the clinical significance of malfunction of these transporters.

Interestingly, one textbook published in 2003 and recently released in the market (7) has provided the reader with detailed information on bile salt transporters including, transporters at the basolateral membrane of hepatocytes [e.g., the Na+/K+ pump. Na+/taurocholate-cotransporting peptide (NTCP), organic anion-transporting protein (OATP1) and OATP2], and those at the apical canalicular membrane of hepatocytes (e.g., the ATP-dependent transporter bile salt exporter pump (BSEP), multidrug resistance-associated protein (MRP)2, MDR1, and MDR3). The authors have successfully explained the function of each transporter and its role in bile salt transport. It is also of interest to note that the chapter on hepatobiliary physiology in the fifth (2004) edition of Ref. 5 has been amended and currently contains detailed information about the bile salt transporters at the sinusoidal and canalicular domains of the liver cells (hepatocytes) and at the terminal ileum enterocytes.

In conclusion, this study reflects the presence of an imbalance in the content of current medical textbooks and the lack of information about hepatobiliary physiology, bile salt transporters, bile formation, and mechanisms underlying cholestasis and drug-induced hepatic injury. The failure of medical textbooks to integrate information and provide up-to-date concepts in this area cannot be justified by the assumption that textbooks are out of date because of the time needed for preparing and publishing them. Authors, editors, and publishers of medical textbooks need to keep textbooks up to date in the area of bile salt transporters and highlight the significance of bile salt transport in understanding the pathogenesis of hepatobiliary disorders.

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