

Cholecystectomy and gallstone dyspepsia

Clinical and physiological study of a symptom complex

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Summary

The symptom complex of gallstone dyspepsia is defined and then analysed before and after cholecystectomy in 108 patients. Only 46% of patients were symptom-free after operation and 30% were no better. When pyloric function was studied patients with these symptoms before or after cholecystectomy and those with normal radiographs showed duodenogastric reflux, often precipitated by intraduodenal fat. Symptomless matched control subjects showed no reflux.

Synchronous radiology and pressure recordings demonstrated that the pylorus in these patients failed to contract in response to a duodenal contraction, whereas the normal pylorus could prevent the reflux produced by an isolated duodenal contraction. The effect of metoclopramide on gastroduodenal contractions and in treating the symptoms was assessed. Gallstone dyspepsia is essentially a functional disease—a disorder of gastroduodenal motility.

Introduction

Generations of students have been taught that gallstones typically occur in 'fat, fair, flatulent females of fifty'. This is only partly true and

in particular the relationship between flatulence and gallstones is far from clear.

A leading article in the *Lancet* some years ago¹ summarized the problem of cholecystectomy and gallstone dyspepsia like this: ' "It is increasingly recognised that unsatisfactory results [after cholecystectomy] are more common in . . . patients whose presenting symptom has not been real pain, but flatulent dyspepsia . . . and biliousness." . . . The surgeon is unable to tackle the unknown underlying cause'. Searching for underlying causes was the aim of John Hunter's scientific life and it therefore seems appropriate that a lecture in his memory should be devoted to the pathophysiology of a common symptom complex.

Any surgeon who has followed up his patients must be aware of the significant number whose symptoms of flatulent dyspepsia and fatty food intolerance are not relieved by cholecystectomy. When these are the only preoperative symptoms the patients are less than satisfied. The term 'postcholecystectomy syndrome' has not helped, as it implies that it is the result of operation and embraces symptoms that may be unrelated. Some clinicians maintain that gallstones and flatulent dyspepsia are entirely coincidental because

they have found these symptoms in the same proportion of patients with a normal gallbladder²—those with ‘radiograph-negative dyspepsia’.

Clinical syndrome of flatulent dyspepsia

Definition Rhind and Watson³ describe this well-known syndrome in this way: ‘epigastric discomfort after meals, a feeling of fullness so that tight clothing is loosened. Eructation with temporary relief and regurgitation of sour fluid to the mouth with heartburn’. In order to assess it more accurately it has been divided into 9 individual symptoms.

Flatulence

- 1) Repeated belching.
- 2) Full feeling after normal-sized meals.
- 3) Inability to finish a normal-sized meal.
- 4) Abdomen becomes blown out so that clothes have to be loosened.

Dyspepsia after meals

- 5) Burning discomfort in the epigastrium.
- 6) Burning discomfort in the chest (‘heartburn’).
- 7) Bitter fluid regurgitating into the mouth.
- 8) Vomiting (? bile).
- 9) Nausea.

These symptoms are clearly distinguishable from the true pain of duodenal ulcer and are described as ‘vague indigestion’ in the patient’s case notes; but the patient can often describe the exact time of onset after the meal, the progression of the symptoms, and the type of aggravating food—the vagueness is on the part of the clinician! In all these studies I have been careful to exclude patients with associated peptic ulceration, hiatus hernia, or pancreatitis and the operations were performed for proven pathology of the gallbladder to prevent future serious complications.

Incidence in gallstone patients and effect of cholecystectomy

Initially I studied the incidence of these 9 symptoms in 108 patients with gallstones but no other upper abdominal disease before and again between 3 months and 3½ years after cholecystectomy alone. The patients could be divided into four groups: 18 (17%) had no preoperative flatulent dyspepsia (Group 1); of the 90 (83%) who had preoperative symptoms, 27 (30%) were no better after operation (Group 2), 22 (24%) were improved (Group 3), and 41 (46%) were cured by operation (Group 4). The groups were similar in respect of average age and average length of follow-up, but the preponderance of females in the series as a whole was most marked in Group 2 and least in Group 4. It is interesting that follow-up by interview and postal questionnaire gave very similar results⁴

Most patients found that fatty foods made their symptoms worse and food intolerance has been analysed in more detail elsewhere⁴. In none of these patients did flatulent dyspepsia develop after the operation if it had not been present before. Rhind and Watson³ found similar results, 70% of their patients being cured or improved by operation.

Predicting results of cholecystectomy

The patient wants to know the chances of being cured by the major operation she has been advised to have. Although the surgeon can give her some idea from the overall figures for Groups 2, 3, and 4, perhaps individual symptoms may be a better guide. At this point I enlisted the help of the Medical Computing Department and we used a stepwise discriminant analysis. This programme picks out those symptoms that discriminate best between the 3 groups of patients and it also traces the effect of operation on individual symptoms. The computer gave some

interesting pointers which can be summarized in the following statements :

1) If both symptom 3 and symptom 4 are *absent* the patient is likely to be cured (Group 4). Symptom 4 occurs in any of the groups only if there are 5 or more different symptoms present. This may reflect severity or chronicity of the symptom complex.

2) If symptoms 3, 4, and 9 are all *present* the patient is likely to be improved but not cured (Group 3).

3) In Group 3 symptoms 1 and 9 tend to persist but symptom 3 is relieved most often.

The other factor that separated the groups was preoperative gallbladder function as assessed by cholecystography. Those with good function had their symptoms cured or improved more often than those with poor or nil function ($P < 0.01$).

Cause or coincidence ? Certain facts stand out: (a) flatulent dyspepsia occurs in most but not all patients with gallstones; (b) it is present before operation and is not the result of operation; and (c) nearly half (46%) of the patients with gallstones are completely cured of their symptoms by cholecystectomy but nearly a third (30%) are no better.

If the patient is a man who can finish a normal-sized meal, does not suffer from abdominal distension, and has stones in a well-functioning gallbladder he is particularly likely to be cured of his flatulent dyspepsia by cholecystectomy. This suggests that an association does exist between flatulent dyspepsia and gallbladder disease, but it is not a direct causal relationship nor does it seem to be entirely coincidental. Flatulent dyspepsia alone is not an adequate indication for cholecystectomy, although the gallbladder should be removed if shown to be diseased to prevent future serious complications.

Studies in pyloric function

Rains⁵ pointed out some years ago that the symptoms of flatulent dyspepsia are not really biliary but gastric in origin and Capper *et al.*⁶ reported that in some gallstone patients with these symptoms pyloric reflux of duodenal juice could be demonstrated. I therefore decided to do a detailed study of pyloric function in patients with flatulent dyspepsia. Forty-two patients were studied in 3 clinical groups.

Group A: 14 preoperative patients with gallstones and flatulent dyspepsia; 10 female, 4 male; average age 48 yr.

Controls for Group A: 6 preoperative patients with gallstones and *no* flatulent dyspepsia; 5 female, 1 male; average age 42 yr.

Group B: 3 patients after cholecystectomy with persistent flatulent dyspepsia; all female; average age 60 yr.

Controls for Group B: 6 patients after cholecystectomy who had lost their flatulent dyspepsia; 4 female, 2 male; average age 48 yr.

Group C: 9 patients with a normal cholecystogram and barium meal but with flatulent dyspepsia ('radiologically negative dyspepsia'); 4 female, 5 male; average age 42 yr.

Controls for Group C: 4 patients with a normal cholecystogram and barium meal and *no* flatulent dyspepsia; 2 female, 2 male; average age 40 yr.

Pyloric reflux was assessed by a modification of Capper's technique⁷ in which radiographic evidence of reflux (Fig. 1A), which is limited to a few minutes, is supplemented by intermittent gastric and duodenal sampling for 1-1½ h. The gastric samples were analysed for bile and trypsin. In 25 cases 7 ml of arachis oil was instilled into the duodenum during the test. The details of the technique have been discussed elsewhere⁸.

Results A close correlation was found between a strong history of flatulent dyspepsia

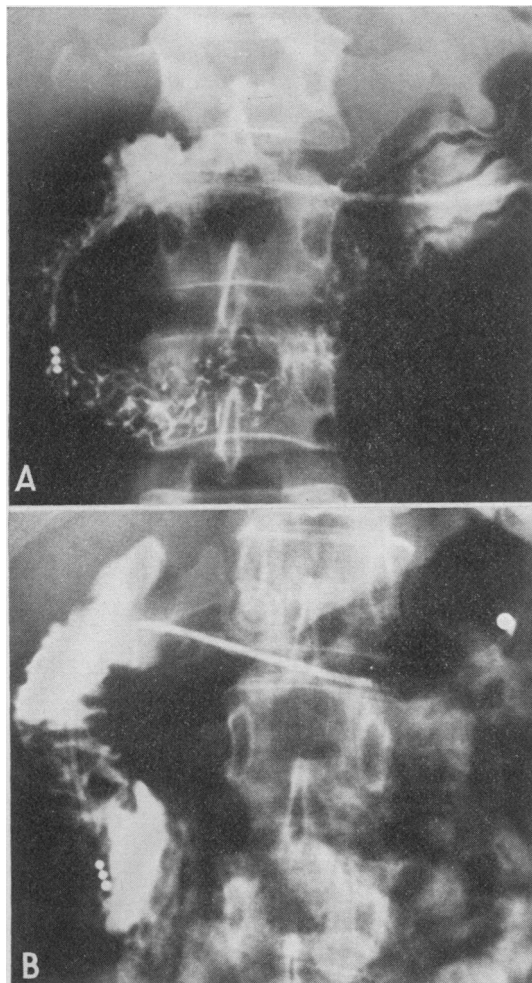


FIG. 1 Pyloric regurgitation tests showing (A) free reflux of barium, (B) no reflux of barium.

and the detection of pyloric reflux during the test in each matched pair of groups and in the series as a whole ($P < 0.001$). Four of the patients were tested both before and after cholecystectomy and the response changed in 3, correlating with the change in symptoms. Moreover, one-half of those showing reflux complained of typical symptoms during the test. Reflux was not observed in any of the symptomless subjects (Table 1).

TABLE I Correlation between symptoms and regurgitation during test

Recent history of flatulent dyspepsia	Regurgitation observed	Regurgitation not observed
Present	23	3
Absent	0	16
$\chi^2 = 33.1, P < 0.001.$		

It was particularly interesting to see that in some patients reflux only occurred about 20 min after fat had been instilled into the duodenum. We have already noted that fat commonly precipitates the symptoms in these patients. Figure 2a gives the results of sampling in one such subject before cholecystectomy; the appearance of bile and trypsin in the gastric samples towards the end of the test is shown. Figure 2b gives the results from a symptomless control subject, also with gallstones, showing the failure of duodenal juice to reflux into the stomach despite the instillation of fat into the duodenum and a rise in duodenal bilirubin concentration.

These studies suffer from the criticism that there is a thin tube across the pylorus. That is why it was so important to include control subjects (Fig. 1B). Reflux can be observed when the duodenal cap is filled with barium and the tube withdrawn and also postoperatively when the duodenum is filled with contrast medium via a T tube in the common bile duct. This last observation has been used to support the argument that reflux is a normal physiological variant⁹, but a few days after a major abdominal operation with a tube in the bile duct is hardly a physiological situation and, as we have already seen, a proportion of gallstone patients do continue to show reflux postoperatively.

It can be concluded from this part of the study that there were three types of subject: (1) those with flatulent dyspepsia who showed reflux freely with barium and throughout the

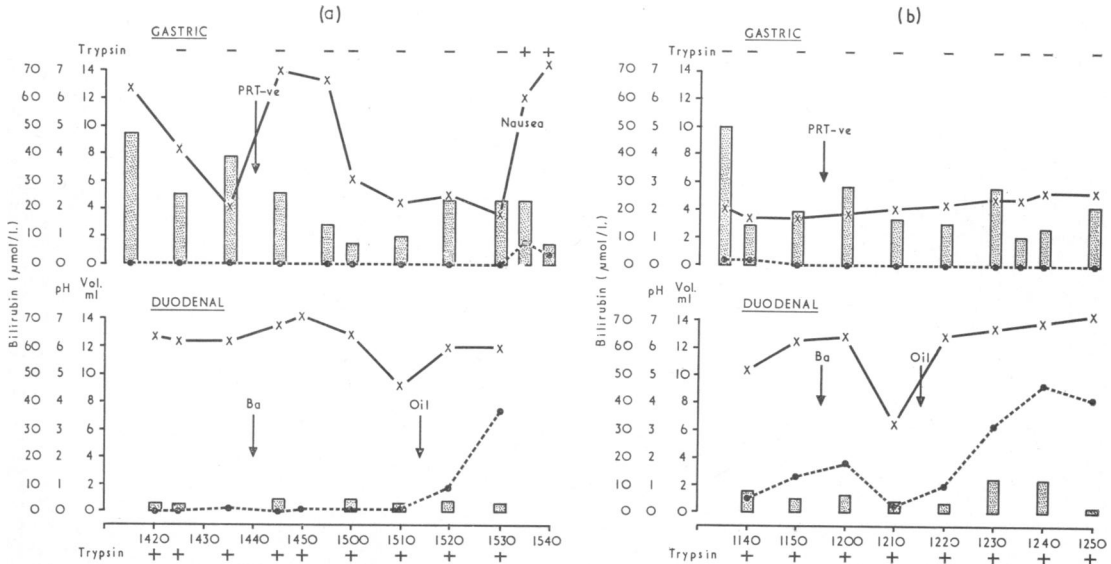


FIG. 2 Pyloric regurgitation tests showing (a) reflux of bile and trypsin into gastric samples after fat, (b) no reflux of bile or trypsin into stomach after fat. Continuous line = pH, interrupted line = bilirubin concentration, columns = volume of samples. (Conversion: bilirubin 1 $\mu\text{mol/l}$ = approximately 0.06 mg/100 ml.)

test; (2) those with flatulent dyspepsia who did not show reflux with barium but only after the stimulus of intraduodenal arachis oil; and (3) symptomless subjects with or without gallstones who did not show reflux despite the presence of arachis oil in the duodenum. In other words the pylorus was (1) incompetent most of the time, (2) usually competent but allowed reflux occasionally, or (3) competent all the time. It is particularly interesting that patients of the second type were distinguished clinically by experiencing their symptoms regularly within half an hour of the meal.

My self-satisfaction on finding that the symptoms of flatulent dyspepsia were associated with reflux of duodenal juice into the stomach was short-lived when I found that John Hunter himself had made this observation 200 years ago—‘Again, we cannot suppose that the bile assists in digestion or

the stomacic fermentation as it never enters the stomach in a natural state, and, when it does it produces a contrary effect, viz. a nausea²¹⁰.

Hypothesis

Recent work by Fisher and Cohen¹¹ provides a possible explanation for these observations. They found in normal subjects that pyloric pressure increased in response to endogenous release or exogenous administration of cholecystokinin (CCK) but in certain patients (in their case, gastric ulcer patients) the pylorus failed to respond to the hormone. Fat in the duodenum, which often precipitates flatulent dyspepsia and reflux, is a potent releaser of CCK. Figure 3 summarizes its effects: the duodenum becomes distended with bile, gastric motility is partly inhibited, and the stage is set for reflux unless it is prevented by an increase of the pyloric pressure. It is possible that there is a similar temporary failure of

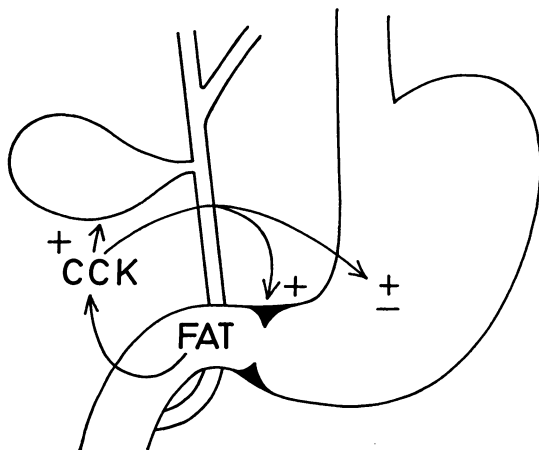


FIG. 3 Diagram of effect on motor activity of cholecystokinin release.

the pyloric function in those patients who show a sudden reflux of duodenal juice in response to fat.

Antroduodenal motility patterns associated with pyloric reflux

How does a macroscopically normal pylorus allow reflux?

There has been discussion for many years about whether the pylorus is or is not a true sphincter. Anatomically, it is formed by a thickening of gastric circular smooth muscle and there is a hypomuscular segment between this and the duodenum. Those of us who spend much time looking down gastroscopes are well aware that the pylorus is open except when a gastric contraction reaches it. This would suggest that functionally it behaves like the terminal antrum, and Carlson *et al.*¹² in dogs found that during gastric emptying the pylorus was closed only with terminal antral contraction while the first part of the duodenum was contracting (Fig. 4). If this is so, reflux is likely to occur whenever there is a duodenal cap contraction that is not the result of a progressive antral wave. In the fed animal 70–80% of duodenal cap

contractions follow those of the antrum, but in the fasting state this association is far more random.

The linkage between antral and duodenal contractions across the pylorus has been well shown by radiological¹², pressure, and myoelectrical studies¹³. The linkage is interrupted when the pylorus is divided by a circular myotomy down to the mucosa¹³, but whether the transmission is muscular or nervous remains to be seen.

We therefore studied subjects who were likely to show regurgitation and normal volunteers to see what pressure changes occurred in the antrum, pylorus, and duodenum at the time of reflux. The only way this can be done is to have synchronous radiological and pressure observations. This means that the observation time must be strictly limited to 5 min to avoid any undue exposure to radiation. Careful calculations were made of the radiation dose and a timing alarm set before the observations began. The field was as small as possible and limited to the upper abdomen.

Techniques Two techniques were used. In the earlier studies fine saline-filled open-tipped catheters were used, one in the distal antrum and one in the first part of the duodenum. They were connected via pressure transducers to a UV recorder. After a resting period barium/saline suspension (10–15 ml) was instilled into the duodenum and

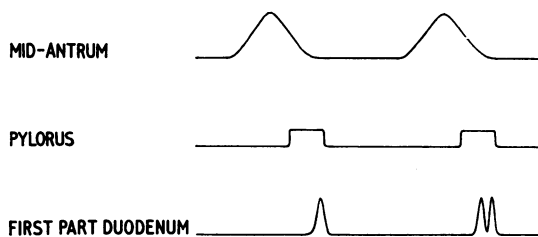


FIG. 4 Diagram of relationship of antroduodenal contractions during gastric emptying.

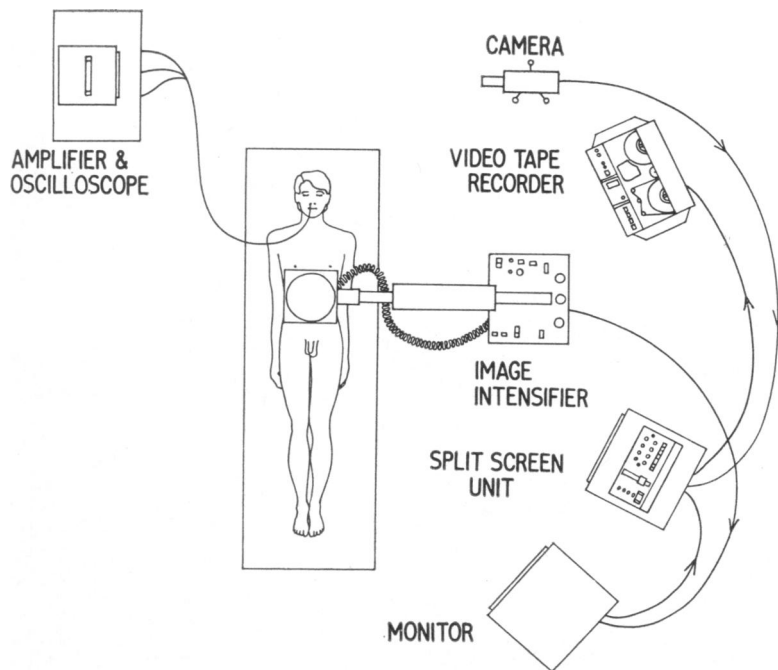


FIG. 5 *Diagram of apparatus for synchronous radiological and pressure recordings in studying pyloric function.*

radiological screening started. When pyloric reflux was observed it was marked by a second observer on the pressure tracing.

More recently the Honeywell (Model 31) motility probe has been used which has miniature transducers at the tip which can be located accurately on X-ray. The duodenum is filled with barium by the patient drinking a small amount and then lying semiprone on the right side for a minute. The image intensifier picture and the pressure recording are synchronized via a split-screen mixer on to the same videotape, which can then be played back repeatedly and analysed at leisure, in slow motion if necessary (Fig. 5). Any alteration in position of the gauges can be seen, it being difficult to maintain the exact position of intraluminal devices.

Results Twenty subjects were studied; 12 had non-ulcer flatulent dyspepsia, 2 had Type 1 gastric ulcers, and 4 were normal control subjects.

In the patients pyloric reflux was observed on 16 occasions with 2 motility patterns: (a) when a single duodenal contraction was not linked to that of the antrum or when duodenal contractions occurred in the absence of antral contractions (Fig. 6a) and (b) when there were rapid duodenal contractions even in the presence of antral contractions. Reflux did not occur if the antral and duodenal contractions were closely linked (Fig. 6b). In the normal subjects, however, reflux did *not* occur with an isolated duodenal contraction on 25 observations and these differences were highly significant. This suggests that in the normal subject the pylorus can resist the reflux that might occur in response to a duodenal contraction in the presence of a relaxed antrum and must therefore be able to contract in response to a duodenal contraction as well as an antral contraction. The gastric mucosal 'plug' in the pyloric canal may also help to prevent reflux. In the dyspeptic patients, how-

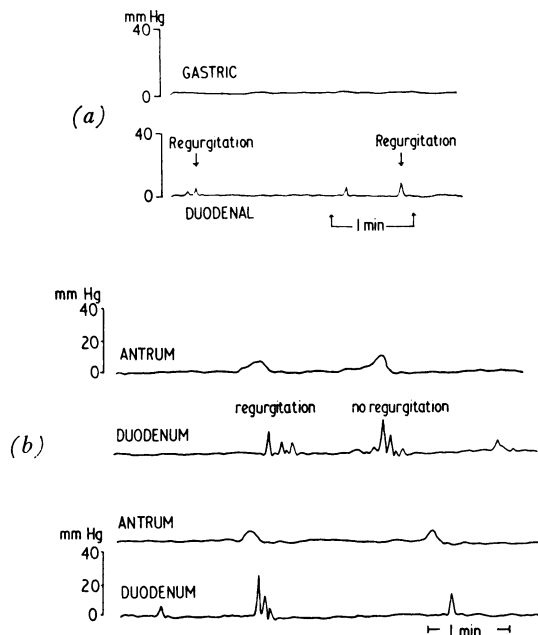


FIG. 6 (a) Recording in which duodeno-gastric regurgitation was observed with an unlinked duodenal contraction. (b) Recording in which no regurgitation was observed with closely linked duodenal contractions but occurred with a late duodenal contraction. ($1 \text{ mm Hg} = 0.133 \text{ kPa}$.)

ever, reflux was usually prevented only when the antral and duodenal contractions were synchronized so that the pylorus was closed as part of terminal antral contraction.

What is the pyloric abnormality?

There are several possible explanations of these observations:

1) The pyloric muscle may be dilated and thinned so that when it contracts it does not close off the canal. Certainly in Type 1 gastric ulcer patients who reflux freely the pylorus is frequently wide and 'patulous'. Figure

7 is a recording from such a patient showing no activity of the pylorus despite contractions on either side.

2) The duodenal cap contraction in normal subjects may originate close to the pylorus. If man is like the dog in this respect there is a duodenal pacemaker within a few millimetres of the pylorus¹⁴ which would mean that the pyloric end of the cap would close first, preventing reflux. It is possible that the co-ordination of the cap contraction, or its spread to the pylorus itself, is at fault.

3) There may be something wrong with the pyloric muscle or its innervation which makes it unresponsive to normal physiological stimuli or it could be blocked by high levels of other hormones. As mentioned above, in gastric ulcer patients it is unresponsive to CCK. A similar defect but to a lesser degree could be present in the pre- and postcholecystectomy patients and those with non-ulcer flatulent dyspepsia.

Explanation of clinical observation

How can a pylorus that is malfunctioning before cholecystectomy return to normal after the operation? In other words, if the primary defect causing these symptoms is at the py-

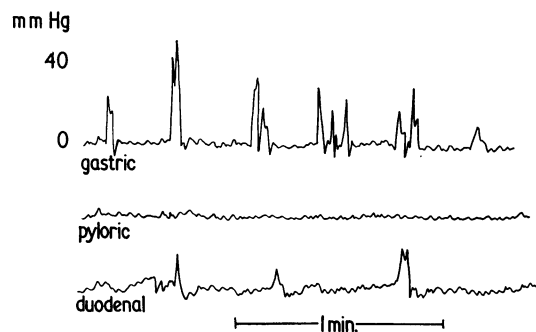


FIG. 7 Recording from patient with patulous pylorus showing no pyloric activity despite strong contractions on either side. ($1 \text{ mm Hg} = 0.133 \text{ kPa}$.)

lorus how do we account for nearly half the patients (Group 4) being completely symptom-free postoperatively? It will be remembered that this group contained a significantly higher proportion of those with a functioning gallbladder. If a non-functioning gallbladder is removed—one, for example, with a stone impacted in Hartman's pouch—the physiology of the biliary tract and duodenum is not altered. When a functioning gallbladder is removed there is no longer a 'bolus of bile' emptied into the duodenum after a fatty meal and this could well alter duodenal motility and possibly CCK levels. Why many gallstone patients have pyloric malfunction in the first place remains a mystery. Perhaps the motility disorder comes first.

By measuring pyloric function we are probably looking at only one aspect of the total motility abnormality. In many cases the gastro-oesophageal junction is also incompetent, even in the absence of hiatus hernia, giving rise to reflux and heartburn. The belching and feeling of distension may be due to sudden release of carbon dioxide in the stomach and the foaming produced by bile, which is a detergent. The inability to finish a normal-sized meal is probably a defect of receptive relaxation of the body and fundus of the stomach.

Correction of abnormal motility patterns

We have so far seen that malfunction of the pylorus with duodenogastric reflux persists in some patients after cholecystectomy associated with persistent flatulent dyspepsia. The surgeon may be tempted to re-explore the patient in case he has missed an ulcer, a common bile duct stone, or hiatus hernia. If a thorough laparotomy has been done at the first operation, with operative cholangiography, a second operation is likely to be unrewarding. 'None of these explanations or attempted cures has so far proved altogether acceptable.

Neither are mistakes in the original diagnosis commonly at the root of the late postoperative trouble. Even when the surgeon is led to re-explore in the hope of finding retained stones, he rarely finds them, and when he does, their culpability often remains in doubt. The surgeon who expects to find one of the variety of abnormalities which may follow cholecystectomy common is doomed to bitter disappointment¹. What is needed is a drug that can alter motility, especially during gastric emptying after a meal.

The most promising drug at present is metoclopramide, which is used as an anti-emetic and in radiology for speeding gastric emptying. It has a unique action in enhancing the effect of acetylcholine on gastric smooth muscle. Much work has been done on both animals and man since metoclopramide was first introduced. I will not here give details of my work on dogs, which has been previously published¹⁵, but it may be summarized as follows: metoclopramide increases the strength of gastric contractions; it increases the strength of duodenal contractions and links these more closely to those of the antrum; it potentiates the effects of CCK on gastric and duodenal contractions in the anaesthetized animal; and it has no effect on the relaxed or contracting gallbladder.

On the basis of these findings tests were performed on patients and controls to study the effect of the drug on gastroduodenal contractions; in particular, its effect on the synchronization of antral and duodenal contractions which had been found to be important in the prevention of reflux in patients with flatulent dyspepsia. Figure 8 shows an example of the antral and duodenal contractions before and after metoclopramide, the start of each contraction being represented in diagrammatic form. If these are already linked there is an effect only on the size of the contraction. The change in linkage is sum-

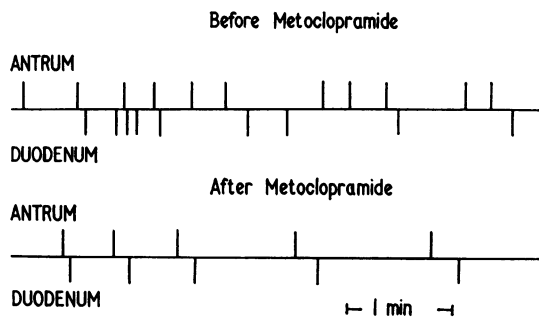


FIG. 8 *Diagram showing increase in antroduodenal linkage after metoclopramide. Each vertical line represents the start of a contraction.*

marized in Table II with reference to both antral and duodenal contractions. There was a significant increase in the linkage between antral and duodenal contractions after metoclopramide. This effect on linkage has been confirmed by other workers using recording of pressure waves¹⁰ and electrical activity¹⁷. In summary, it changes the 'breaking' effect on gastric emptying of the contraction of the whole of the terminal antrum into vigorous peristaltic waves that sweep right down to the pyloric ring and beyond¹⁸. The drug has also been found to increase the pressure of the gastro-oesophageal sphincter and reduce the reflux into the oesophagus which produces heartburn¹⁹.

As metoclopramide probably acts by enhancing the effect of locally released acetyl-

choline it would be expected to be most effective in patients with mild malfunction in those sphincters that still have some remaining contractile activity. It may not help those with gross pyloric incompetence and severe reflux²⁰. The other question about the drug at present is its length of action and the timing of its administration. Its effect on motility probably lasts for only about half an hour and the time it is given in relation to the onset of symptoms is important.

Effect of metoclopramide on flatulent dyspepsia

If all the above thesis is correct it would be expected that metoclopramide would relieve the symptoms of flatulent dyspepsia. A double-blind placebo crossover trial was performed on 46 patients with flatulent dyspepsia. The results have been reported in detail elsewhere^{21,22}, but two points are relevant here.

Metoclopramide was significantly more effective than placebo in relieving the symptoms, but it seemed to be most effective in those whose symptoms occurred within about half an hour after the meal. These are mainly the subjects whom we found earlier to show regurgitation in response to fat (p. 72, Type 2) whose pylorus was usually competent. It was also noted that the dyspeptic symptoms of epigastric burning, nausea, vomiting, and heartburn were relieved more than those of flatulence and full feeling.

TABLE II *Effect of metoclopramide on antroduodenal synchronization in 12 human subjects*

	<i>Antral contractions</i>			<i>Duodenal contractions</i>		
	<i>Linked</i>	<i>Unlinked</i>	<i>Total</i>	<i>Linked</i>	<i>Unlinked</i>	<i>Total</i>
Before metoclopramide (5 min.)	30	29	59	28	44	72
After metoclopramide (5 min.)	56	18	74	57	15	72
	$\chi^2 = 8.5, P < 0.01$			$\chi^2 = 25.9, P < 0.001$		

In the treatment of persistent flatulent dyspepsia after cholecystectomy drugs such as metoclopramide which alter gastroduodenal motility and speed gastric emptying are a useful form of therapy, particularly in patients whose pyloric malfunction is not too severe and whose symptoms bear constant time relationship with meals so that the drug can be given just beforehand. No doubt new drugs will be developed which are even more specific and effective in altering motility. The avoidance of fatty foods will help many patients, but as 46% will be completely symptom-free it is quite unnecessary to put all patients on a low-fat diet after cholecystectomy. Avoidance of fat before operation makes sense as fat may precipitate gallbladder colic, but I still see patients who stick to a very-low-fat diet for years after cholecystectomy because no one has told them it is all right to eat normally!

Conclusion

The common symptom complex of flatulent dyspepsia which occurs frequently, though not exclusively, in patients with gallstones is due to a motility disorder of the stomach, pylorus, and duodenum associated with reflux of duodenal juice into the stomach and sometimes into the oesophagus as well.

We have become accustomed to the term 'pathology' implying obvious macroscopic and microscopic structural changes as seen in ulcers, neoplasms, and chronic inflammatory disease. But disorders of physiology are just as pathological and may be accompanied by minute structural change we have yet to recognize. Gallstone dyspepsia, then, is a *functional* disease in the true sense of that term—there is a disorder of function as opposed to structure. Psychological stress, through the autonomic nervous system, may be a factor in some cases, as may changes in hormone levels or a change in sensitivity of the pylorus to these hormones.

I hope that this work will prevent so many patients with persistent dyspepsia after cholecystectomy being sent away from the follow-up clinic with the words, 'There is nothing organically wrong with you my dear, you will have to learn to live with your symptoms'. There *is* something organically wrong, but being a disorder of motility it needs special techniques to reveal it. I also hope that this work will remind us how important it is for our surgical practice to be illuminated throughout by the basic medical sciences.

I am very grateful to Mr A E Stevens, who first started my interest in gallbladder disease, and to Professor A J Harding Rains, who has advised and encouraged me over the past 6 years. I am also grateful to all the staff of the Department of Surgery, Charing Cross Hospital, particularly Mr Clive Kirk and Mrs Catherine Bulley, who have helped with all aspects of this work. The staff of the Animal Unit, the Medical Computing Department, and the Department of Medical Illustration have all helped greatly in their particular fields. Finally I would like to thank the volunteers who acted as controls, without whom it is impossible to evaluate work of this kind.

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