Progress report

Gall-bladder water and electrolyte transport and its regulation

Diemerbroek in 1672 appreciated that bile entered the gall bladder to 'acquire greater strength and digestive power'. A study by Rous and McMaster in 1921 and later work by Ravdin and his coworkers provided direct experimental support for the notion that the gall bladder concentrates hepatic bile by selective reabsorption of bile constituents. These early studies have been reviewed in detail by Ivy. The nature of water and electrolyte absorption by gall-bladder mucosa has been extensively studied by Diamond and his colleagues whose work has provided an important basis for understanding of transport by this and other more complex epithelia. Subsequent studies using isotope and electrophysiological techniques which have sought to define the ionic basis for salt and water transport by gall bladder are the subject of several reviews. Recent experiments on the effects of gastrointestinal hormones and other secretagogues on gall-bladder transport have established that the gall bladder, like the intestine, is able to reverse the direction of its transport from a net absorption to a net secretion. The finding that feeding in the conscious monkey can abolish gall-bladder fluid absorption and reverse it to a net secretion provides for the first time direct evidence that the rate and direction of fluid absorption by the gall-bladder mucosa are subject to physiological regulation during digestion.

In this report we review recent studies contributing to the understanding of fluid and electrolyte transport by the gall bladder with particular reference to physiological control mechanisms and pathological changes which modify it.

Transport mechanisms

SODIUM AND CHLORIDE TRANSPORT

The rate of transcellular sodium transport depends on the rate of sodium entry across the luminal cell membrane and the active sodium extrusion across the basolateral cell membrane. Sodium enters gall-bladder epithelial cells passively across the luminal membrane down an electrochemical gradient maintained by its extrusion across the basolateral membrane by a sodium pump. Ion replacement studies in rabbit gall bladder have revealed that active Na⁺ absorption does not occur when luminal Cl⁻ is replaced by a variety of non-transported cations. The passive permeability of the luminal cell membrane to Na⁺ has been found to be too low to account for the observed transepithelial active sodium flux by diffusional Na⁺ entry. On the basis of influx studies in rabbit gall bladder non-diffusional Na⁺ entry has been postulated to occur by a one to one electrically neutral coupled entry mechanism for Na⁺ and Cl⁻. Such a carrier mediated
mechanism would facilitate charge neutralisation with Cl\(^{-}\) entry against an
electrochemical gradient.\(^6\)

\(\text{Na}^{+}\) exit against its electrochemical gradient is facilitated by a \(\text{Na}, \text{K},\) ATPase whose activity correlates directly with the rate of fluid transport.\(^7\)

Its activity, however, is not saturated under \textit{in vitro} conditions and is
dependent on the intracellular \(\text{Na}\) activity which in turn depends on \(\text{Na}^{+}\)
entry across the luminal membrane, the rate limiting step for trans-
epithelial \(\text{Na}^{+}\) transport.\(^14\)

The mechanism of the sodium extrusion at the basolateral membrane is
controversial, both electrogenic (rheogenic)\(^18 \, 19\) and non-electrogenic\(^20 \, 21\)
mechanisms have been proposed.

**Solute-Linked Water Absorption**

The gall-bladder mucosa like numerous other epithelia is able to perform
‘isotonic’ fluid transport – that is, it can transport solute and water between
equiosmolar bathing media so as to maintain equal tonicities of the bulk
media.\(^22\) Movement of water is believed to be passive and secondary to
active solute movement resulting from osmotic equilibration of transported
solute within the epithelium. The mechanism and site of the coupling of
solute and water fluxes by this and other epithelia is unsolved and remains
a central problem of current epithelial research.

In 1967 Diamond and Bossert\(^23\) proposed the standing gradient osmotic
flow theory to explain the intraepithelial osmotic coupling. According to
this, solute is pumped into the long narrow spaces between adjacent
epithelial cells. This creates a hypertonic compartment into which cellular
water is drawn by osmosis resulting in flow towards the serosal end of the
lateral intracellular space and a standing osmotic gradient within the space
under steady state conditions. Early support for this mechanism was the
finding that the lateral intercellular spaces of rabbit gall bladder \textit{(in vitro)}
were distended during fluid transport and collapsed by procedures which
inhibit transport such as low temperature, ouabain, metabolic inhibitors,
and ion replacements.\(^24\) Though compatible with the standing gradient
theory changes in cell volume and accumulation \textit{in vitro} of transported
fluid in the subepithelial space may account for these changes. On the basis
of morphological studies in living unfixed frog\(^25\) and rabbit\(^26\) gall bladder it
has been proposed that widening of the lateral intercellular spaces is a
fixation artefact and that the paracellular route does not contribute
significantly to isosmotic net fluid absorption.

Hill\(^27 \, 28\) has criticised the standing gradient theory on the grounds that
the epithelial water permeability of membranes adjacent to the lateral
intercellular space is insufficient to account for osmotic equilibration across
them. In its place he has proposed an electroosmotic theory. As discussed
by Diamond\(^29\) the above criticism is based on erroneous analysis because
of inappropriate selection of transport parameters.

The rate of NaCl and fluid absorption is enhanced by bicarbonate.\(^30\)
Recent studies suggest that HCO\(_3\)\(^-\) is required for the maintenance of
intracellular H\(^+\) which in turn maintains a Na/H exchange. This
mechanism is compatible with the presence of a double ion exchange
mediating parallel counter-transport of Na-H and Cl-HCO\(_3\) in the apical
membrane.\(^31 \, 32\) The above discussion has considered only the transcellular
movement of ions. In the last decade it has been recognised that ions also
move across epithelia by the paracellular pathway. In 1972 Fromter and Diamond\textsuperscript{33} showed by quantitative cable analysis that the transjunctional (paracellular) route in Necturus gall bladder accounted for some 97% of passive ion permeation. Their survey of other epithelia showed marked differences in junctional tightness on which basis they classified epithelia as 'tight' or 'leaky'. The leakiness of gall-bladder tight junctions has also been shown using electron microscopy. A study in rabbit gall bladder has shown that lanthanum, used as an electron dense marker, is able to move from the gall-bladder lumen across the tight junction to the lateral intercellular space without penetrating the epithelial cells.\textsuperscript{34}

**FLUID SECRETION BY GALL-BLADDER MUCOSA**

Early reports reviewed by Ivy\textsuperscript{35} documented secretion by gall-bladder mucosa. In particular Burch and Spong\textsuperscript{35} in 1887 reported observations on gall-bladder secretion in two patients who had undergone cholecystotomy. The secretion collected was clear, slightly opalescent, almost colourless, slightly alkaline and contained a high proportion of mucin. In view of the normal appearance of the gall-bladder wall and the unaltered composition of the secretion in one patient over two years these authors believed the secretion to be a normal product of the mucosa acting to lubricate the gall-bladder wall.

More than 80 years later Schafer and his colleagues\textsuperscript{36} reported a similar secretion in the dog gall bladder after instillation of a crude vibrio cholerae extract. This procedure reversed the direction of transport from a net absorption of 3–6 ml/h to a net secretion of 0.5–1 ml/h which continued for more than 24 hours. The secreted fluid was clear, viscid and alkaline being rich in bicarbonate. Purified cholera toxin has subsequently been reported to inhibit fluid absorption by isolated guinea pig\textsuperscript{37} and rabbit\textsuperscript{38} gall bladders, reversing it to a net secretion only in the former species. Prostaglandins,\textsuperscript{39,40} prostacyclin,\textsuperscript{41} and gastrointestinal hormones\textsuperscript{42-44} can also induce a net fluid secretion by the guinea pig gall bladder in vitro. Secretion has been reported *in vivo* in the anaesthetised cat after intravenous infusions of gastrointestinal hormones\textsuperscript{45,46} and local intraarterial infusion of prostaglandin E\textsubscript{2}.

Gall-bladder secretion after feeding has been observed in the conscious monkey.\textsuperscript{13} The failure of cholera toxin,\textsuperscript{38} prostaglandins,\textsuperscript{48} and secretin\textsuperscript{49} to induce secretion by rabbit gall bladder suggests an absence of a secretory mechanism in this species.

The secretion of water and electrolytes by the gall-bladder mucosa is an active process which can take place against hydrostatic and osmotic gradients\textsuperscript{50} and is inhibited by ouabain. The ionic events occurring during secretion have been studied in the guinea pig gall bladder. In this species under non-secretory control conditions bicarbonate is secreted into the gall-bladder lumen in exchange for chloride.\textsuperscript{30} This transport continues and is enhanced during prostaglandin-induced secretion where it is associated with a considerable reduction in chloride absorption and a reversal of sodium and potassium absorption to a net secretion. These ionic changes are accompanied by an increase in both short circuit current (Isc) and tissue conductance (Gt). Secretion is abolished by omission of bicarbonate from the bathing solution and is independent of the external calcium concentration. These findings suggest that bicarbonate is secreted electrogeneically into the gall-bladder lumen.\textsuperscript{51}
Humoral and neural influence on transport

**Effects of biologically active substances on fluid transport**

A variety of local mediators have been found to affect the rate of NaCl and water transport both *in vivo* and *in vitro*. Some of these could act to regulate gall-bladder water and electrolyte transfer under physiological conditions by modification of NaCl influx, active Na⁺ extrusion, and/or junctional permeability. Cyclic AMP has been proposed as a second messenger for the effects of several such mediators and has been found in rabbit [15] and Necturus gall bladder [52] to inhibit the NaCl coupled influx, the rate limiting step for transepithelial Na⁺ transport. In addition to effects on luminal membrane function cAMP may also regulate transport by influencing tight junction permeability. [53]

**Gastrointestinal peptides**

Secretin and extracts of islet cell tumours but not cholecystokinin or gastrin were reported to inhibit fluid absorption by the isolated rabbit gall bladder. [48] The extent of this inhibitory effect and concentrations of each substance used was unfortunately not documented in this report. Experiments using the isolated guinea pig gall bladder have shown that natural porcine secretin, synthetic secretin, PHI (a recently isolated secretin-like peptide whose molecular sequence starts with histidine and ends with isoleucine), and natural porcine VIP inhibit fluid absorption concentration-dependently with half maximal inhibition values of 1.8, 6.0, and 8.2 ng/ml for the latter three peptides respectively. [42-44] At the highest concentrations studied these peptides reversed the direction of transport from net absorption to net secretion.

Studies *in vivo* in the anaesthetised cat have provided similar results. VIP (1 μg/kg/h) infused intravenously inhibited gall-bladder water and electrolyte transport and reversed its direction to a net secretion, an effect which was readily reversible. [45] Similar findings were reported with natural porcine secretin (2 U/kg/h) though the secretory effect was less consistent. Natural porcine cholecystokinin (2 U/kg/h) was without effect on transport. [46]

A recent study [54] has examined the effects of VIP and secretin on cAMP production by isolated epithelial cells of human and guinea pig gall bladder. VIP was a potent stimulant of cAMP production by human gall-bladder cells with half maximal and maximal stimulation at 0.2 and 10 nM respectively. Secretin was also a potent stimulant of cAMP formation by guinea pig but not human gall bladder. The effects of VIP and secretin on fluid transport by human gall bladder have yet to be reported. The above findings suggest that VIP-ergic nerves shown by immuno-histochemistry in the gall-bladder wall of several species [55] may release VIP to act on receptors on the serosal surface of gall-bladder epithelial cells and thereby modify the direction and rate of transmucosal fluid transport. Glucagon and gastric inhibitory peptide (GIP) which belong to the same hormone family as secretin and VIP have been studied in the cat [56] and guinea pig. [43] In the latter species glucagon inhibited transport dose-dependently at high concentrations producing half maximal inhibition at 4.4 μg/ml. The absence of an effect with this peptide in the anaesthetised cat probably reflects the lower concentration studied. Natural porcine GIP
was without effect in both species. A variety of other gastrointestinal peptides have been studied in the isolated guinea pig gall bladder. Neurotensin, bombesin, motilin, cholecystokinin, caerulein, and somatostatin were all without effect on absorption. The effects of almost all gastrointestinal peptides on human gall-bladder fluid transport are as yet unreported. Onstad and colleagues found an inhibitory effect of natural cholecystokinin on transport by gall bladders removed at cholecystectomy. This finding may reflect an increased serosal pressure within their everted human gall-bladder preparation rather than a direct effect of cholecystokinin on the epithelium per se.

It is of interest that glucagon has been reported to increase the size of the human gall bladder before or after a fatty meal. The mechanism of this effect is uncertain as in vitro studies on the effect of glucagon on human gall-bladder strips failed to show any effect. It is possible that an increase in gall bladder size may result from a secretion into the lumen.

The gall-bladder mucosa is subject to a complex series of neural and endocrine-paracrine regulatory influences during digestion. Of the above regulatory peptides whose effects have been studied only VIP and secretin are able to modify gall-bladder fluid transport at concentrations which may be considered physiological. Peptides without effect on transport in vitro when administered alone may, however, act to potentiate or inhibit the effects of these candidate peptides and other as yet unrecognized regulatory factors. Thus, for example, though somatostatin had no effect on basal transport it completely reversed the inhibitory effect of VIP and secretin on absorption.61

**Prostaglandins and Related Substances**

Prostaglandins are synthesised from arachidonic acid released from membrane phospholipids by the action of phospholipases. Recent research has shown that arachidonic acid may be converted via the unstable cyclic endoperoxide intermediates PGG2 and PGH2 not only to prostaglandins but to other potent biologically active prostanoids the thromboxanes and prostacyclin.

The effects of prostaglandins of the E and F series have been studied in vitro using rabbit and guinea pig gall bladder preparations. In rabbit gall bladder serosal application of prostaglandins E1, E2, or F2α inhibited fluid absorption dose-dependently. The response to prostaglandin E was 10 times more potent in the presence of indomethacin, an inhibitor of endogenous prostaglandin formation. Prostaglandin E1 and prostaglandin E2 were equipotent, 100 fold more effective than prostaglandin F2α, and inhibited fluid absorption at a maximum by 50%. On luminal application the two E prostaglandins had only weak inhibitory effect. A similar rank potency and lower efficacy of the above prostaglandins on mucosal as compared with serosal application has been reported for guinea pig. The inhibitory potency of prostaglandins on fluid absorption was found to vary inversely with animal body weight by one to two orders of magnitude between younger lighter animals and older heavier animals. In contrast with the findings with rabbit gall bladder prostaglandins E1, E2, and F2α were able to totally inhibit fluid absorption, reversing it to a net secretion. These prostaglandins and prostaglandin A1 were less effective on luminal than on serosal application.
Prostaglandin E₂ (5 μg/kg/min) infused intraarterially into the anaesthetised cat reversibly inhibited net gall-bladder absorption and in half the animals tested reversed the direction of transport to a net secretion.⁴⁷

The above studies show that prostaglandins have potent effects on gall-bladder transport. Prostaglandin E and prostaglandin F-like substances have been isolated from the mucosa and muscle of pathological human gall bladders⁶³ and from homogenates of guinea pig gall bladder (J R Wood and I F Stamford, unpublished). The ability of indomethacin, a prostaglandin synthesis inhibitor, to antagonise inhibition of gall-bladder fluid absorption by arachidonic acid⁶⁴ provides further evidence for endogenous synthesis of prostanoids by gall bladder. Whether or not prostanoid formation acts to modify transport under physiological conditions is unknown. There is, however, good evidence to support a role for prostaglandins and other prostanoids in the pathological changes in gall-bladder transport observed in cholecystitis. This will be considered in a later section.

Bile Acids

Bile acids are present in the gall-bladder lumen in high concentration. Three studies have examined their effects on gall-bladder fluid absorption. In dog gall bladder⁶⁵ in vivo 16.7 mM taurodeoxycholate or taurochenodeoxycholate applied intraluminally completely abolished net water absorption. Taurocholate was ineffective at this concentration but had a small inhibitory effect at 40 mM. In contrast with findings in the intestine these substances did not induce a net fluid secretion. The lack of effect of taurodeoxycholate on rabbit gall-bladder⁶⁶ transport may reflect the relatively low concentration studied. In the guinea pig gall bladder in vitro chenodeoxycholate (0.3-2.5 mM) and its glycine conjugate (0.6-5 mM) inhibited fluid absorption concentration dependently to a maximum of 80%. Chenodeoxycholate also inhibited fluid absorption when applied serosally but was less potent than on mucosal application. Glycocholate was without effect and the inhibitory effect of cholate at high concentrations may result from its contamination by deoxycholate.⁶⁷ The effects of bile acids on water and electrolyte transport under physiological conditions will be modified by other constituents of bile. In particular lecithin has been shown to block the inhibitory effect of taurodeoxycholate on water absorption by dog gall bladder. Effects of bile acids on gall-bladder concentrating function are therefore more likely to have relevance to pathological conditions resulting in their deconjugation within the gall-bladder lumen than to physiological events.

Hormones and Other Agents

Female sex hormones have been reported to inhibit gall-bladder fluid absorption in vitro.⁶⁸ ⁶⁹ The concentrations of 17β oestradiol and progesterone used in these experiments are unfortunately pharmacological and provide no information concerning any possible physiological effects. It is not known whether gall-bladder absorptive function is influenced by different phases of the ovulatory cycle. Early studies, however, suggest that gall-bladder concentrating function may be impaired during pregnancy and parturition.
Riegel and her colleagues\textsuperscript{70} studied the composition of gall-bladder bile in women at term and found changes consistent with impaired gall-bladder concentrating function. Potter\textsuperscript{71} in 1936 observed that the gall bladder in pregnant women undergoing caesarian section was distended, containing bile of similar composition to hepatic bile.

A miscellany of other hormones and biologically active substances including prolactin,\textsuperscript{72} oxytocin and ADH,\textsuperscript{6, 73-75} angiotensin II \textsuperscript{76} and serotonin\textsuperscript{77} inhibit absorption or are without effect. There is no evidence at present to support a role for any of these substances in the physiological regulation of gall-bladder water and electrolyte transport.

**Influence of the Autonomic Nervous System**

Adrenergic cholinergic and peptidergic nerve fibres have been shown in gall bladder. Nerve fibres with noradrenergic immunofluorescence have been visualised in the gall-bladder wall using histological techniques.\textsuperscript{78} The tissue concentrations of noradrenaline in the extrahepatic biliary tract have been reported to exceed those in the small intestine.\textsuperscript{75} Studies of the distribution of adrenergic fibres in the gall-bladder wall have shown a direct and an indirect system.\textsuperscript{79} The nerves in the direct system terminate mainly on blood vessels and smooth muscle cells and the fibres in the indirect system are believed to act on intrinsic excitatory neurones. Kyösola and Penttilä\textsuperscript{78} in the human gall bladder found a sparse noradrenergic innervation of the mucosa and a dense innervation of the muscle layer. Cholinergic nerve fibres have also been shown in the gall-bladder wall by histological methods.\textsuperscript{80} The possible role of nerve fibres immunoreactive to VIP has already been considered.

The adrenergic nerve supply to the gall bladder travels in the splanchnic nerves but as adrenergic fibres have also been visualised in the vagus nerve\textsuperscript{81} a part of the adrenergic nerve supply may take this route. Cholinergic fibres are received from the vagus nerves.\textsuperscript{82} Peptidergic fibres have been found in the vagus nerves\textsuperscript{82} and electrical stimulation of these nerves is known to release VIP and gastrin into the portal blood.\textsuperscript{83-85} Peptidergic fibres are also found in the splanchnic nerves,\textsuperscript{86} electrical stimulation of which has been found to reduce the VIP concentration in the portal blood.

Noradrenaline increased net water absorption by the everted human gall bladder.\textsuperscript{58} the gall bladder of the anaesthetised cat,\textsuperscript{87} but not by the isolated guinea pig gall bladder.\textsuperscript{58} Acetylcholine had no effect on water transport by the guinea pig gall bladder\textsuperscript{88} *in vitro* or the cat gall bladder\textsuperscript{89} *in vivo* in doses causing gall-bladder contraction. Of other possible neurotransmitters gastrin has been reported to reduce net water absorption by the dog gall bladder *in vitro*\textsuperscript{90} and VIP has potent effects considered above.

It has been recently found that electrical stimulation of the splanchnic nerves stimulates the rate of water absorption by the gall bladder of the anaesthetised cat, an effect which can be abolished by alpha-adrenergic receptor blockade. The precise site of action of the sympathetic nerves on net water transport by the gall bladder is unknown. Apart from a possible direct effect on mucosal cells, sympathetic nerves may act on local ganglia to inhibit release of a neurotransmitter which inhibits water absorption. A possible transmitter set free by local reflexes is VIP.

Westphal and coworkers\textsuperscript{91} in 1931 reported that electrical stimulation of
the vagus could increase water absorption by the dog gall bladder. Their results were not consistent, however, and in a few experiments a reduced water transport was noted. In a recent study, electrical stimulation of the cervical vagus nerves in the cat failed to influence the rate of fluid transport in the gall bladder measured by a perfusion technique. Using the same technique vagal stimulation significantly reduced the net water absorption in atropinised animals. Electrical stimulation of the vagus nerves at the level of the neck will influence the gall bladder directly. A complex of the direct effects of the nerve fibres might, however, be masked by secondary effects because of released gastrointestinal peptides and other blood borne factors. Evidently there seems to be a non-cholinergic mechanism capable of reducing net water absorption by the gall bladder.

Histological study of the gall-bladder mucus secretion has shown an increased discharge of glycogen granules in response to cholinergic drugs while adrenergic or alpha-adrenergic blocking drugs had no effect.

Physiological changes in transport

Classical physiology views the gall-bladder mucosa as continuously absorbing water. Several studies, however, suggest that gall-bladder transport is subject to physiological regulation. Johnston and coworkers in 1932 found that the hourly absorption of water by dog gall bladder was three times greater during the day than at night during sleep. More recently Lindemann and Rund attempted to study the absorption of sodium chloride from the gall bladder of the dog after feeding but were unable to detect any variation in the transport rate. They studied only four dogs, however, and the report is most inconclusive. In a recent study, the influence of fasting and feeding on the concentrating function of the gall bladder was studied in conscious monkeys. During the day fasting animals had a net hourly absorption rate corresponding to one third of the fasting gall-bladder volume. Feeding resulted in a reversal of the direction of gall-bladder transport from a net absorption to a net secretion into the gall-bladder lumen. This study also confirmed the findings of Johnston and coworkers that compared with the awake fasting state net water absorption from the gall bladder was reduced at night during sleep.

The net water transport across the gall-bladder wall may be influenced by both humoral factors and autonomic nerves as seen above. The gall-bladder secretory response to feeding may result from an increased release of VIP from intramural nerves. Exogenous VIP as discussed above can induce a net fluid secretion into the gall bladder. VIP receptors have been shown on the epithelial cells and histochemical studies have visualised VIP-containing nerve fibres in close proximity to the gall-bladder epithelium. The greater net water absorption during daytime compared with sleeping may be explained by a general increase in the activity of the sympathetic nervous system as alpha-adrenergic stimulation has been shown to increase net water absorption in the cat gall bladder.

Variations in the concentrating function of the gall bladder may affect the enterohepatic circulation of substances such as bile salts. In addition to the frequency of gall-bladder contraction a net secretion by the gall bladder may influence the rate of bile acid entry into the gut. An increased net fluid absorption under conditions of increased adrenergic activity would have
the opposite effect. Fluid secretion into the gall bladder resulting in dilution of the organic constituents of bile might be of importance for efficient evacuation of the gall bladder after a meal, and may also help eliminate precipitation nuclei that form in the gall-bladder lumen.

**Pathological changes in transport**

*Congenital transport defect*

A recent study has attempted to examine the concentrating ability of the gall bladder of a child with congenital chloridorrhoea, a rare autosomal recessive disturbance of intestinal chloride transport. Gall-bladder transport was assessed indirectly by measurement of duodenal bile acid concentrations before and after presumed gall-bladder contraction stimulated by exogenous cholecystokinin. The absence of a change in duodenal bile acid concentration in this child, in marked contrast with the increase in three control children was taken as evidence for a defect in gall-bladder electrolyte transport. This conclusion must, however, remain in doubt in view of the absence of evidence to substantiate gall bladder evacuation in the affected child.

*Neuroendocrine tumour syndromes*

Abnormalities of gall-bladder function have been reported in the Verner Morrison syndrome (pancreatic cholera or WDHA syndrome). Patients with this syndrome have raised circulating VIP concentrations and large atonic gall bladders containing a dilute bile rich in bicarbonate. These changes may be accounted for by a relaxant effect of VIP on gall-bladder muscle, by its ability to antagonise the contractile effects of cholecystokinin, by its effects on gall-bladder fluid transport similar to those described above for guinea pig and cat, and by changes in the composition of hepatic bile. Though changes in bile composition have not yet been reported in association with hypersecretion of other gastrointestinal hormones it is of interest that cholelithiasis is a feature of the somatostatinoma syndrome. Somatostatin has been reported to reverse cholecystokinin induced gall-bladder contraction in the dog in vivo but not in vitro. It is also able to reverse the inhibitory effect of VIP and secretin on gall-bladder fluid transport. Whether or not the susceptibility to cholelithiasis results from reduced postprandial gall bladder evacuation or from impaired regulation of gall-bladder fluid transport remains to be determined.

**Gall-bladder fluid transport in cholecystitis**

The absorptive function of the gall bladder in gall-stone disease in man is known only from visualisation at cholecystography or from studies in vitro. The general consensus from radiological studies is that the gall bladder can be visualised in chronic but not acute cholecystitis. In a study of transport by human gall bladdersexcised at cholecystectomy absorptive function correlated with histological and clinical findings. Patients with more marked clinical findings were found to have more extensive histological changes and poor absorptive function in the gall bladder. In experimental cholelithiasis in the rabbit Kyd and Bouchier, however, found no difference in the rate of water absorption between stone forming and
control gall bladders. Lee in a subsequent study in isolated guinea pig and rabbit gall bladder has reported an enhanced water absorption per unit gall-bladder weight during lithogenesis. This in vitro function may not be comparable with the ability of the gall bladder to absorb water and electrolytes in vivo where blood supply, lymphatic drainage and nervous and humoral factors influence its function.

In a recent study fluid transport by the gall bladder was studied in experimental cholecystitis in the cat. Cholecystitis was induced by implanting human gall stones into the cat gall bladders. Three months later the concentrating function of the gall bladder was studied in vivo in the anaesthetised animal. It was found that in animals with a patent cystic duct the concentrating function of the gall bladder was intact despite a slight or moderate inflammation of the mucosa. In contrast, animals with gall-stone induced cystic duct obstruction whose gall-bladder mucosa was markedly inflamed continuously secreted fluid into the gall-bladder lumen, forming a hydrops. Indomethacin, a prostaglandin synthetase inhibitor, promptly reversed this fluid secretion to an absorption suggesting that endogenous prostaglandin formation may be responsible for the observed fluid transport change. In a recent study in dogs it was found that obstruction of the gall bladder in combination with infection of its contents induced a continuous fluid secretion into its lumen that was sustained for several days. This secretion was markedly reduced by indomethacin further supporting the role of prostaglandins in secretion by the inflamed gall bladder.

A factor considered important in the pathophysiology of cholecystitis is formation of lysolecithin by hydrolysis of phospholipids in the gall bladder. It has recently been reported that addition of lysolecithin to an electrolyte solution in the gall-bladder lumen at a concentration comparable with that found in the bile of patients with acute cholecystitis reversed the direction of transport to a net secretion. This fluid secretion was abolished by indomethacin suggesting that at least part of the change in fluid transport may result from endogenous prostaglandin formation.

In acute cholecystitis the gall-bladder neck is often obstructed by a gall stone. A reversal of the direction of fluid transport across the gall-bladder mucosa to a net secretion into the lumen will cause distension of the obstructed gall bladder. Distension has recently been reported to stimulate prostaglandins synthesis by the gall-bladder wall. The clinical course of acute cholecystitis with necrosis and gall-bladder perforation can be explained by these changes. This hypothesis is further supported by the finding that the intraluminal pressure in the gall bladder in acute cholecystitis is markedly raised, sometimes to values exceeding 90 mm Hg.

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Received for publication 2 September 1982
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References

29. Diamond JM. Twenty first Bowditch lecture. The epithelial junction, bridge, gate and


Brennan LJ, McLoughlin TA, Mutt V, Tatemoto K, Wood JR. Effects of PHI, a newly isolated peptide, on gallbladder function in the guinea pig. *J Physiol (Lond)* 1982; 329: 71P–72P.


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69 Che Rosali BCM, France VM. Effect of 17β-oestradiol on progesterone induced inhibition of fluid transported by male guinea pig gallbladder in vitro. J Physiol (Lond) 1978; 278: 30P.


102 Vagne M, Troitskaja V. Effect of secretin, glucagon and VIP on gallbladder contraction.
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117 Niederhiser D, Thornell E, Björck S, Svanvik J. The effect of lysophosphatidylcholine on gallbladder function and hepatic bile outflow in the cat. (In preparation.)


120 Thornell E. Mechanisms in the development of acute cholecystitis and biliary pain; a study on the role of prostaglandins and effects of indomethacin. Scand J Gastroenterol suppl 76, 1982.
