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# Gall bladder emptying in normal subjects – a data base for clinical cholescintigraphy

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SUMMARY Biliary excretion scintigraphy with a cholagogic test meal may be used to assess patients with suspected disorders of gall bladder motility. The interpretation of results is frustrated, however, by the lack of information about the range of normal responses in a form suitable for comparative analysis. We present the results of 41 gall bladder emptying studies on 32 normal healthy subjects (14 men, 18 women) 30 minutes after intravenous injection of 74 MBq $^{99}Tc^{m}$-EHIDA. Gall bladder emptying was provoked by the ingestion of 300 ml milk. Gamma camera scintigraphy was used to plot gall bladder activity against time. Gall bladder emptying occurred within 10 minutes in all men and 12/18 women ($p=0{\cdot}02$). Gall bladder ejection fractions were significantly greater in women ($p<0{\cdot}05$). Duplicate studies in nine subjects showed good reproducibility ($r=0{\cdot}959$). A plot of mean and (m+2 SD) values of gall bladder activity against time has been derived. The data provide an estimate of normal gall bladder emptying response, which may be used to aid interpretation of clinical studies.

It is now possible to quantify gall bladder emptying in response to a standard cholagogic stimulus, using biliary excretion scintigraphy.[1] The technique is simple to do, well tolerated by patients, and inexpensive. The equipment required is now standard in most larger hospitals. The clinical requirement for such a test is limited, but recent reports[2-4] identify groups of patients with abnormalities of gall bladder emptying, for whom the use of such a test might provide valuable diagnostic information.

At present the normal range of responses to a standard gall bladder emptying test is poorly defined. It is therefore difficult to view an individual patient's response to testing and say with any confidence that it is abnormal. The purpose of this report is to present an analysis of 41 gall bladder emptying studies carried out on 32 normal healthy volunteers. These studies, carried out between November 1980 and May 1981 were part of a research protocol developed for the study of enterogastric reflux.[5] Ethical Committee approval was obtained for the study of patients and normal volunteers. Informed consent was obtained from all subjects. No pregnant or lactating woman was studied. A '10 day rule' was not applied.

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## Methods

### SUBJECTS

Thirty four healthy subjects were studied. There were 15 men (mean age 36 years: range 23–66 years) and 19 women (mean age 43 years: range 21–74 years). Subjects were hospital staff, medical students and patients convalescing after minor non-gastrointestinal operations. None had a past history of known or suspected gastrointestinal disease. None had any gastrointestinal symptoms or were taking any medications. Subjects fasted and refrained from smoking for four hours before receiving an intravenous injection of 74 MBq (2mCi) $^{99}Tc^{m}$-EHIDA (N-(2,6,diethylacetanilido) iminodiacetic acid) (Radiochemical Centre, Amersham). Subjects then waited quietly for 30 minutes after which they were positioned standing facing a gamma camera for a one minute control view of the abdominal field. They then drank 300 ml milk taking two to four minutes to finish the drink. At five minutes after the start of the control view, the abdominal field was again scanned

for one minute. Thereafter, serial one minute views were obtained every five minutes until one hour after the initial control scan. Subjects stood for imaging but sat down between scans. Earlier studies were carried out using a Technicare Series 100 gamma camera with a 25 cm field of view and fitted with a standard low energy collimator. Later studies used an IGE 535 gamma camera (International General Electric Company) with a 53 cm field of view and fitted with a standard low energy collimator. The scanning equipment was linked to a Nodecrest Nuclear Medicine Data Aquisition and Analysis System with interactive colour monitor and magnetic tape and floppy disk data storage systems.

From control scans the gall bladder area was identified and mapped and the percentage of total field counts found within the gall bladder area at 30 minutes postinjection was calculated. Gall bladder activity in subsequent views was expressed as a percentage of its starting value, and plotted against time to produce a gall bladder emptying curve. All values were corrected for isotope decay. The results were grouped by taking the means of normalised values for each time point, and subgroups were compared using Wilcoxon's two sample rank test to individual normalised values at each time point.

Nine subjects underwent repeat studies after a minimum period of two months. They were six men, ages 25–58 years (mean 39 years) and three women, ages, 20, 21, and 66 years.

## Results

The results for two subjects were excluded from further analysis and have not been used in the formulation of our normal response range. One failed to show gall bladder accumulation of activity and may have had a diseased gall bladder. No further clinical investigations were carried out. For the second subject a technical error during data acquisition rendered the study valueless. The remaining 32 subjects each showed a clear pattern of gall bladder activity with emptying after the milk drink.

The proportion of total field activity found within the gall bladder area at 30 minutes after the injection was 41±16% (mean±SD). Four subjects (12%) had less than 25% gall bladder activity at this time. Initial gall bladder activity appeared to be independent of residual liver activity but rather reflected variable partitioning of excreted activity between gall bladder and bowel.

There was no significant difference between men and women in the gall bladder activity at any time point throughout the study. The onset of gall bladder emptying occurred less than 10 minutes after starting the milk drink in studies on all 14 men and 12/18 women ($p=0{\cdot}02$, Fisher's exact test) (Table). There was no overall correlation between the time of onset of gall bladder emptying and the proportion of activity partitioned to the gall bladder on the control scan. Three of the four subjects, however, with less than 25% starting activity were late emptiers.

Table *Time to onset of gall bladder emptying*

| Minutes after milk | <5 | 5–10 | 10–15 | 15–20 | 20–25 |
|---|---|---|---|---|---|
| Men (n=14) | 12 | 2 | 0 | 0 | 0 |
| Women (n=18) | 9 | 3 | 1 | 4 | 1 |

p=0·02 (Fisher's exact test) for 2×2 contingency shown.

Among the 12 women with early emptying (onset of emptying less than 10 minutes after the milk drink), the mean values of residual gall bladder activity were uniformly less than the corresponding values for men (all early emptiers) the difference being statistically significant from 35 minutes onwards ($p<0{\cdot}01$: Fig. 1). When all data were recalculated normalising individual values in time and activity to peak gall bladder activity, a similar difference was noted between all 18 women (early and late emptiers combined) and the 14 men. The per cent reduction from peak to least gall bladder activity during the study, the ejection fraction, was 76±11% (mean±SD) for men (n=14) and 83±10% for

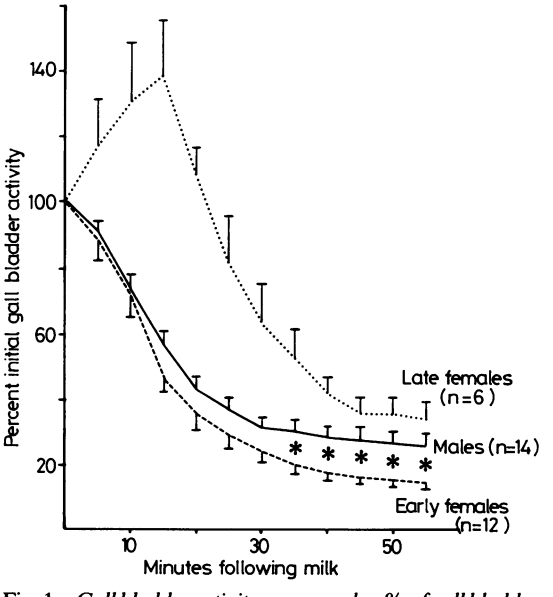


Fig. 1 *Gall bladder activity, expressed as % of gall bladder counts immediately before milk drink, plotted against time. Values are mean±SEM. Separate plots are shown for women with early onset of emptying (<10 min following milk: n=12), women with late onset of emptying (>10 min: n=6), and men (all early: n=14).*

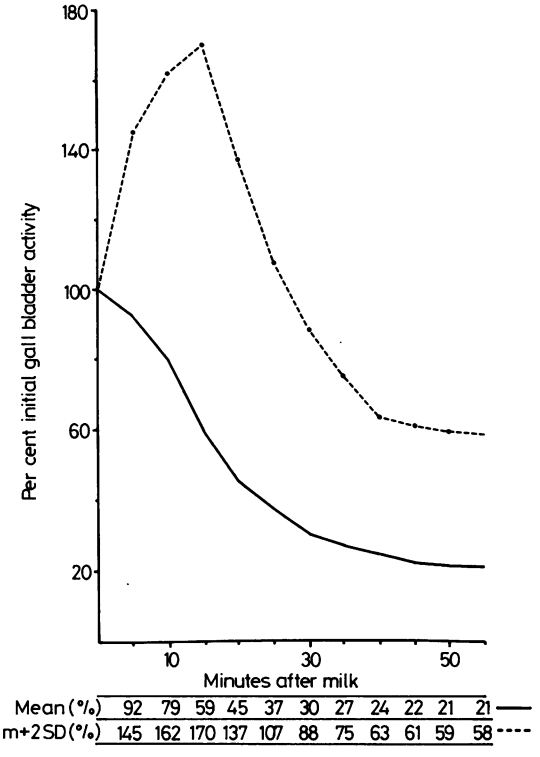


Fig. 2 *Gall bladder activity, expressed as % of gall bladder counts immediately before milk drink, plotted against time. Values are mean and (M+2 SD) for all subjects (n=32) plotted as antilog values of corresponding natural logarithms.*

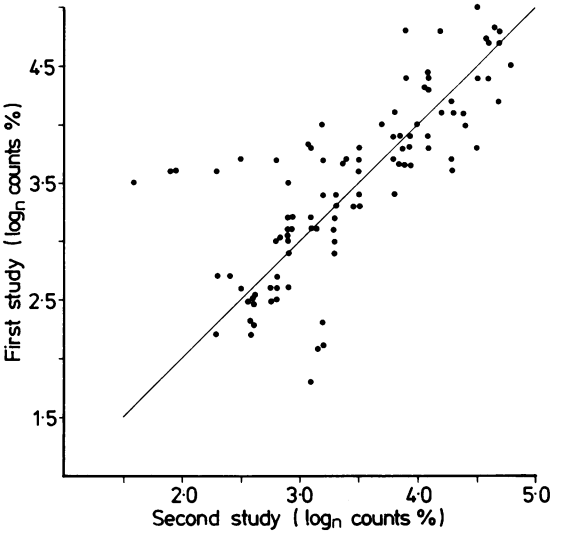


Fig. 3 *Reproducibility of studies on nine subjects. Plot shows scatter of paired data points about line of identity. Values are % of initial gall bladder activity at all corresponding times after milk drink. Common correlation coefficient=0·959 (Log$_n$ values have been plotted).*

women (n=18; $p<0·05$). There was, however, no significant difference between men and women in the duration of emptying which varied between 15 minutes and 55 minutes (men (n=14) 46±9 min (mean±SD); women (n=18) 40±10 min).

No correlation was found between the rate or pattern of gall bladder emptying and the age of subjects.

Figure 2 shows the grouped data for all subjects. Median values of residual gall bladder activity were uniformly slightly lower than corresponding mean values at all time points, indicating skew distribution of data points. These data are therefore presented as antilog values of the means of corresponding natural logarithms.

Repeat studies in nine subjects showed a similar rate and pattern of gall bladder emptying in eight subjects (correlation coefficient for paired data points for each subject was in the range 0·815–0·994). One woman gave an initial study showing only 21% of total field activity within the gall bladder at 30 minutes after the injection. Gall bladder emptying started between 15 minutes and 20 minutes after the milk drink in this study. The corresponding values for the repeat study were 62% starting activity and onset of emptying between 5 minutes and 10 minutes (r=0·643). For all nine subjects who had repeat studies, the scatter of paired data points is shown in Fig. 3. The common correlation coefficient was 0·959. Deviation of log$_n$ values from the line of identity was least for values representing approximately 33% of initial gall bladder activity.

## Discussion

The purpose of this analysis of gall bladder emptying in normal subjects was to provide a normal range of responses with which to compare results obtained from patients suspected of having an abnormality of gall bladder function. In our clinical practice there are two main groups of patients for whom we are now exploring the diagnostic value of this test. These are patients suspected of having autonomic neuropathy, and patients suspected of having acalculous biliary pain. Patients from both groups would be expected to show delayed or diminished gall bladder emptying in response to a cholagogic test meal, but for different reasons. Patients with neuropathic gall bladders might be expected to exhibit diminished contractile responsiveness to cholagogic stimuli in the absence of any mechanical obstruction to gall bladder emptying.[6] Patients with acalculous biliary pain are thought

to have an obstruction to gall bladder efflux, a consequence of inflammatory or dystonic impairment of cystic duct patency.[6 7] Bearing in mind these clinical applications of the test, several comments should be made about the protocol and results of this study.

A possible criticism of our study is that subjects were not screened by cholecystography or ultrasonography to exclude the presence of gall stones. It has recently been reported,[8] however, that the majority of patients with gall stones have normal gall bladder emptying. Furthermore, there would be no method, other than prolonged follow up of excluding subjects having a lithogenic motility disturbance who had not yet formed gall stones, a theoretical possibility[8] which diminishes the value of such screening for normality. None of our subjects had any symptoms suggestive of gall stone disease.

For the studies reported here, subjects were scanned standing so as to facilitate the identification of enterogastric reflux. This part of our studies has been reported elsewhere.[5] We are unaware of any evidence to suggest that gall bladder emptying is influenced by posture. For convenience, we now do gall bladder emptying studies with patients semi-recumbent.

The majority of previous reports on normal and abnormal gall bladder emptying are based on protocols in which cholecystokinin, given by intravenous injection or infusion has been used to provoke gall bladder contraction.[1-3 8 9] This method is unphysiological and, in our experience, produces results quite different from the gall bladder response to a test meal. A prohibitively complex infusion protocol would be required in order to simulate, by intravenous administration, the endogenous cholecystokinin response to a test meal.[10] Furthermore, the contribution of neural pathways may be partially bypassed by this technique. It would therefore be unsuitable as a method of studying autonomic neuropathy.

In the studies reported here, the test meal was given 30 minutes after the injection of $^{99}Tc^{m}$-EHIDA. At this time the gall bladder is continuing to accumulate activity. Other workers have shown that a plateau of activity is usually reached after 40–60 minutes and they have chosen to evaluate gall bladder emptying from well established plateau levels.[1 4 8 9 11] We feel there may be advantages to studying emptying from an earlier point in the filling phase. Firstly, after a plateau of activity has been reached, it may be difficult to decide whether the gall bladder has stopped filling or whether it is continuing to fill with unlabelled bile, the supply of labelled hepatic bile having been exhausted. It would not then be possible to observe the change from filling to no longer filling, in relation to the time of administration of the cholagogic stimulus. This may not mar the interpretation of a normal response, but the cessation of filling may be a helpful poststimulatory observation in the patient with normal filling but gall bladder outflow obstruction. Furthermore, sequential emptying and filling without net reduction in gall bladder volume could appear as erratic but progressive emptying when liver clearance of label is near completion. Earlier provocation of gall bladder evacuation may give a more truly representative plot of gall bladder bile flux in relation to gall bladder motility. Secondly, a prolonged gall bladder filling period may be interrupted by spontaneous gall bladder evacuation.[12] This may complicate the study not only by reducing gall bladder activity but also perhaps by invoking a refractory period during which the gall bladder is unresponsive to cholagogic stimuli. In the present study we did not screen for spontaneous gall bladder contractions but it may be significant that three of four subjects with low (<25%) starting gall bladder activity were among the six who showed delayed (>10 min) onset of gall bladder emptying. Based on the results reported here, our current policy is to give the milk meal at 30 minutes, but to wait a further 10–15 minutes if the initial gall bladder activity is low.

It could be argued, probably correctly, that a more precise definition of normal gall bladder emptying could be rendered by separate consideration of the three essential variables – delay to onset, duration of emptying, and residual activity. Our aim in the present analysis, however, was to produce a single graph on which to plot the results of individual studies on patients in order to aid interpretation. A study might be abnormal in any of these variables but it would be difficult to describe a blunted response in these terms.

In the present study, further analysis showed that gall bladder emptying was well described by a single exponential function when the least activity recorded in each study was subtracted from all values and any refilling of the gall bladder was ignored. This single function thus describes the decremental evacuation of the ejection fraction (Fig. 4). The duration of emptying was too variable (15 min to 55 min) to allow a satisfactory description of gall bladder response to testing by this single function, and we doubt the practical value of rendering the data in this way.

Our results have shown a significant difference in gall bladder emptying between men and women. Women exhibited more complete emptying, that is, greater ejection fractions. This was independent of the delay to onset of emptying and of the duration of emptying. The decremental evacuation of the ejection fraction was similar for men and women

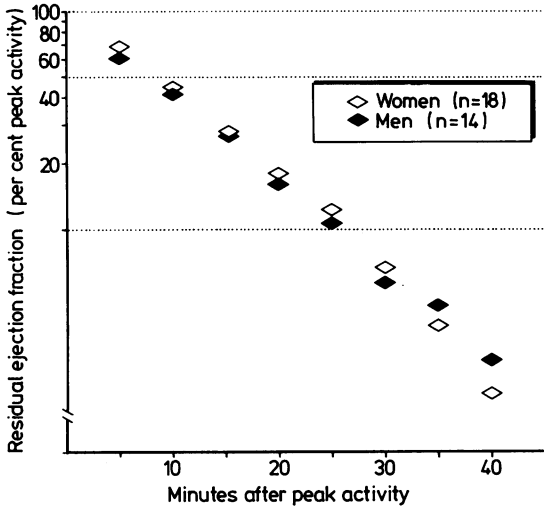


Fig. 4 *Plot of mean residual ejection fraction (log scale) against time after peak gall bladder activity. (In this context 'residual ejection fraction' refers to that part of the ejection fraction still to be emptied from the gall bladder at time points during emptying.) Individual values calculated as % peak gall bladder activity minus least activity (% peak) counted during study. Refilling has been ignored. Ejection fractions were 76±11% (mean±SD) for men and 83±10% for women ($p<0.05$). Linear regression analysis of all data points: $f=1.02$; $r=0.87$; $T1/2=7.98$ min.*

(Fig. 4). The difference was not immediately apparent, as a third of women studied showed a prolonged delay before the onset of emptying during which the gall bladder continued to accumulate activity. The explanation for this observation is not clear. It has been reported that gall bladder emptying is reduced during the progesterone peak of the menstrual cycle[13] and this might account for the subgroup of women with delayed onset of emptying. We have not the data on our subjects' menstrual status to check this, however, as the '10 day rule' was not applied in this study.

The present study constitutes one of the largest series of normal subjects assessed by excretion cholescintigraphy. It provides an estimate of normal gall bladder response to a simple reproducible cholagogic stimulus. It is reassuring that our estimate of mean response of subjects in this study is closely similar to that reported by others.[4 11] It might be felt that the range of responses we present is too broad for 'normal value' purposes. We need much more information about gall bladder motility disorders, however, before the definition of normality can be refined. For the present, these data provide a guide against which the results of individual studies on patients can be compared.

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