Filling of the Gallbladder as Studied by Computer-Assisted Tc-99m HIDA Scintigraphy: Concise Communication

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Gallbladder filling was studied using computer-assisted cholescintigraphy in normal subjects who had fasted overnight. The gallbladder tended to visualize earlier than the distal part of the common bile duct. It appeared at approximately the same time regardless of whether or not there was passage of activity into the duodenum. This suggests that filling is not dependent on contraction of the sphincter of Oddi. Sequential images demonstrated that the activity entering the gallbladder rapidly reached the fundus. Time-activity curves showed a gradual buildup of activity in the bile ducts followed by sudden entrance into the gallbladder. Time-activity curves of the gallbladder's proximal and distal parts showed signs of an exchange of activity, suggesting that the gallbladder's motor function is not quiescent during fasting. Gallbladder motility could explain the periodic irregularities on the time-activity curve. These irregularities were smaller but no less frequent after morphine administration.

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It is often assumed that filling of the gallbladder occurs passively. Passive filling is believed to take place as a consequence of the back-pressure produced by the pileup of bile against the closed sphincter of Oddi (*1–4*). We tested the validity of this concept with computer-assisted Tc-HIDA cholescintigraphy.

MATERIAL AND METHODS

Thirty subjects were studied: 15 healthy volunteers and 15 patients in whom liver tests had been found normal—serum-bilirubin, ASAT, ALAT, LD, alkaline phosphatase, and oral cholecystography. There were 15 men and 15 women, age range 32 to 82 yr, median 53. The radionuclide studies were performed after an overnight fast, using a scintillation camera with a high-resolution collimator (15,000 parallel holes) and interfaced to a minicomputer system. With the subject in the supine position 2.2 mCi (80 MBq) Tc-99m HIDA was injected into an arm vein. Sequential scintigrams were recorded of the liver and biliary tract with 1-min exposures during the next hour.

The time after administration was noted when the proximal part of the bile ducts became visible on the scintigram. So was the time after injection when the activity reached the distal part of the common duct and when it passed into the duodenum. We also noted when the gallbladder became visible and when the activity reached the most distal part of the fundus of the gallbladder. Regions of interest (ROI) were chosen by light-pen on the 60 added one min views. One region represented the gallbladder and another the depot of activity present in the duct in the immediate vicinity of the gallbladder (Figs. 1 and 2). The exact locations of these two regions were checked with the help of the sequential images. Time-activity curves were normalized, setting the maximum count rate to 100%. To study the initial transport of activity, these two curves were compared until 10–15 min after visualization of the gallbladder.

The gallbladder was divided into two equal regions of

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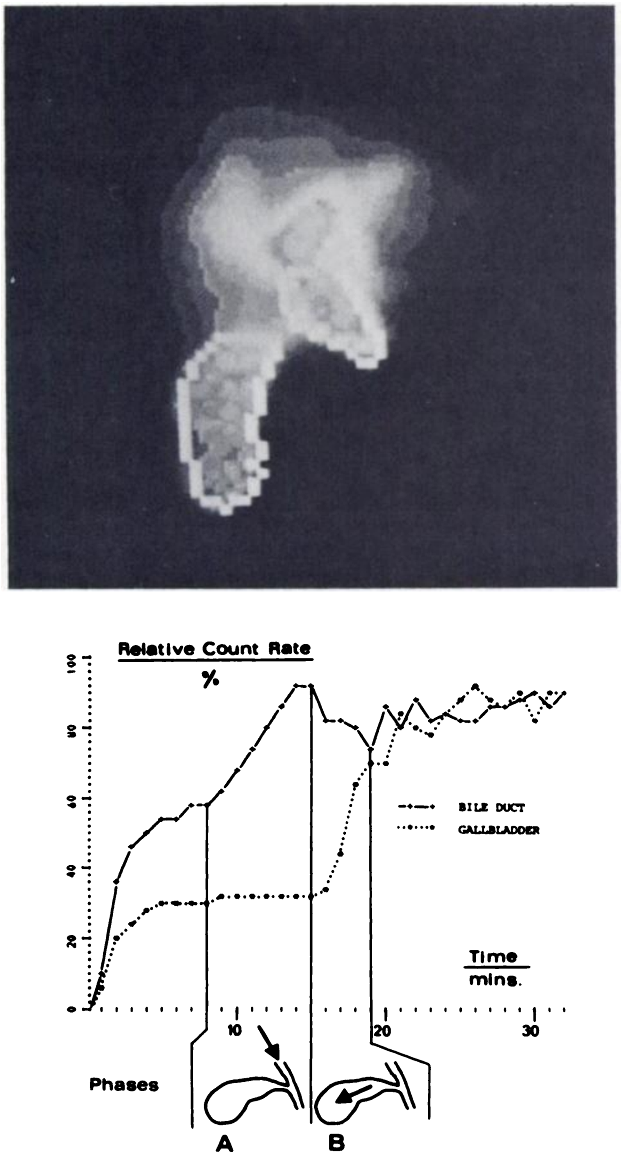


FIG. 1. Regions of interest (upper): gallbladder and proximal part of bile ducts. Time-activity curves lower of gallbladder and proximal part of bile ducts during initial phases of gallbladder filling. No correction for liver background.

interest, a proximal and a distal part. When the gallbladder, as seen on the display, was situated within the contours of the liver, a similarly sized region of the liver was chosen close to the gallbladder (Figs. 3 and 4), to be used for correction of liver background. Liver background was subtracted in such cases for two reasons: (a) to facilitate comparison with cases in which the gallbladder was situated outside the contours of the liver, and (b) to demonstrate more clearly the relative changes of activity within the gallbladder. Time-activity curves were created and normalized as described above. To study the initial transport of activity inside the gallbladder, the two curves were compared until 10–15 min after visualization. We restricted ourselves to the first 10–15 min because the bolus effect is soon lost.

In ten of the volunteers the procedure was repeated 1 to 2 wk later. Forty-five min before the repeat study, 10 mg of morphine were injected intramuscularly, time-activity curves of the gallbladder were obtained as described above, and similar curves of the liver were created as described in earlier papers (*5,6*). The number of easily discernible dips (i.e., dips of four percentage points or more) in the gallbladder curves obtained with and without morphine was noted. Four percent was chosen since this was the lowest value clearly exceeding the uncertainty due to counting statistics ($\leq$ 1.8%). These dips were expressed as percentages of the activity present in the gallbladder at the moment of their occurrence and their mean value was calculated. The mean values of the dips in the curves obtained with and without morphine were compared.

Significance was tested with nonparametric methods as described by Siegel (*7*). The uncertainty due to counting statistics was negligible in every single case. None of the curves was subjected to any form of smoothing.

RESULTS

The proximal part of the bile ducts became visible on sequential images between 7 and 15 min after injection, median value 10.5 min. Visualization of the gallbladder started after 9–27 min, median 17 min. In nine subjects the distal part of the duct was not seen on the screen after 1 hr. In the remaining 21 studies the distal part of the duct became visible after 9–52 min, median 23 min (Fig. 5). Thus, the distal part of the duct tended to visualize after the gallbladder had started to fill. With the Wilcoxon matched—pairs signed—ranks test the difference was significant ($p < 0.01$). Even after exclusion of the nine subjects in whom the distal part of the duct was not seen on the screen after 1 hr, the difference was significant ($p < 0.05$).

The time following injection when the first activity entered the gallbladder was compared with the time when it reached the most distal part of the fundus, as seen on subsequent sequential images. The comparison showed a difference ranging from 2 to 14 min, median value 6 min. Figure 6 compares an image obtained 21 min following administration with added views obtained later, i.e., 22–60 min after injection, in the same study. Visualization started at 18 min after injection and 3 min later the activity had almost reached what subsequent images showed to be the most distal part of the fundus. As seen in Fig. 6, the activity first appeared near the long axis of the gallbladder. Later it spread laterally. This we found to be a very regular phenomenon.

Passage of activity into the duodenum was observed in 14 of the 30 studies. In those 14 studies the gallbladder image appeared after 9–27 min, median 18 min. In the 16 subjects without passage of activity into the duodenum, visualization of the gallbladder started after 11–24 min, median 17 min. Thus, the time when the

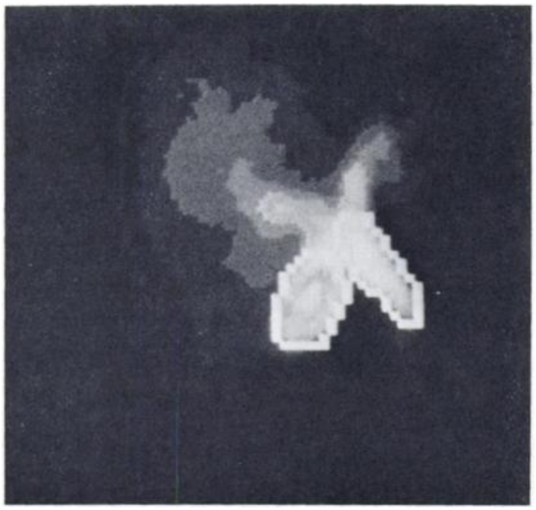
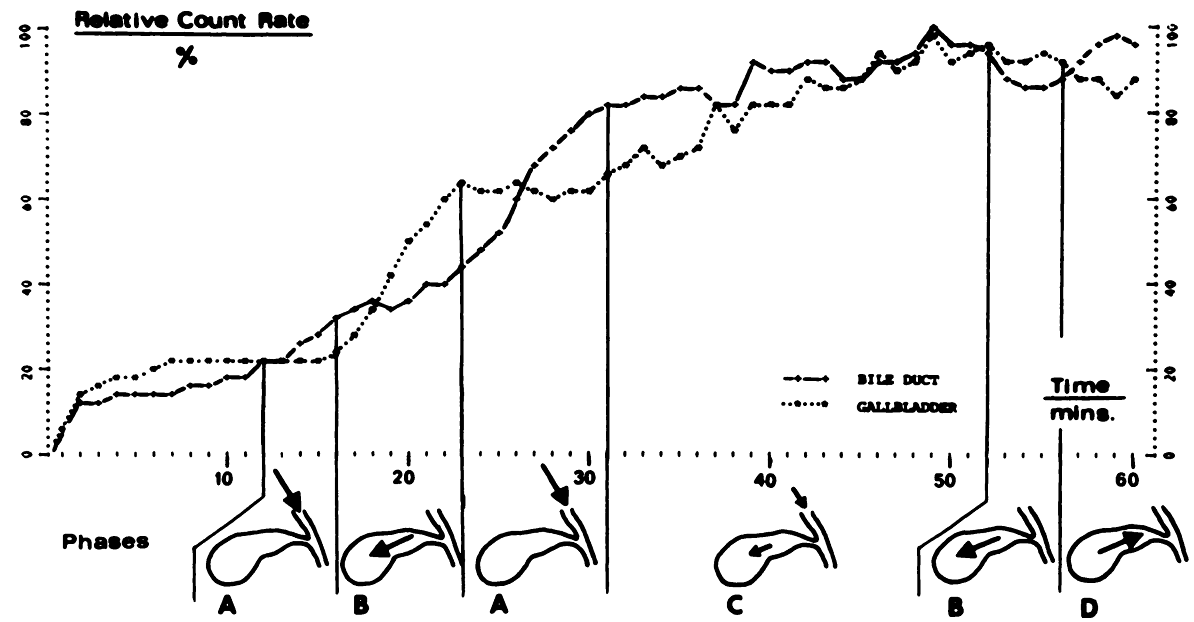


FIG. 2. Regions of interest (upper): gallbladder and proximal part of bile ducts. Time-activity curves (lower) of gallbladder and proximal part of bile ducts during 1 hr. No correction for liver background.



gallbladder first appeared was almost identical in subjects with or without passage of activity.

In 24 studies the time-activity curve for the ducts started with a steady rise and during this rise the curve for the gallbladder region of interest (ROI) remained unchanged. This divergence of the two curves in these 24 cases lasted from 2 to 14 min, median 7.5 min (Figs. 1 and 2). In the remaining six cases there was no such initial divergence of the two curves. The gradual rise of the bile-duct curve continued during the initial period in five of the 30 studies. In the other 25 cases the rise of the bile-duct curve was eventually interrupted by a dip (Fig. 1) or alternatively the curve temporarily leveled off (Fig. 2). When the rise of the bile-duct curve was thus interrupted, the gallbladder curve showed a sudden rise in 24 of the 25 cases. The curves kept their new directions for 1 to 7 min, median 3 min, after which they again changed course. The analysis was then stopped.

Comparison of the time-activity curves of the proximal and the distal parts of the gallbladder showed one characteristic that recurred regularly. The first rise of the proximal curve was nearly always accompanied by a similar rise of the curve of the distal part (Figs. 3 and 4, Stage a). Only in three cases was there a rise of the proximal curve without a corresponding rise of the distal curve. In five of the remaining 27 subjects, the curve for the distal part leveled off after its initial rise, whereas the curve for the proximal part kept its original course. Thus, during Stage b (Fig. 2) the two curves diverged. When the first rise of the proximal curve was finally interrupted, the interruption coincided with, or was closely followed by, a rise of the distal curve. During this Stage c (Fig. 3) the two curves converged. In the other 22 studies the behavior of the two curves after their initially synchronous rise was more complex. Stages b and c were not clearly separable. A recurrent feature was a less steep rise of the distal curve while the proximal curve kept its course, causing divergence of the two curves. After a few

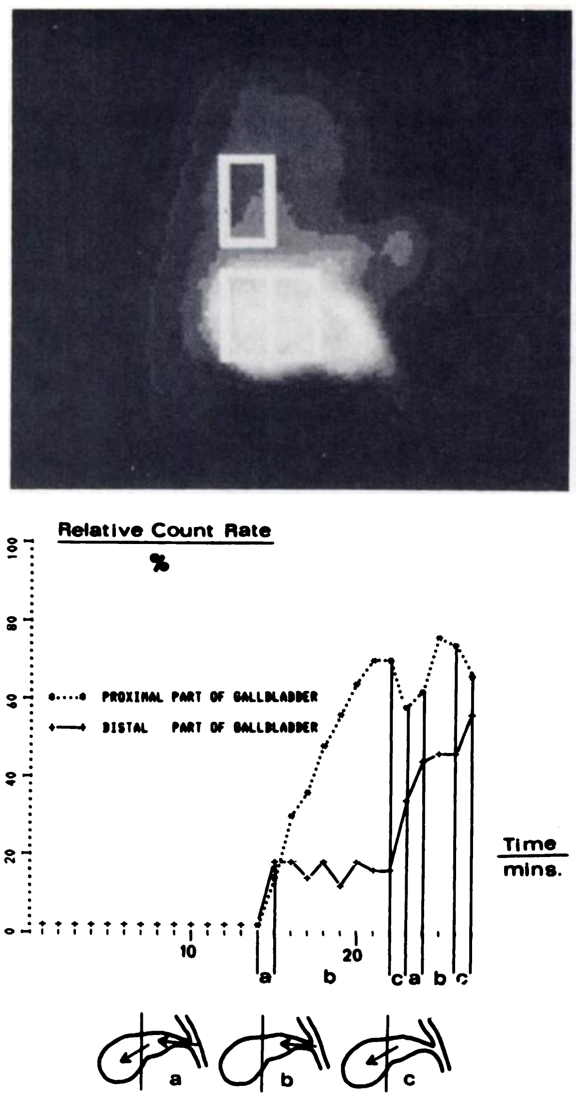


FIG. 3. Regions of interest (upper): proximal and distal parts of gallbladder and for liver background correction. Time-activity curves (lower) of proximal and distal parts of gallbladder, corrected for liver background, during initial phases of gallbladder filling.

minutes the curves again converged or even crossed each other (Fig. 4, div. and conv.). The rest of the curves seldom showed a uniform pattern but in some studies the exchange between the two parts of the gallbladder could be followed in the later stages (Fig. 4, exchange).

The gallbladder curves obtained with and without morphine did not show any difference in the number of easily discernible dips—i.e., of four percentage points or more. In all subjects (except one in whom there was no change), the size of the dips was smaller in the curve obtained with morphine than in the one without (Fig. 7). The difference in size of the dips was significant by the Wilcoxon test ($p < 0.01$).

DISCUSSION

The summary accounts published so far on filling of the gallbladder attribute a key role to the sphincter of Oddi. During fasting the sphincter is assumed to be closed (*2,8*), allowing bile flowing from the liver to accumulate gradually above the contracted sphincter. Filling of the gallbladder is thought to result from the ensuing gradual increase in pressure and not from motor activity in the gallbladder wall or anywhere else. Such activity is believed to be quiescent in the interdigestive state.

Cholescintigraphy refutes the foregoing chain of events on several counts.

First, the sphincter is not permanently closed in the interdigestive state. All our studies were performed after an overnight fast, but in about half of them radioactivity passed into the duodenum during the 1-hr study. It should be stressed that the duodenum can nearly always be distinguished easily from the duct. If there is any doubt whether a depot of activity is situated in the distal part of the duct or in the duodenum, the time-activity curve will reveal its true location (*5*). Recently, Weissmann et al. (*9*) have even suggested that the rapidity of the transit from biliary tract to bowel can be used in scintigraphic diagnostics. The frequent observation of passage of activity into the duodenum after an overnight fast is in keeping with the studies of Northfield and Hofmann (*10*) and of von Bergmann et al. (*11*), who found that bile acids were secreted into the duodenum during overnight fasting. Belgian workers (*12*) have even been able to show that the bile-acid discharge into the duodenum varies cyclically during a fast.

Second, in subjects in whom activity passed into the duodenum, visualization of the gallbladder was not delayed. The time after administration when visualization started was almost identical with that in subjects in whom such passage was absent. Thus, closure of the sphincter of Oddi is not a prerequisite for filling of the gallbladder. This is in keeping with an earlier study in which we found that morphine closes the sphincter but does not affect filling of the gallbladder (*13*).

Third, in most of our 1-hr studies the gallbladder was visualized first and the distal part of the duct later (Fig. 5) or not at all (Fig. 6). It may be argued that when the distal part of the duct was not visualized, it was obscured by the gallbladder. However, even when all such cases were discarded as unreliable, a significant difference remained. It may also be objected that bile already present in the duct prevented the activity from reaching the region of the sphincter. But such bile is unable to prevent activity from rapidly reaching that region when the gallbladder is absent (*5,14*). Neither does bile already present in the gallbladder prevent activity from rapidly reaching the fundus (Fig. 6).

Fourth, the gallbladder's motor activity does not seem to be quiescent in the interdigestive state. Time-activity curves of the gallbladder, unlike those of the liver, showed periodic irregularities. These irregularities tended to be less pronounced after morphine (Fig. 4).

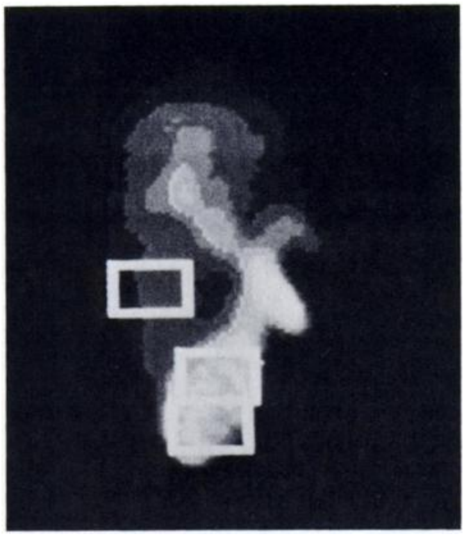
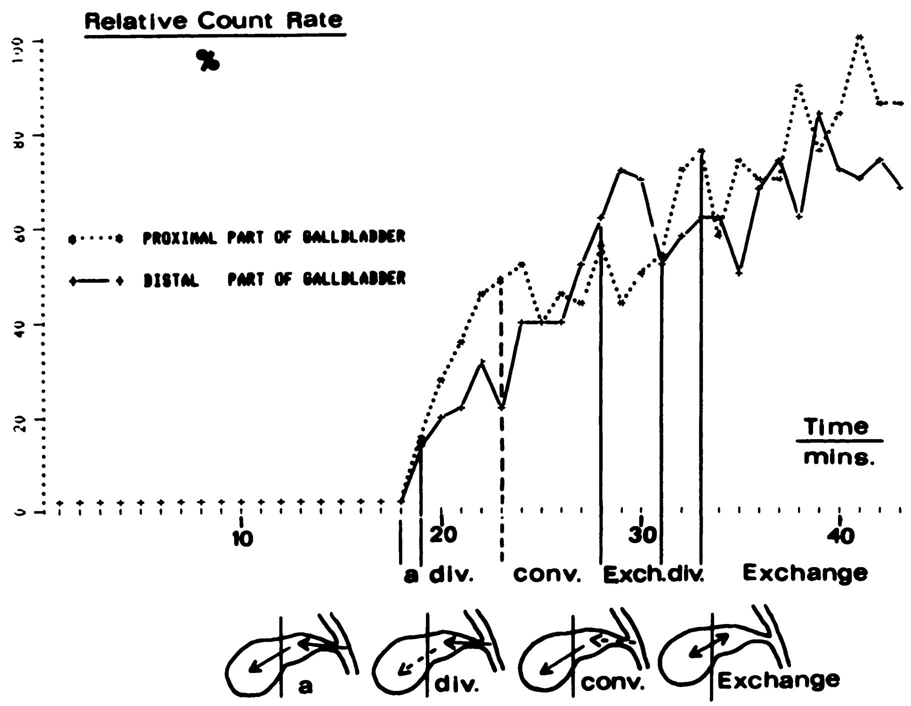


FIG. 4. Regions of interest (upper): proximal and distal part of gallbladder and for liver background correction. Time-activity curves (lower) of proximal and distal parts of gallbladder during 40 min after injection, corrected for liver background. Note exchange of activity in later stages.



How then does the gallbladder fill? In the great majority of cases the gallbladder curves showed a steep and irregular rise in activity. This is shown in Figs. 1 and 2 by the computer printout curves, obtained without any form of smoothing. In Fig. 1 the gallbladder curve suddenly rises from 32% to 70% in 4 min (15–19 min after administration); in Fig. 2 the curve suddenly rises from 22% to 64% in 7 min (16–23 min after administration). A similar steep and irregular rise can be seen in the normal gallbladder curves presented by Nicholson et al. (*15*), by Hall et al. (*16*), by Tjen (*17*), by Clarke et al. (*18*), and by Krishnamurthy et al. (*19*). The initial part of such a curve presented by Ronai et al. (*20*) also shows a very steep rise. All these curves differ from those of Shaffer et al. (*21*), whose curves show a smooth and gradual rise leading them to conclude that bile enters the gallbladder in an uninterrupted manner. This type of rise we have seen only after major surgery when the gallbladder was found to be dilated at ultrasonography (*13*). Thus, the filling pattern observed after unrelated surgery deviated markedly from that under normal conditions.

In 24 of our 30 studies the gallbladder curve showed no change when the first rise of the bile-duct curve took place. This period lasted from 2 to 14 min. When the gallbladder curve finally started to rise, its rise was often seen to coincide with a sudden fall or a leveling off of the bile-duct curve. This fall or leveling off took place in spite of the continuous flow of activity from the liver. Figure 1 shows a curve in which the first rise of the gallbladder curve coincides with a fall of the bile-duct curve. In Fig.

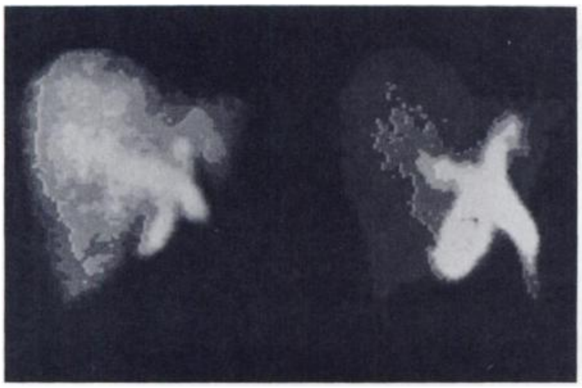


FIG. 5. Added views obtained 15–22 min (left) and 44–49 min (right) after injection. Gallbladder is seen before activity reaches distal part of duct.

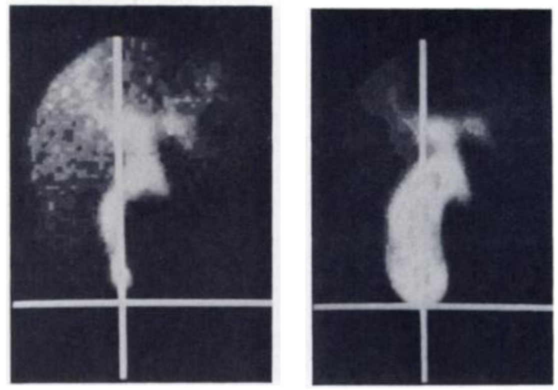


FIG. 6. One-minute exposure at 21 min after injection (left) and added views obtained at 22–60 min (right). Gallbladder is seen at 18 min, and 3 min later activity has almost reached most distal part of fundus. Activity then spreads laterally. Note absence of activity in distal part of duct.

2 the bile-duct curve levels off when the gallbladder curve starts to rise. Such a combination of findings is not compatible with smooth, uninterrupted filling. Rather, it suggests a gradual buildup of activity in the proximal part of the duct followed by abrupt and forcible entry of part of this activity into the gallbladder.

As stated above, we analyzed only the initial stage of gallbladder filling. Due to the loss of bolus effect, the filling pattern is usually not easily discernible in the later stages. Even so, in a few subjects in whom the entry of activity occurred less abruptly, the exchange could be followed for the whole 60 min. Figure 2 provides an example.

With few exceptions, the time-activity curves of the gallbladder's proximal and distal parts started with an almost synchronous rise (Figs. 3 and 4, Stage a). This means that activity that first more or less forcibly enters the gallbladder penetrates into the distal part. The almost synchronous rise of both curves confirms our findings on sequential images, which show that the activity needs little time to reach the distal part of the gallbladder (Fig. 6). The initial rise of both curves was followed by a continued rise of the proximal curve coinciding with a less steep rise of the distal curve, (Fig. 4, div.), or even its leveling off (Fig. 3, Stage b). This suggests less forceful entrance during which most of the activity entering the gallbladder stays in the proximal part while a minor portion (Fig. 4), or none at all (Fig. 3), reaches the fundus. Finally, the two curves approached or crossed each other. Convergence or crossing

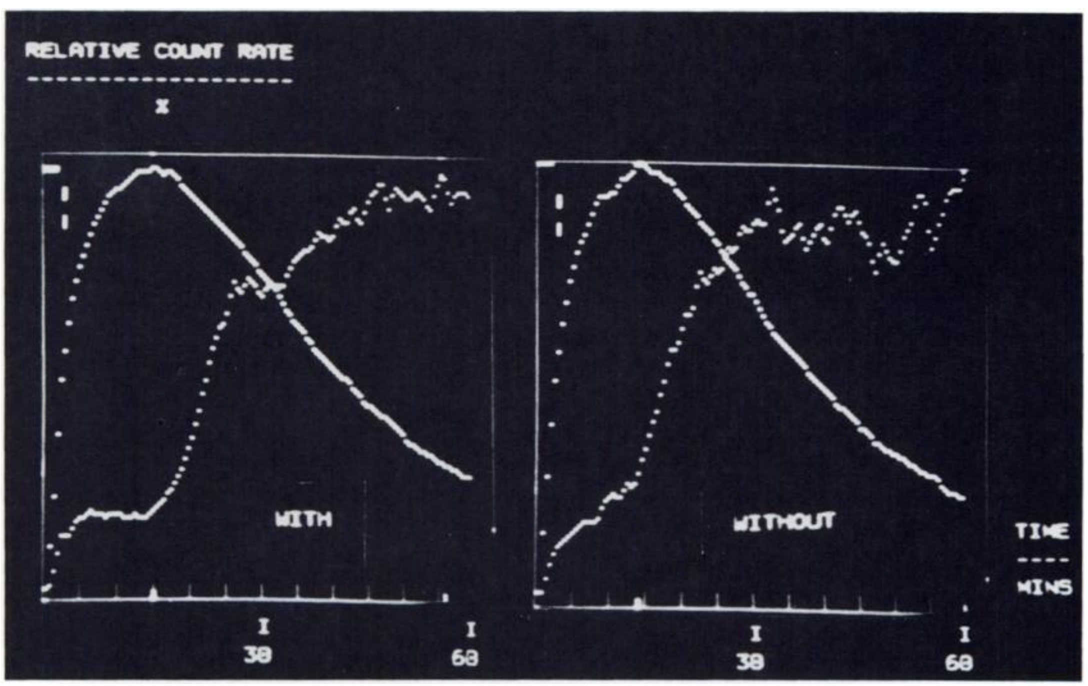


FIG. 7. Time-activity curves of liver and gallbladder obtained with (left) and without (right) premedication with morphine. Irregularities in gallbladder curve are smaller with morphine. No correction for liver background.

of the curves suggests movement of activity from the proximal to the distal part of the gallbladder. Exchange between the two parts suggestive of a to-and-fro movement of activity could also sometimes be seen (Fig. 4).

In their elegant studies on conscious dogs, Itoh and Takahashi (*22*) provided evidence of contractions of the gallbladder in the interdigestive state. The results obtained here support their findings. In another study on dogs, Itoh et al. (*23*) found signs of periodic dilution of gallbladder bile. They ascribed this phenomenon to the periodic inflow of hepatic bile. Cholescintigraphy confirms the occurrence of periodic inflow (Figs. 1 and 2). The curves obtained from the common duct and the gallbladder suggest a gradual buildup of activity in the duct, followed by abrupt entry into the gallbladder. The initial resistance to entry may, for instance, be due to the valvulae of Heister. It is here that the limitations of the technique become apparent. Although very informative on the flow of bile in the biliary tract, cholescintigraphy does not permit any conclusion as to the nature of the forces responsible for that flow.

To sum up, the present study showed that in the interdigestive state newly formed bile tends to accumulate in the proximal part of the bile ducts before entering the gallbladder, that it tends to enter the gallbladder abruptly, thus quickly reaching the fundus, and that it does so before it reaches the region of the sphincter.

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