"STUDIES OF GASTRIC EMPTYING IN MAN"

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Degree of Doctor of Medicine
University of Edinburgh
1980

CONTENTS

DECLARATION

Much of the work described in this thesis has been conducted in collaboration with colleagues. Their contributions are identified and acknowledged on Page 4. I certify that the thesis has been composed by me alone.

ABSTRACT

Measurements of gastric emptying in man have been made by scintigraphic methods based on a rectilinear scanner or gamma camera. In the initial studies with a scanner, indium-113m DTPA was evaluated as a possible radionuclide marker for a test meal and was found to be satisfactory. Technetium-99m DTPA was subsequently assessed in similar studies with a gamma camera. It also proved satisfactory, although it differed from the indium compound in being substantially adsorbed to the solid component of a mixed solid and liquid meal. To establish the reproducibility of the gamma camera method, repeated measurements were carried out and in studies with saline test meals, comparison was made with measurements based on aspiration of gastric contents.

Recognition of the marked differences between gastric emptying of solids and liquids led to the development and validation of a double isotope method for simultaneous study of solid and liquid components of a test meal. This method was then applied to the study of patients who had undergone gastric surgery in an attempt to learn more about the emptying abnormalities consequent upon gastric surgery. Studies were also undertaken in diabetic patients with suspected gastric stasis due to autonomic neuropathy. The effects of metoclopramide therapy for such patients were examined.

Studies of the histamine H_2 receptor antagonists, metiamide and cimetidine were undertaken to determine whether they had any effect on gastric emptying. No clinically significant effect was detected.

Gastric emptying was found to be a major regulator of the rate of absorption of orally administered paracetamol. Pharmacological modification/

modification of gastric emptying, namely acceleration by metoclopramide and inhibition by propantheline or by narcotic analgesics was associated with corresponding changes in paracetamol absorption. The absorption of orally administered paracetamol was also delayed by the gel fibres pectin and guar, which delay gastric emptying.

Scintigraphic measurements of gastric emptying are not free from experimental error. Measurement of the errors due to count attenuation by tissues demonstrated the superiority of bilateral detection over unilateral detection, especially if relatively low energy gamma emitting radionuclides are being used. The errors associated with unilateral (anterior) detection of indium-113m and technetium-99m were determined in studies with a rectilinear scanner and with a gamma camera.

ACKNOWLEDGEMENTS

Most of the studies described in this thesis have been undertaken in collaboration with colleagues whose involvement and participation must be recorded. In particular, I gratefully acknowledge the work of Drs. A.J. Greenwald and Tapan K. Chaudhuri in the technetium-DTPA studies, Drs. J. Nimmo, W.S. Nimmo and L.F. Prescott in the studies with paracetamol, Dr. J. Millar and Mr. I.B. Macleod in the studies of surgical patients and Drs. I.W. Campbell and B.F. Clarke in the studies of diabetic patients. Dr. S. Holt, who has worked with me since 1976, carried out the studies with labelled chicken liver (Chapter 4) and the investigation of gel fibre (Chapter 10) and in addition has generated much useful thought and discussion which I have especially valued. From the Department of Medical Physics, Mr. G.P. McLoughlin and Mrs. W. Brown have provided unfailing support over many years and their efforts are appreciated.

I am grateful also to Professor D.J.C. Shearman, who first drew my attention to the early reports of scintigraphic methods of studying gastric emptying and suggested that I should attempt to develop them further. Finally, I offer my thanks to Dr. Peter Tothill who has been the principal collaborator in my work on gastric emptying for almost ten years. His guidance, support and friendship are greatly valued.

PUBLISHED PAPERS

Observations described in this thesis have also been included in the following published papers:-

1. An evaluation of 113m indium DTPA chelate in the measurement of gastric emptying by scintiscanning.
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1. An evaluation of 113m indium DTPA chelate in the measurement of gastric emptying by scintiscanning.
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Scottish Society for Experimental Medicine, January 1980.

INTRODUCTION

In 1966, Griffith, Owen, Kirkman & Shields first reported a method for the measurement of gastric emptying in man based on the use of a rectilinear scanner to locate and quantitate the amount of a radioisotopically-labelled meal which remained in the stomach at intervals after its ingestion. There were two particular merits of the method they described. Firstly, it was non-invasive, which avoided causing any discomfort or distress to the subject under study, and secondly, it provided a measurement relating to an ordinary meal of mixed liquid and solid composition. The avoidance of distress and discomfort was not only desirable from an ethical point of view, but was also important because of the possibility that procedures producing anxiety or discomfort (e.g. nasogastric intubation) might themselves alter gastric motility and thus compromise the value of any measurements obtained. Most earlier quantitative studies of gastric emptying in man had been undertaken using methods based on gastric intubation and although much information about the nature and control of normal emptying had been obtained, these methods were necessarily restricted to the study of liquid test meals. Studies of mixed solid and liquid test meals had been undertaken by some investigators using radiographic methods, but the results were qualitative or at best semi-quantitative. Thus the development of a non-invasive procedure which allowed measurement of gastric emptying after ingestion of a mixed meal represented a major methodological advance, with potential for the acquisition of new knowledge of gastric motor function and its disorders. This thesis describes some methodological developments and applications of scintigraphic measurements of gastric emptying.

CHAPTER 1

INDIUM-113m DTPA IN THE MEASUREMENT OF GASTRIC EMPTYING BY SCINTISCANNING

INDIUM-113m DTPA IN THE MEASUREMENT OF GASTRIC EMPTYING BY SCINTISCANNING

The first scintigraphic measurements of gastric emptying in man were carried out with a rectilinear scanner and with sodium ^{51}Cr chromate as the radioactive isotopic label in the test meal. (Griffith et al, 1966). Subsequently, in the first reported application of a gamma camera to gastric emptying studies, ^{51}Cr chromate was again employed as the marker isotope, although the likely advantages of short-lived isotopes such as indium-113m and technetium-99m were noted (Harvey, Brown, Mackie, Keeling & Davies, 1970). It seemed that the properties required of an isotopic marker in gastric emptying studies were:-

1. It should give a gamma emission suitable and sufficient for external quantitation whilst exposing the subject to an acceptably low radiation dose.

2. It should not be adsorbed to the gastrointestinal mucosal surface.

3. It should not be absorbed by any section of the gastrointestinal tract.

4. It should not have any pharmacological activity.

Although these requirements were met by ^{51}Cr chromate, it was apparent that ^{113m}In might be an improvement. Higher count rates could be expected, since 65% of ^{113m}In disintegrations give rise to gamma radiation whereas only 9% of ^{51}Cr disintegrations do so. In addition, the short physical half-life of ^{113m}In (approximately 100 minutes) raised the possibility that it would expose the subject to a lower/

lower radiation dose. The short half-life also presented the possibility of performing repeated tests on the same subject without waiting for administered isotope to pass through the gastrointestinal tract completely. If ^{51}Cr were used for successive tests on the same subject without waiting for complete clearance on each occasion, there was a risk that isotope in the colon would be confused with isotope in the stomach.

Indium-113m, in the form of a chelate with diethylene-triamine-penta acetic acid (DTPA) was therefore assessed and compared with sodium ^{51}Cr chromate as a marker for gastric emptying measurements using the sequential scintiscanning method described by Griffith et al (1966). This chelate was chosen, since by analogy with EDTA chelates of divalent cations such as calcium, chromium and lead, the compound seemed likely to be suitably inert - i.e. not absorbed by the alimentary tract nor adsorbed to the mucosal surface.

Methods

Indium-113m was eluted from a generator (Radiochemical Centre, Amersham) and the DTPA chelate prepared by the method of Stern, Goodwin, Scheffel, Wagner & Kramer (1967). Sodium ^{51}Cr chromate was also obtained from the Radiochemical Centre.

Studies in vivo

Adult male and female hospital patients were studied. After fasting overnight, each was given a meal of 20g cornflakes, 15g sugar (sucrose) and 150ml milk to which 200μCi of either ^{51}Cr chromate or ^{113m}In DTPA had been added. The time taken to consume the meal was between 4 and 8 minutes. Each subject was studied on two successive mornings/

mornings; eight were given the meal with ^{113m}In DTPA on both occasions and eighteen were given the indium compound on the first day and chromate on the second. A further two subjects were then studied, first with the indium compound and then with the chromate to which physically decayed indium DTPA had been added. None of the patients were taking drugs known to influence gastrointestinal motility.

The scanning procedure was similar to that described by Griffith et al (1966). After ingestion of the meal, four scans of the subjects' abdomens were obtained at intervals of approximately 25 minutes, with the subjects supine. The position of the xiphisternum was marked on each scan as a reference point. Each scan took about 8 minutes and between scans the subject was allowed to sit or walk around. Smoking was not permitted. Three different scanners were used during the course of the study but each subject was studied with only one.

Absorption of ^{113m}In DTPA was assessed in four subjects from the isotope content of a 4-hour urine collection begun at the time of meal ingestion and from a blood sample taken at the end of this period. Absorbed isotope was assumed to be distributed in the subject's extra-cellular water volume.

Calculation

The scans from each subject were inspected and an identical area which included the stomach was marked on each. The dot count within this area was then determined and corrections applied for the background count and for physical decay of ^{113m}In. A plot of logarithm of counts against time was then drawn, complete ingestion of the meal being taken as zero time. The best fit straight line through these points was judged by eye and from it, the half time of gastric emptying was measured/

measured directly.

Studies in vitro

Distribution of isotope within a mixture of cornflakes, milk and gastric juice was examined by direct counting of the supernatant fluid after addition of a known quantity of isotope. Similar measurements were made on mixtures of cornflakes with citrate buffers and hydrochloric acid over a pH range of 1 to 6. In all cases the gastric juice was obtained fresh from patients undergoing studies of pentagastrin stimulated gastric secretion.

In order to compare directly the distribution of the two isotopes in these mixtures, 1ml of a solution containing both ^{51}Cr chromate and ^{113m}In DTPA was added to a mixture of 2g cornflakes and 10ml water and to a mixture of 2g cornflakes and 10ml gastric juice. After mixing, these were centrifuged and 5ml of the supernatant removed and replaced by water. The procedure was then repeated until five sequential supernatant samples were obtained. The ratio of ^{51}Cr to ^{113m}In in the supernatants was then determined by first counting both the ^{51}Cr and the ^{113m}In in the samples and then leaving them for 24 hours and counting again. During this time, the short-lived ^{113m}In isotope had decayed substantially, so that the counts obtained on the second day could be regarded as representing the ^{51}Cr content in the sample.

Further in vitro experiments were prompted by a report that ^{113m}In DTPA became adsorbed to bread included in a test meal (Grimes & Goddard, 1977). Six grams of white or wholemeal bread was incubated for 60 minutes at 37°C in 20ml 0.05 M HCl containing ^{113m}In DTPA. The mixture was then centrifuged and the counts in supernatant and precipitate measured. The amount of fluid trapped in the precipitate was determined from/

from its weight (compared with the 6g bread used initially) and trapped fluid was assumed to have the same isotope concentration as the supernatant. The fractional adsorption of the isotope was then calculated as the counts associated with the solid, expressed as a fraction of the total counts in the mixture.

In addition to these studies with bread, a mixture of 2g cornflakes and 15ml 0.05 M HCl was also examined to obtain a similar measurement of fractional adsorption.

Results

Gastric Emptying Rates

The results obtained from the subjects studied with ^{113m}In on two occasions are shown in Table 1. There is good agreement between the two measurements. In contrast, Table 2 shows the comparison of emptying rates determined with ^{113m}In and ^{51}Cr and demonstrates a significant difference in the measurements obtained with the two isotopes ($p < 0.01$, sign test). There was also considerable variation between subjects in the indium-chromium difference. There was no evidence for a pharmacological action of the indium compound on gastric emptying, since considerable differences in emptying half-time were still observed in two subjects when physically decayed indium chelate was added to the chromate labelled meal.

Subject 18 gave identical emptying half-times with both isotopes and therefore provides an opportunity to compare directly the results obtained with the two methods. Figure 1 shows the points obtained for the two determinations of emptying half-time in this subject and illustrates the smaller potential error of the points obtained with indium, as a consequence/

Patient	Gastrointestinal disease	Day 1	Day 2
1	None	27	25
2	Previous duodenal ulcer	26	25
3	Cirrhosis, duodenal ulcer	30	31
4	Prepyloric ulcer	25	23
5	Coeliac disease	40	46
6	None	55	49
7	None	25	27
8	None	28	27

Table 1 Gastric emptying half-times (minutes) determined with ^{113m}In DTPA on two successive days.

Patient	Gastrointestinal disease	Day 1 (^{113m}In DTPA)	Day 2 (^{51}Cr Chromate)
9	None	38	55
10	Duodenal ulcer and prepyloric ulcer	41	44
11	None	41	65
12	Duodenal ulcer	52	89
13	None	20	32
14	Prepyloric ulcer	20	28
15	None	39	45
16	Alcoholic gastritis	37	62
17	Previous dudenal ulcer	59	26
18	None	26	26
19	Previous duodenal ulcer	47	60
20	Gastric ulcer	32	40
21	None	25	41
22	None	35	47
23	Gallstones	39	43
24	Duodenal ulcer	35	43
25	None	35	60
26	None	29	30
27	Duodenal ulcer	20	32
28	None	37	66

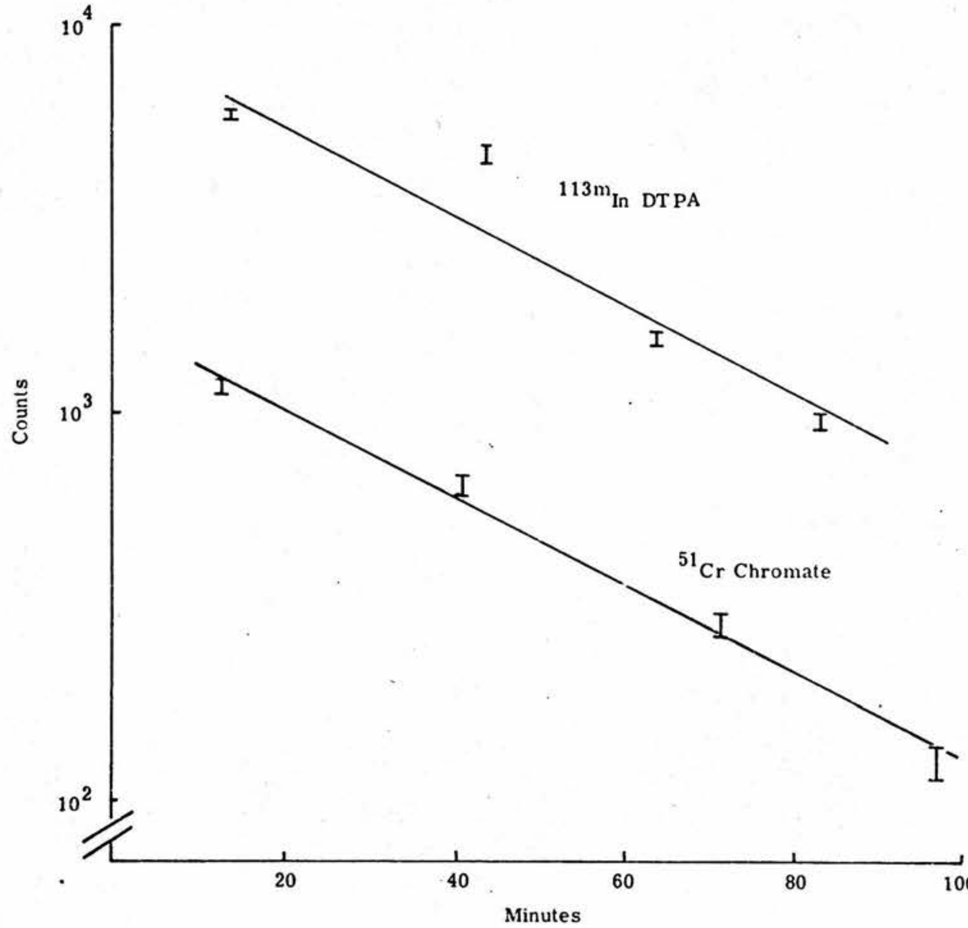
Table 2 Gastric emptying half-times (minutes) determined with ^{113m}In DTPA and ^{51}Cr chromate on successive days.

For patients 27 and 28, physically decayed ^{113m}In DTPA was included with chromate on Day 2.

Figure 1

Gastric emptying of the two isotopes in subject 18.

Counts are indicated ± their square root.



10^4
10^3
10^2
Counts
113m In DTPA
51 Cr Chromate
20
40
60
80
100
Minutes

consequence of the greater precision inherent in the greater count rate.

In the four subjects in whom systemic absorption of ^{113m}In was assessed, less than 2% of the ingested dose was absorbed.

Studies in vitro

Chromate was adsorbed to cornflakes whereas the ^{113m}In DTPA was not. Adsorption was particularly marked in a mixture of cornflakes, water and isotope only, and was less when gastric juice, milk or citrate buffer was incorporated in the mixture. The degree of adsorption was independent of pH.

The differing behaviour of the two isotopes is illustrated by the experiment using the solution containing both ^{51}Cr chromate and ^{113m}In DTPA (Table 3). The Cr/In ratio in the first supernatant is lower than that of the isotope solution, due to adsorption of chromate to the cornflakes but rises in later supernatants as the chromate is eluted back into the aqueous phase.

Substantial adsorption of ^{113m}In DTPA to white bread was demonstrated by the subsequent in vitro experiments. The fractional adsorption to white bread was 0.38 but there was lesser adsorption to wholemeal bread, the fractional adsorption being 0.21. Negligible adsorption to cornflakes was confirmed (fractional adsorption 0.03).

Discussion

The use of any external counting method for the measurement of gastric emptying depends on the assumption that emptying of the isotope from the stomach corresponds to emptying of the meal. The present results show clearly that two non-absorbable isotopes may give differing values for gastric emptying rate measurements. If the gastric contents, comprising meal, isotope and secretion are a completely homogeneous mixture/

	Cr/In ratio in isotope solution	Supernatant Cr/In ratio				
		1	2	3	4	5
Cornflakes and water	1.00	0.59	0.68	0.96	1.48	4.08
Cornflakes and gastric juice	1.00	0.89	0.94	1.15	1.50	2.40

Table 3 Cr/In concentration ratios in supernatants successively removed from cornflakes-water or cornflakes-gastric juice mixtures to which a solution containing ^{51}Cr chromate and ^{113m}In DTPA had been added.

mixture at all times during the period of observation, identical results would necessarily be obtained from two non-absorbable radioactive substances provided they were not adsorbed to the gastric mucosa and did not affect gastric motility. However, the higher value for emptying half-time given by chromate in these studies, coupled with the demonstration of chromate adsorption to the solid matter of the meal suggests that the gastric contents do not leave the stomach as a homogeneous mixture but that in most of the subjects, the more fluid component empties more rapidly. This is in agreement with several older observations (Cannon, 1911; Klein, 1926; Thomas, 1957).

With the cornflakes meal, emptying of ^{113m}In DTPA thus reflects emptying of the liquid phase of the gastric contents. Unfortunately, emptying of the chromate does not provide a satisfactory indication of emptying of the solid phase of the meal, since chromate adsorption to the solid is incomplete and elution readily occurs. It seems that the behaviour of ^{113m}In DTPA may be similar with meals based on bread (Grimes & Goddard, 1977).

Compared with ^{51}Cr, the use of ^{113m}In permits greater precision in individual measurements of intragastric radioactivity, simply as a consequence of the greater count rate (Fig. 1). This is not achieved at the expense of increased radiation dosage to the subject. For the same external count rate, the radiation dose to the critical organ (stomach for ^{113m}In, large intestine for ^{51}Cr) is ten times greater with ^{51}Cr. However, since the radiation dose from either isotope is quite acceptable, it seems reasonable to make use of the advantage of ^{113m}In to obtain higher counting rates. Using 200 μCi of ^{113m}In, the radiation dose to the stomach is approximately 150 millirads (Heading, Tothill, Laidlaw & Shearman, 1971).

These results indicate that ^{113m}In DTPA is a satisfactory material for scintigraphic measurements of gastric emptying rate. Since the findings were published (Heading et al, 1971), ^{113m}In DTPA has been widely used for this purpose (see reviews by Sheiner, 1975; Cooperman & Cook, 1976). It has recently been reappraised and was subsequently adopted in an investigation described by Ralphs, Thomson, Haynes, Lawson-Smith, Hobsley & Le Quesne (1978). Their findings confirm the observations described above.

SUMMARY

Serial abdominal scintiscanning was used to measure gastric emptying rates in adult subjects given a meal of cornflakes, sugar and milk to which a gamma emitting radioactive isotope had been added. Comparison of the rates determined using ^{113m}In DTPA and ^{51}Cr chromate showed that slower emptying was recorded with the latter. Studies in vitro showed that chromate was partially adsorbed to the solid component of the meal whereas the indium compound was not.

The findings imply that the liquid phase of the gastric contents after a meal is discharged through the pylorus more rapidly than the solid phase. ^{113m}In DTPA appears to be a suitable material for use in the measurement of gastric emptying by scintiscanning and provides a measurement which relates to the liquid phase of the gastric contents.

CHAPTER 2

TECHNETIUM-99m DTPA IN THE MEASUREMENT OF GASTRIC EMPTYING WITH A GAMMA CAMERA

TECHNETIUM-99m DTPA IN THE MEASUREMENT OF GASTRIC EMPTYING WITH A GAMMA CAMERA

A major practical disadvantage of the scintiscanning method described in the previous chapter was that the manual counting of dots on the printed scan was time consuming and tedious. Furthermore, the whole procedure gave rise to only four data points for each emptying measurement, which seemed meagre in comparison with the detailed information that could apparently be obtained using a gamma camera. (Harvey et al, 1970; Jones, Clark, Kocak, Cox & Glass, 1970). In consequence, an appraisal of the use of a gamma camera to measure gastric emptying rate was undertaken. For the reasons presented in the previous chapter, ^{51}Cr chromate was rejected as a possible tracer for incorporation in the meal, although it had been used in the work reported by Harvey et al. However, ^{113m}In is not a very satisfactory alternative to ^{51}Cr for quantitative work with a gamma camera, because the relatively high energy of its gamma emission (390 KeV) causes difficulty with collimation and a relatively low counting efficiency by the detector crystal. Technetium-99m (^{99m}Tc), as a DTPA chelate, was therefore considered as a possible alternative.

Preliminary experiments in four dogs given ^{99m}Tc DTPA orally demonstrated that more than 94% of the ingested dose could be recovered in the gastrointestinal luminal contents. Approximately 1% of the dose was detectable in the stomach after the luminal contents had been removed, implying negligible adsorption to or absorption into the gastric mucosa. Minimal quantities (approximately 0.1%) were detectable in the thyroid and kidneys and less than 1% was present in the total blood volume and urine. Thus it appeared that ^{99m}Tc DTPA would be a suitable non-absorbable/

non-absorbable and non-adsorbed marker for studies in human subjects and these were then initiated.

Two main questions were posed, namely:

1. Could a gamma camera be used to produce satisfactory gastric emptying measurements using a cornflakes sugar and milk meal labelled with ^{99m}Tc DTPA?

2. How does the gamma camera compare with a well-established aspiration method in the measurement of gastric emptying of saline?

Methods

Three different measurements of gastric emptying were each made on three occasions in eight normal male volunteers aged 26-30 years. Each study was carried out on a different day after the subject had fasted overnight. Smoking was forbidden during the test.

Gastric emptying of a test meal

The test meal consisted of 20g cornflakes 15g sugar and 150ml milk and was labelled by adding 500 µCi ^{99m}Tc DTPA to the milk. The chelate was prepared using a Renotec (Squibb) kit. The subject was positioned on a couch with a backrest set at 45° and then consumed the test meal over a period of about 2 minutes. Images of the subject's abdomen were then obtained with an Ohio Nuclear gamma camera over consecutive 60 second periods for 1 hour and were stored on magnetic tape. At the end of the study the tape was retrieved and the area of the stomach flagged. Integration of the counts in the flagged area was performed using a PDP8 computer and after correction for physical decay of the isotope/

isotope, the counts within the stomach area were plotted on semilogarithmic graph paper against time. The 'best fit' straight line was assessed visually and the emptying half-time determined from its slope.

Blood samples were obtained from each subject during the test and urine samples up to 4 hours afterwards. These were counted to determine their ^{99m}Tc content.

Gastric emptying of saline - gamma camera

The procedure in these studies was similar to that used for the test meal except that 1 mCi of ^{99m}Tc DTPA was given in 500ml 0.9% (w/v) Na Cl with the subject supine. Images of the stomach were obtained over 10-20 second periods for 30 minutes after ingestion of the saline solution.

Gastric emptying of saline - aspiration method

A 16F gauge rubber nasogastric tube was positioned along the greater curvature of the stomach under fluoroscopic control. With the subject supine, 500ml of a 0.9% Na Cl solution containing 1g polyethylene glycol 4000 (PEG) was instilled into the stomach through the tube as rapidly as possible (within 2 minutes). After 30 minutes the stomach was aspirated and the recovered volume recorded. PEG concentrations in aliquots of the instilled saline solution and in the aspirate were measured by the method of Hyden (1956).

The emptying half-time (in minutes) of the saline solution was then calculated as:

$$T_{\frac{1}{2}} = \frac{t \times \ln 2}{\ln Vi - \ln \left(\frac{V_f C_f}{Ci}\right)}$$

where/

where t = interval between saline instillation and aspiration, i.e. 30 minutes

V_i = instilled volume, i.e. 500ml

V_f = aspirated volume

C_i = PEG concentration in instilled saline

C_f = PEG concentration in aspirate

In vitro studies

A comparison of ^{51}Cr chromate and ^{99m}Tc DTPA adsorption to cornflakes was assessed in vitro by adding the appropriate isotope to a mixture of cornflakes, milk and human gastric juice. After mixing and centrifugation, the supernatants were counted for radioactivity.

More recently the adsorption of ^{99m}Tc DTPA to cornflakes has been more accurately assessed, using the procedure described for ^{113m}In DTPA (p.15)

Results

Test meal

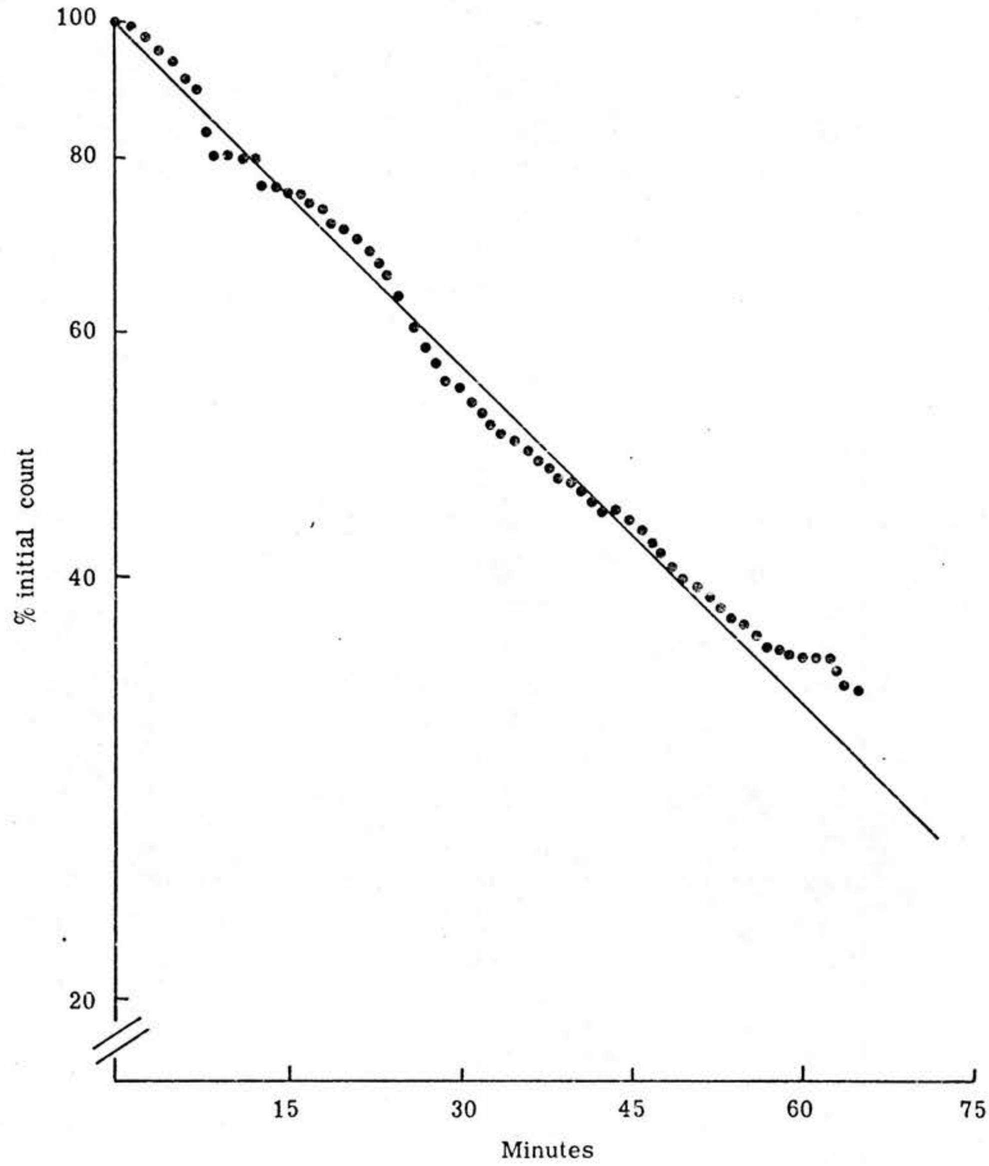
In all subjects, the emptying pattern of the labelled test meal approximated closely to a straight line on the semilogarithmic plot. The example shown in Figure 2 is typical. The emptying half-times determined in all 24 studies are given in Table 4. The mean half-time was 36.8 minutes with an overall standard deviation of 6.1 minutes. The between subject standard deviation was 7.7 minutes and the within subject standard deviation 5.3 minutes, corresponding to coefficient of variation in replicate studies of 14%.

In all subjects, less than 0.5% of the ingested isotope was distributed in the blood volume and urine.

Saline/

Figure 2

Gastric emptying of the cornflakes meal in one subject.


100
80
60
40
20
% initial count
15
30
45
60
75
Minutes

Subject	Study No.	Emptying half-time (minutes)	Mean ± SD
A	1	38	39.7 ± 4.7
	2	45	
	3	36	
B	1	43	38.7 ± 4.0
	2	35	
	3	38	
C	1	30	37.0 ± 7.0
	2	37	
	3	44	
D	1	30	32.3 ± 3.2
	2	31	
	3	36	
E	1	37	39.0 ± 4.4
	2	36	
	3	44	
F	1	30	35.0 ± 4.6
	2	36	
	3	39	
G	1	25	29.3 ± 8.4
	2	24	
	3	39	
H	1	40	43.3 ± 4.2
	2	42	
	3	48	

Mean (± SD) of all 24 studies = 36.8 (± 6.1) minutes

SD between subjects = 7.7 minutes

SD within subjects = 5.3 minutes

Coefficient of variation (within subjects) = 14%

Table 4 Gastric emptying half-times (minutes) of a cornflakes, sugar and milk meal labelled with ^{99m}Tc DTPA. Eight normal subjects were each studied on three occasions.

Saline solution

Gastric emptying of the isotopically labelled saline solution also approximated closely to a monoexponential pattern. (Fig. 3). The emptying half-times determined by the gamma camera method and by the aspiration technique are shown together in Table 5 and comparison of the within subject variations shows that in all subjects, smaller variations were obtained with the gamma camera method than with aspiration. However, the half-times measured with the gamma camera were significantly greater than with the aspiration procedure ($p<0.05$, sign test).

In vitro studies

The initial in vitro study of ^{99m}Tc DTPA adsorption to cornflakes demonstrated considerable adsorption, 50% greater than that which occurred with ^{51}Cr chromate. Using the procedure described on p. 15, the fractional adsorption of ^{99m}Tc DTPA to the cornflakes was found to be 0.53. It was not significantly altered by the addition of free pertechnetate to the mixture, the fractional adsorption then being 0.48.

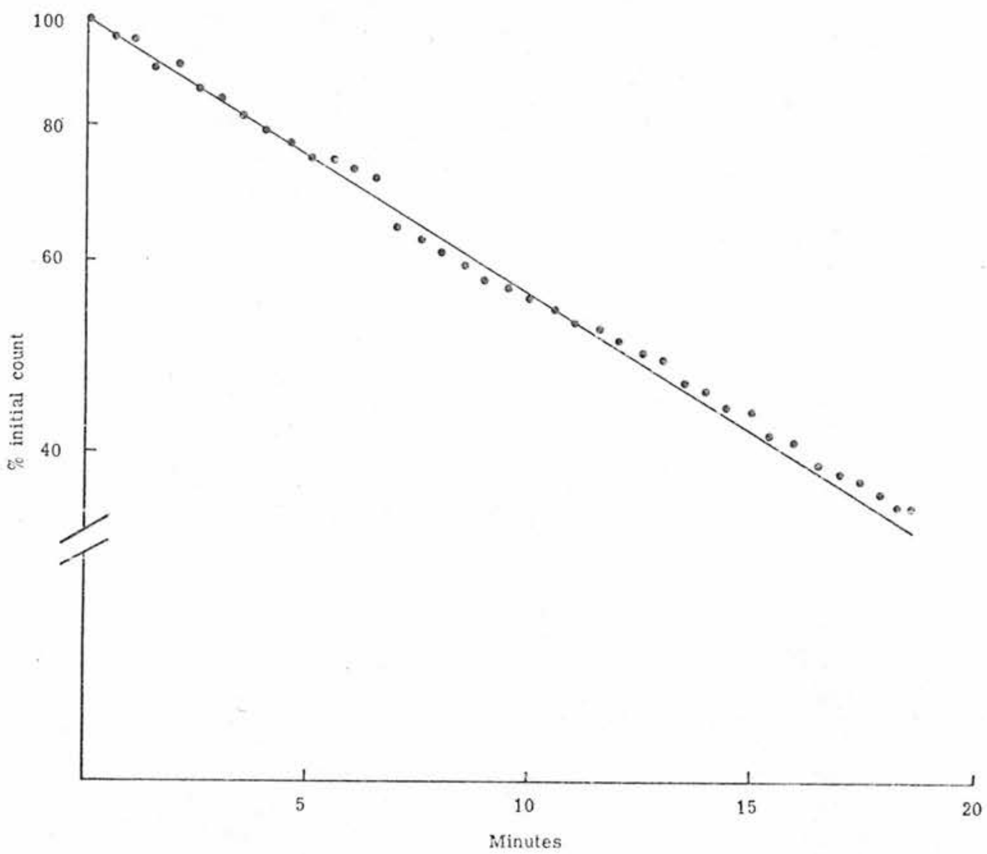
Discussion

At the time these results were first presented (Chaudhuri, Heading, Greenwald & Chaudhuri, 1974) only one previous report on the use of scintigraphy for study of gastric emptying had originated in North America and there had been no previous advocacy of the use of ^{99m}Tc DTPA. Appraisal of the significance of these results therefore requires that this temporal context be borne in mind.

The findings suggest that ^{99m}Tc DTPA is a satisfactory isotope for use in scintigraphic studies of gastric emptying in man and that measurements made with a gamma camera plus computer are at least as reproducible as/

Figure 3

Gastric emptying of the saline solution in one subject.


100
80
60
40
% initial count
5
10
15
20
Minutes

		Gamma camera method		Aspiration method	
Subject	Study No.	$T\frac{1}{2}$ (min)	Mean $\pm$ SD	$T\frac{1}{2}$ (min)	Mean $\pm$ SD
A	1	8.0	8.1 $\pm$ 2.1	7.4	10.7 $\pm$ 3.3
	2	10.2		14.0	
	3	6.0		10.7	
B	1	16.0	13.5 $\pm$ 2.2	13.2	10.5 $\pm$ 5.0
	2	12.5		13.5	
	3	12.0		4.7	
C	1	12.0	12.6 $\pm$ 1.0	12.4	8.1 $\pm$ 3.8
	2	13.7		5.2	
	3	12.0		6.6	
D	1	9.0	8.6 $\pm$ 1.8	7.8	8.2 $\pm$ 1.9
	2	6.6		10.3	
	3	10.2		6.6	
E	1	12.0	11.3 $\pm$ 1.2	5.2	6.4 $\pm$ 3.2
	2	10.0		3.9	
	3	12.0		10.0	
F	1	12.4	13.1 $\pm$ 0.8	3.4	5.0 $\pm$ 2.1
	2	14.0		4.2	
	3	13.0		7.4	
G	1	18.0	16.7 $\pm$ 1.5	12.9	12.5 $\pm$ 5.7
	2	15.0		18.0	
	3	17.0		6.6	
H	1	10.4	9.8 $\pm$ 0.7	7.4	9.0 $\pm$ 4.6
	2	9.0		5.4	
	3	10.0		14.2	
Mean $\pm$ SD of all 24 studies			11.7 $\pm$ 3.0		8.8 $\pm$ 4.0

Table 5 Comparison of the gamma camera method and an aspiration technique for measurement of gastric emptying half-times ($T\frac{1}{2}$) of a saline solution. Eight normal subjects each underwent three tests by each method.

as those made by a procedure based on gastric aspiration. Furthermore, the observations demonstrate the ease with which the gamma camera system can be used to generate multiple data points at intervals of less than 1 minute. This advantage, together with the non-invasive nature of the whole procedure renders the gamma camera method highly attractive as a means of measuring gastric emptying in man.

Three aspects of the study merit particular comment with the advantages of hindsight conferred by present knowledge. Firstly, it was noted that the standard deviation of saline emptying rates using the gamma camera method was smaller than that obtained with the aspiration method and this observation was advanced as evidence that the gamma camera technique was "satisfactory". No attention was paid to the fact that the standard deviation of repeated measurements within subjects was only slightly smaller than that between individuals - a finding which, if taken by itself, suggests that the technique is not very sensitive for the detection of differences between individuals. However, it now seems that the variation between individuals in this group of subjects was unusually small.

No explanation was immediately apparent for the difference in saline emptying rates determined by the two methods. At the time, it was suggested that the difference was attributable to incomplete aspiration of the gastric contents (Chaudhuri, Greenwald, Heading & Chaudhuri, 1975) but it now seems more likely that differences in emptying rate would result from the fact that the saline was rapidly instilled into the stomach for the one test and drunk normally by the subject for the other. If rapid early emptying were produced by the former procedure, the emptying half-time measurement would be shortened. With hindsight, this is/

is one of the least satisfactory aspects of this study and it would have been preferable to undertake the measurements of emptying half-time by the two methods simultaneously. However, although the earlier literature contained evidence of the existence of deviations from the monoexponential pattern of emptying during the first few minutes after consumption of a test solution (Hunt & Spurrell, 1951; George, 1968) the importance of the early period has only been fully recognised more recently.

The third aspect of the present results which merits particular attention is the observation that there was substantial adsorption of ^{99m}Tc DTPA to cornflakes in vitro. This was rightly taken to indicate that the technetium compound was better than ^{51}Cr chromate and ^{113m}In DTPA as a marker of the solid element in the meal and it was therefore an improvement on these two radioactive compounds as an agent for measuring the emptying rates of solid food. ^{99m}Tc DTPA fulfilled the important criteria of non-adsorption to the gastric mucosa, non-absorption by the alimentary tract and low radiation dosage to the subject. Calculations using MIRD formulae suggested that the absorbed radiation dosage to the alimentary tract was approximately 30 millirads per millicurie.

Since these observations were published, ^{99m}Tc DTPA has been used by several investigators studying gastric emptying in man (Cooperman & Cook, 1976; Behar & Ramsby, 1978; McCallum & Berkowitz, 1978; Morguelan, Ippoliti & Sturdevant, 1978). However, in a recent reappraisal of the ^{113m}In and ^{99m}Tc DTPA compounds, doubts were raised concerning the suitability of the latter because persistence of ^{99m}Tc was noted in the stomach when radiological assessment suggested emptying was virtually complete/

complete (Ralphs et al. 1978). It should be noted that these workers did not report on the quality control of their compounds. Preparation of the ^{99m}Tc DTPA compound requires more care than ^{113m}In DTPA and any contamination by persisting free pertechnetate will compromise emptying measurements, since pertechnetate is strongly concentrated in gastric mucosa. Inadequate preparation of the technetium-DTPA compound would seem to be a likely cause of unsatisfactory results.

SUMMARY

Scintigraphic measurements of gastric emptying were performed using a gamma camera and ^{99m}Tc DTPA as the radioactive tracer in a meal of cornflakes, sugar and milk. The technetium compound appeared to be a satisfactory tracer and reproducible emptying measurements were obtained. Significant adsorption to the solid phase of the meal was demonstrated by studies in vitro.

In eight volunteer subjects, three measurements of gastric emptying of saline were made with the gamma camera and three using a method based on gastric intubation and aspiration. Results obtained with the gamma camera showed less within-subject variation between tests, although slightly slower emptying rates were usually recorded with the camera than by gastric aspiration.

Measurements of gastric emptying using ^{99m}Tc DTPA and a gamma camera are non-invasive and are relatively simple to perform. They are apparently as reliable as those based on traditional gastric aspiration methods.

CHAPTER 3

A DOUBLE ISOTOPE METHOD FOR SIMULTANEOUS STUDY OF SOLID AND LIQUID EMPTYING

A DOUBLE ISOTOPE METHOD FOR SIMULTANEOUS STUDY OF SOLID AND LIQUID EMPTYING

Despite the technical sophistication of the gamma camera method for the measurement of gastric emptying, there are two major deficiencies in expression of the result as a simple emptying half-time. Firstly, an assumption is made that it is legitimate to represent emptying as a monoexponential function. Although scanner and gamma camera studies, including those presented in the previous chapters, support this assumption (Griffith, Owen, Campbell & Shields, 1968; Harvey et al, 1970; Cowley, Vernon, Jones, Glass & Cox, 1972), other observations indicate that with liquid meals, there is a brief initial period after meal ingestion during which emptying proceeds at a different rate from the one which subsequently becomes established (Hunt & Spurrell, 1951; George, 1968; Moberg & Carlberger, 1974). Both "slow starters" and "fast starters" are encountered among normal subjects. However, rapid early emptying is a major abnormality seen with liquid test meals in patients who have undergone gastric surgery (McKelvey, 1970; Hall & Read, 1970; Clarke & Alexander Williams, 1973) and is apparently associated with the occurrence of the dumping syndrome (Donovan, Gunn, Brown, Alexander Williams & Clarke, 1974). With the scanning and gamma camera methods described in the previous chapters, no measurement of this early period of gastric emptying was made and clearly this deficiency would be especially serious if the clinical relevance of early emptying abnormalities were confirmed. Two attempts were made to modify scintigraphic methods to include a measurement of early gastric emptying. Colmer, Owen & Shields (1973) using a rectilinear scanner, reported the occurrence of abnormally fast early emptying in patients with vagotomy and pyloroplasty and observed an association/

association of rapid early emptying with post operative diarrhoea. In contrast, no early emptying abnormality was detected in post-vagotomy patients by Hancock, Bowen-Jones, Dixon, Testa, Dymock & Cowley (1974) using a gamma camera.

The existence of a distinct early period of emptying was clearly a constraint on the use of emptying half-time as a description of the gastric emptying process but it appeared to be a problem which could be readily understood and, with methodological development, could probably be overcome. However, the second major deficiency of emptying half-time as a measurement of gastric emptying rate lay in the inherent assumption that the meal could be regarded as a homogeneous entity with a single rate of emptying from the stomach. That this assumption is false was apparent from the indium-chromium comparison described in Chapter 1 and the existence of differential gastric emptying of solids and liquids had been known since the work of Cannon (1911). Thus it appeared that adequate definition of the emptying of a mixed liquid and solid meal would require separate labelling of liquid and solid components in the meal. The differing behaviour of the ^{113m}In DTPA and ^{99m}Tc DTPA in the cornflakes meal presented a possible means of approaching this problem but after further consideration, it seemed that a more definite "solid" marker should be sought, so that two isotopes could be clearly and unmistakably identified with the liquid and solid components of the test meal.

Further studies were therefore initiated in an attempt to overcome these two limitations of the simple emptying half-time measurement. After preliminary experiments, it seemed possible to measure early emptying with the rectilinear scanner by counting over the whole abdomen and/

and expressing the initial intragastric count as a proportion of the total. Validation of the procedure was therefore undertaken by comparing it with the method for early emptying measurement described by Colmer et al (1973).

In parallel studies, various "solid markers" were prepared and assessed in vitro. Eventually, it appeared that small plastic-coated paper particles labelled with ^{99m}Tc would be suitable and these were assessed in vivo.

Methods

A total of 41 patients was studied. Twenty-three had no known gastrointestinal disease and formed the control groups for comparison with a total of 14 patients with uncomplicated duodenal ulcer and 4 patients who had undergone Polya partial gastrectomy at least six months previously. As in the previous investigations, none of the patients was receiving drugs known to influence gastrointestinal motility and smoking was forbidden on the morning of study.

After fasting overnight, the patients were given the standard meal of cornflakes, sugar and milk which contained 200 μCi ^{113m}In DTPA and approximately 30 small pieces of paper impregnated with ^{99m}Tc sulphur colloid. The time of meal ingestion was defined as the midpoint of the period during which the meal was consumed, which was approximately 4 minutes. Ten minutes thereafter, the subject was positioned under the scanner and an abdominal scan performed. Four further scans were undertaken at approximately 30, 60, 90 and 120 minutes. Each scan took about 7 minutes, during which time the subject was supine and between scans he sat in a chair.

Early/

Early emptying measurement

Early emptying measurements were initially restricted to ^{113m}In DTPA, the liquid phase marker. Two methods were used and to permit their comparison, were applied simultaneously to 13 patients. A further 12 patients were studied by only one of the two techniques.

Direct Method

The first scan performed after ingestion of the meal included the whole width of the patient's abdomen and extended from above the stomach to below the anterior superior iliac spines. The two detector heads of the scanner moved horizontally above and below the supine patient and counts due to the ^{113m}In gamma emissions were recorded separately. Manual counting of the dots recorded in the stomach area and in the remainder of the abdomen was then undertaken for both the anterior and posterior scans. Geometric means of the anterior and posterior gastric and abdominal counts were used in subsequent calculations to allow for the variable attenuation of the gamma rays resulting from variable depth of activity within the abdomen.

The total amount of indium ingested by the patient could then be represented by the sum of the stomach area counts and those in the remainder of the abdomen. However, performance of the complete abdominal scan took about 7 minutes and counts from the upper abdomen were obtained before those from the lower abdomen. Obviously the stomach continued to empty during this time. Approximately 4 minutes elapsed between the times at which counts from the midpoint of the stomach and the midpoint of the remainder of the abdomen were recorded and an estimate of the quantity of ^{113m}In emptied from the stomach during this time was calculated/

calculated from the exponential gastric emptying rate subsequently determined. This was subtracted from the abdominal area counts so that a valid comparison with counts recorded from the stomach could be made.

The proportion of ingested ^{113m}In emptied by the time of the first scan was thus calculated as:

$$I = \frac{A + S(e^{-kt} - 1)}{A + Se^{-kt}}$$

where A = geometric mean of non-gastric abdominal counts, S = geometric mean of gastric area counts, k = gastric emptying rate constant and t = 4 (min). This equation is derived as follows:-

If S' represents the gastric counts that would be recorded at the time of the abdominal count, then

$$S' = Se^{-kt}$$

$$\text{or} \quad \frac{S'}{S} = e^{-kt}$$

$$\text{so} \quad 1 - \frac{S'}{S} = 1 - e^{-kt}$$

$$\text{or} \quad S - S' = S(1 - e^{-kt})$$

These are the counts 'inappropriately' included with the abdominal counts, so

$$I = \frac{A - S(1 - e^{-kt})}{A + S - S(1 - e^{-kt})}$$

$$= \frac{A + S(e^{-kt} - 1)}{A + Se^{-kt}}$$

Indirect/

Indirect method

The indirect method used for measurement of early emptying was essentially that described by Colmer et al (1973). The geometric mean of counts recorded from the patient's stomach area was compared with a similar scan of an appropriate dummy, constructed to be of a thickness identical to the antero-posterior diameter of the patient's abdomen. The absolute amount of ^{113m}In corresponding to the patient count could then be determined and the difference between it and the amount ingested by the patient calculated.

Comparison of liquid and solid marker emptying

On the second and subsequent scans only the anterior detector of the scanner was used and counts due to each of the two isotopes were recorded separately on the two display systems. The stomach area on successive scans was defined by reference to the first scan and to the position of the xiphisternum, which was noted on each. Quantitation of the two isotopes within the stomach area was by dot counting, as before. Appropriate corrections for interference by ^{113m}In gamma rays in ^{99m}Tc counts and for physical decay of the isotopes were made.

Comparisons of solid and liquid marker emptying were initially undertaken during the period between the second and final scans (approximately 30-120 minutes after meal ingestion) because it was thought that a distinct early phase of emptying would complicate the interpretation of results. It was then realised that a knowledge of early emptying of both markers was highly desirable and the procedure was modified so that the direct method previously used to measure early emptying of ^{113m}In could be simultaneously applied to both isotopes. Two pulse height analysers/

analysers were therefore connected to each detector to permit the appropriate energy selections. As only two display systems were available, indium counts were recorded directly and technetium counts were recorded on magnetic tape for subsequent replay and quantitation. Emptying of both markers over the whole 120 minute period was then compared in 5 controls and 5 duodenal ulcer patients.

Preparation of the solid marker

The solid phase marker consisted of 30-35 pieces of Whatman No. 1 filter paper, each approximately 3mm square which were impregnated with a total of 200-300 μCi of ^{99m}Tc sulphur colloid.. After drying (with a hair dryer) the paper was dipped in a 3% w/v solution of Perspex in chloroform, dried, dipped and dried again. These particles were then mixed into the meal.

The retention of isotope within the paper treated in this manner was established in preliminary experiments. When continuously agitated in water, in gastric juice or in duodenal juice, less than 3% of the isotope was eluted from the particles in 4 hours. Almost all of this was eluted within 60 minutes (Fig. 4). In contrast, particles similarly prepared with ^{99m}Tc pertechnetate lost approximately 75% of the isotope in 60 minutes and even more was eluted from ^{99m}Tc sulphur colloid labelled paper prepared without the plastic coating.

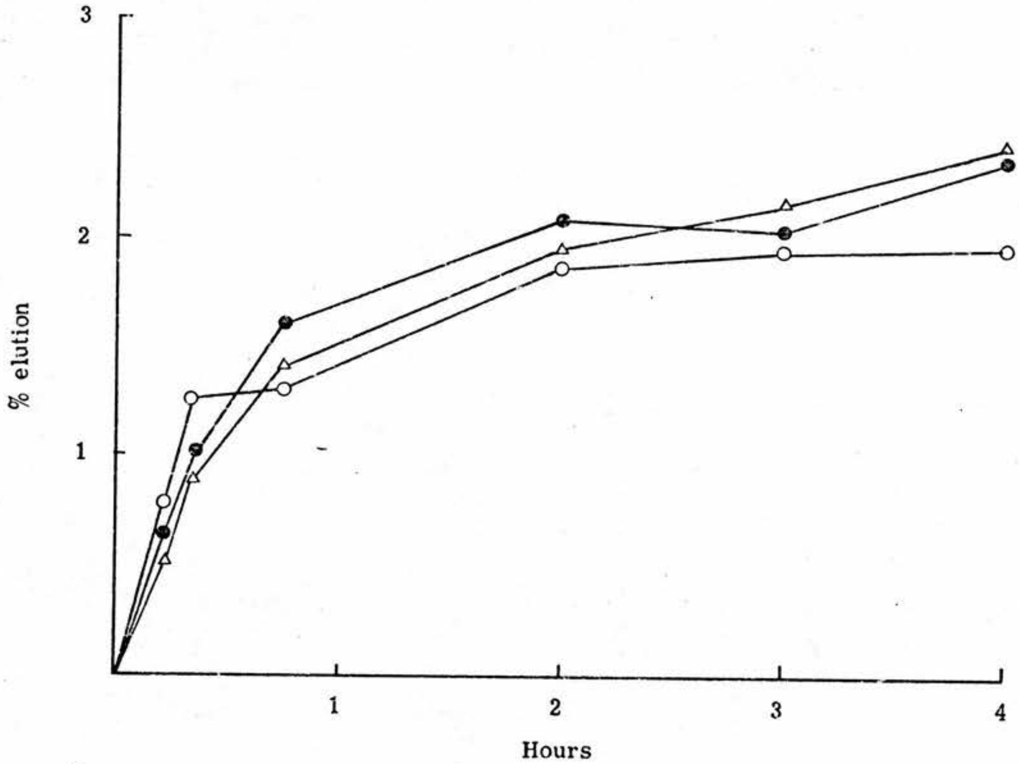
Results

Early emptying of ^{113m}In

The results from the patients to whom both the direct and indirect methods of measuring early emptying were applied showed that in most instances/

Figure 4

Elution of ^{99m}Tc sulphur colloid from Perspex coated paper particles shaken at 2 cycles/sec. in 5ml (open circles) 10ml (closed circles) and 20ml (triangles) of human gastric juice.


3
2
1
% elution
1
2
3
4
Hours

instances there was reasonable agreement between the two determinations (Fig. 5). In the group as a whole, the values obtained by the two methods showed a within patient standard deviation of 8.6% of the amount of ingested marker. There was no evidence of a systematic underestimation or overestimation of early emptying by either technique and thus results obtained by the two methods may legitimately be compared.

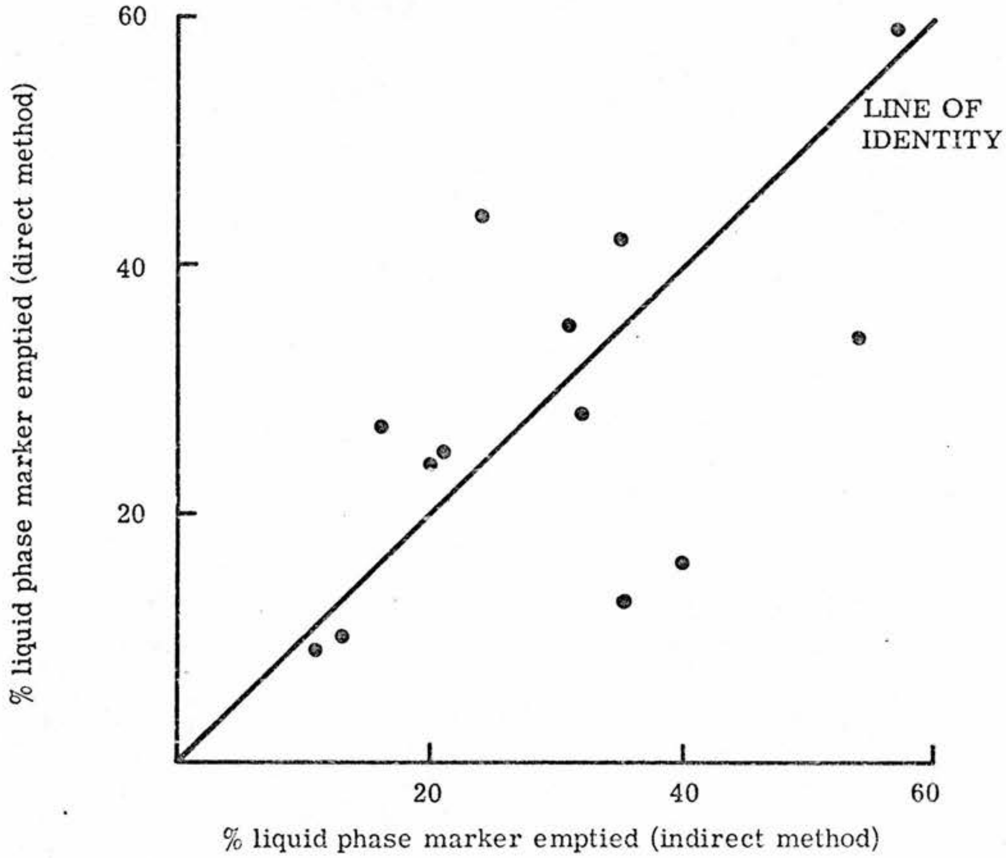
In practice, it was not possible to avoid some variation in the time at which the first scan was performed on each patient. This obviously contributed to inter-patient variation in the amount emptied by the time of the first scan. To standardise the early emptying measurement, observed emptying at the time of the first scan was compared with the amount that would have been emptied at this time, had the subsequent exponential emptying rate operated from the time of meal ingestion. The arithmetic difference between these quantities was designated the "excess early fraction" of emptying and provided a measure of the amount by which emptying exceeded the simple exponential during this early period. The excess early fraction had a positive value when emptying before the first scan exceeded the subsequent simple exponential rate and was negative when emptying during the early period was slower.

The early emptying results obtained in the control and duodenal ulcer patients are shown in Table 6. Values obtained by the direct method have been used for those patients to whom both methods were applied. The mean excess early fraction was small in both groups of patients, indicating that on average, emptying during the early period occurred at a rate similar to the rate which obtained thereafter. However, considerable individual variation in excess early emptying was demonstrated. Positive and negative results were obtained among both groups of patients.

The/

Figure 5

Comparison of the direct and indirect methods for measuring gastric emptying by the time of the first scan.



60
40
20
20
40
60
LINE OF IDENTITY
% liquid phase marker emptied (direct method)
% liquid phase marker emptied (indirect method)

	Control subjects (n= 10)	Duodenal ulcer patients (n=9)
% ingested ^{113m}In emptied by first scan	21.6 ± 10.8	19.9 ± 13.0
Time of first scan (min after meal ingestion)	11.9 ± 4.4	10.2 ± 2.4
Rate constant for subsequent ^{113m}In emptying (min^{-1})	0.0169 ± 0.0064	0.0173 ± 0.0053
Excess early fraction (% ingested ^{113m}In)	3.0 ± 15.9	4.3 ± 12.9

Table 6

Early gastric emptying in control and duodenal ulcer subjects. Results are means ± SD. The excess early fraction is defined in the test (p.47).

The necessity for use of geometric means of the anterior and posterior counts in the measurement of early emptying by the direct method was assessed in 14 patients. Early emptying values were larger when the measurement was based on anterior counts alone ($p < 0.05$; paired t test) and individual discrepancies between the values calculated from anterior counts and those derived from the geometric means, ranged from -11 to +15% (mean + 5%) of the amount of ingested marker. Because the determinations based on geometric means are inherently more accurate, these discrepancies were taken to represent errors in measurement attributable to use of the anterior detector alone.

Emptying of the solid and liquid phase markers

In 16 of the 18 control subjects, emptying of the solid phase marker during the period between the second and final scans was slower than that of the liquid phase marker ($p < 0.01$; paired t test). These results are shown in Figure 6. However, in addition to the differences in amounts emptied, the emptying patterns of the two markers were also different (Fig.7). Emptying of the liquid phase marker approximated closely to a monoexponential function and individual emptying rates were therefore calculated by linear regression of plots of the logarithm of stomach area counts against time and expressed as first order rate constants k, where $k = \frac{\ln 2}{T_{\frac{1}{2}}}$.

In contrast, emptying of the solid marker did not conform to an exponential pattern. Best fit linear and exponential patterns were determined for each patient using a least squares procedure and comparisons of the residual sums of squares of deviations indicated that in 13 of the 18 patients, solid emptying approximated more closely to a process linear with/

Figure 6

Gastric emptying of liquid and solid phase markers during the period between the second and final scans in 18 control subjects. The lines join the points representing liquid and solid emptying in each subject.

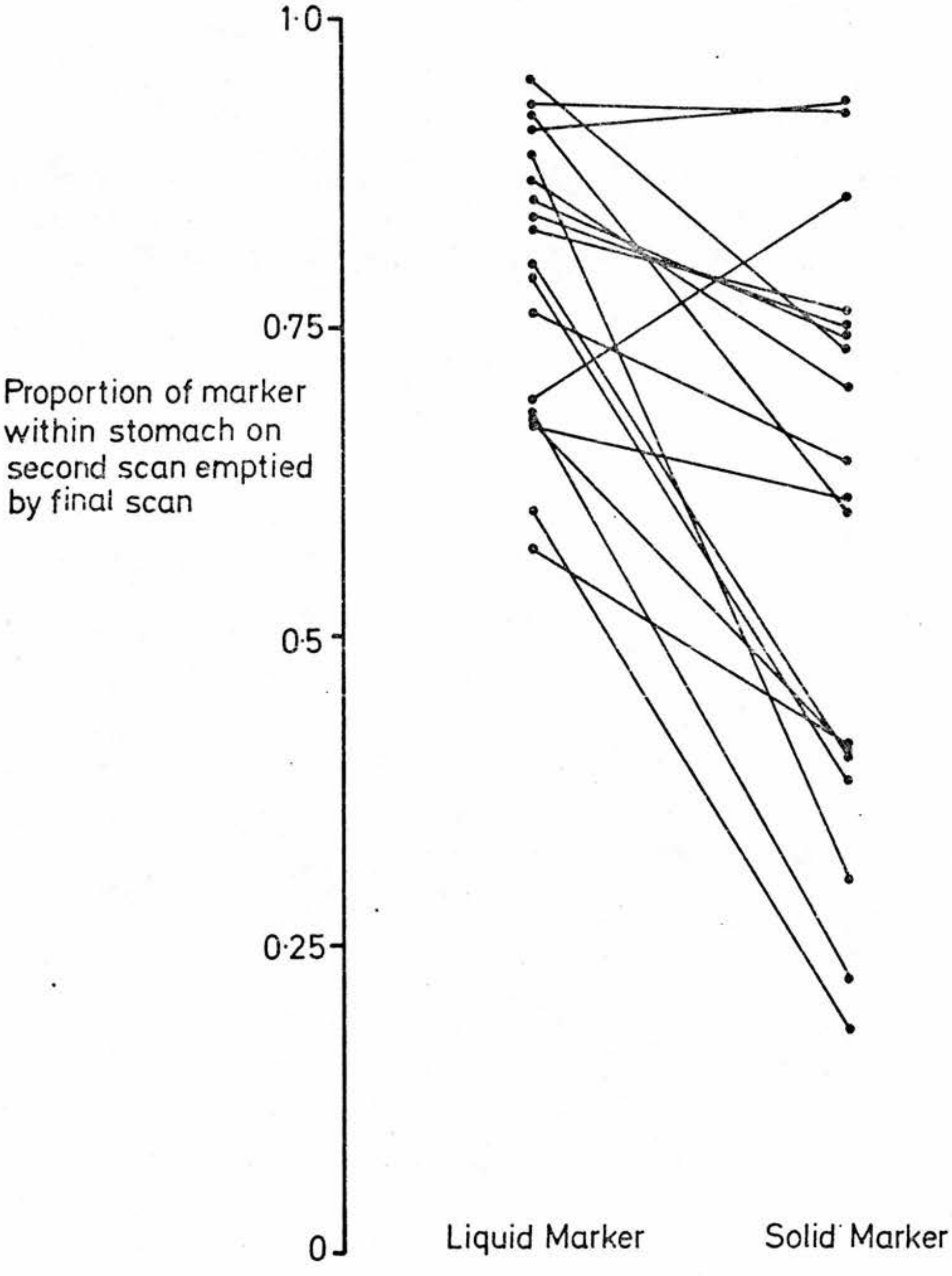
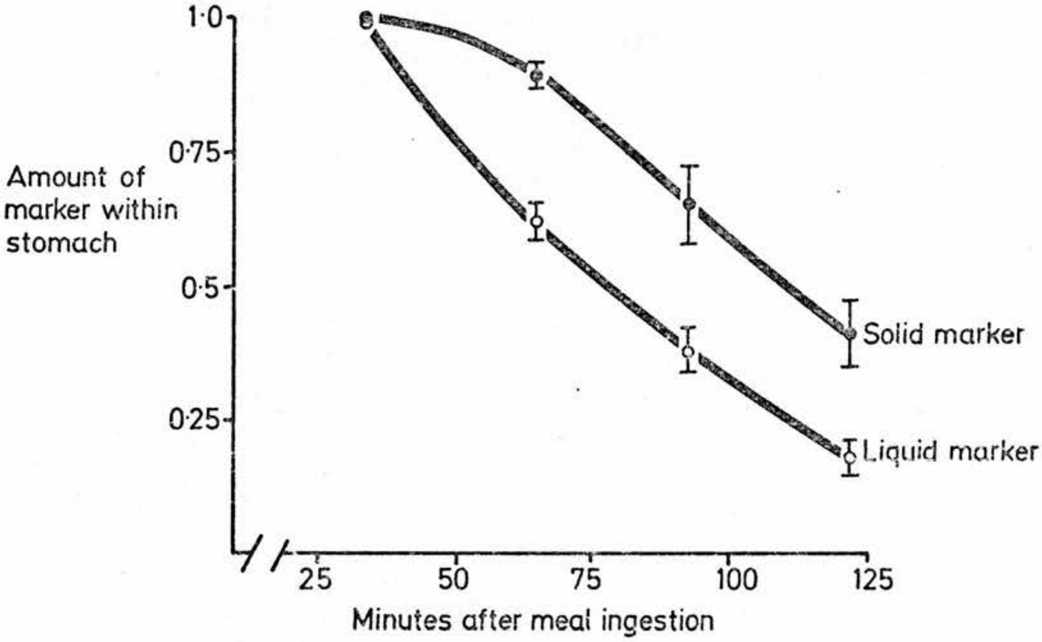

1·0
0·75
0·5
0·25
0
Proportion of marker
within stomach on
second scan emptied
by final scan
Liquid Marker
Solid Marker

Figure 7

Gastric emptying of liquid and solid markers in 18 control subjects. The amount of each marker present in the stomach at the second scan is taken to be 1. Points are means ± SEM.


1·0
0·75
0·5
0·25
Amount of marker within stomach
Solid marker
Liquid marker
25
50
75
100
125
Minutes after meal ingestion

with time than to a monoexponential ($p < 0.05$; sign test). Emptying rates for the solid marker were then calculated from the gradient of linear plots of stomach area counts against time, and expressed as a zero order rate constant, arbitrarily defining the intercept of the regression line with zero time as 100. This permitted solid emptying during the period of observation to be expressed numerically, but was not intended to imply any knowledge of emptying during the earlier period.

Duplicate studies were undertaken in 9 subjects to assess the reproducibility of the measurements and the results are given in Table 7. Differences in the results of two studies of the same patient on successive days obviously include genuine day-to-day variations in the patient as well as errors of measurement, but clearly the measured rates of both solid and liquid marker emptying show less variation between duplicate studies than between patients.

A correlation between emptying rates of the solid and liquid markers was established for the control patients ($p < 0.01$, Fig. 8). Thus although the actual rates and patterns of emptying for liquid and solid were different, individuals within the control group who were fast emptiers of one tended to be fast emptiers of the other.

Comparison of solid and liquid marker emptying over the full two hour period was performed in 5 control and 5 duodenal ulcer patients and the results are shown in Figure 9. In both groups, a difference between liquid and solid marker emptying was seen to occur during the first 30 minutes after meal ingestion as well as from 30 minutes onwards. No significant differences between the controls and duodenal ulcer patients were observed.

Results/

	Mean	S.D. between patients	S.D. within patients
Solid marker emptying rate (% min^{-1})	0.49	0.23	0.10
Rate constant (k) for liquid marker emptying (min^{-1})	0.0207	0.0083	0.0028

Table 7

Emptying rates for the liquid and solid markers during the period between the second and final scans, measured in nine control subjects on two successive days.

Figure 8

Correlation of emptying rates of liquid and solid markers during the period between the second and final scans in 18 control subjects.

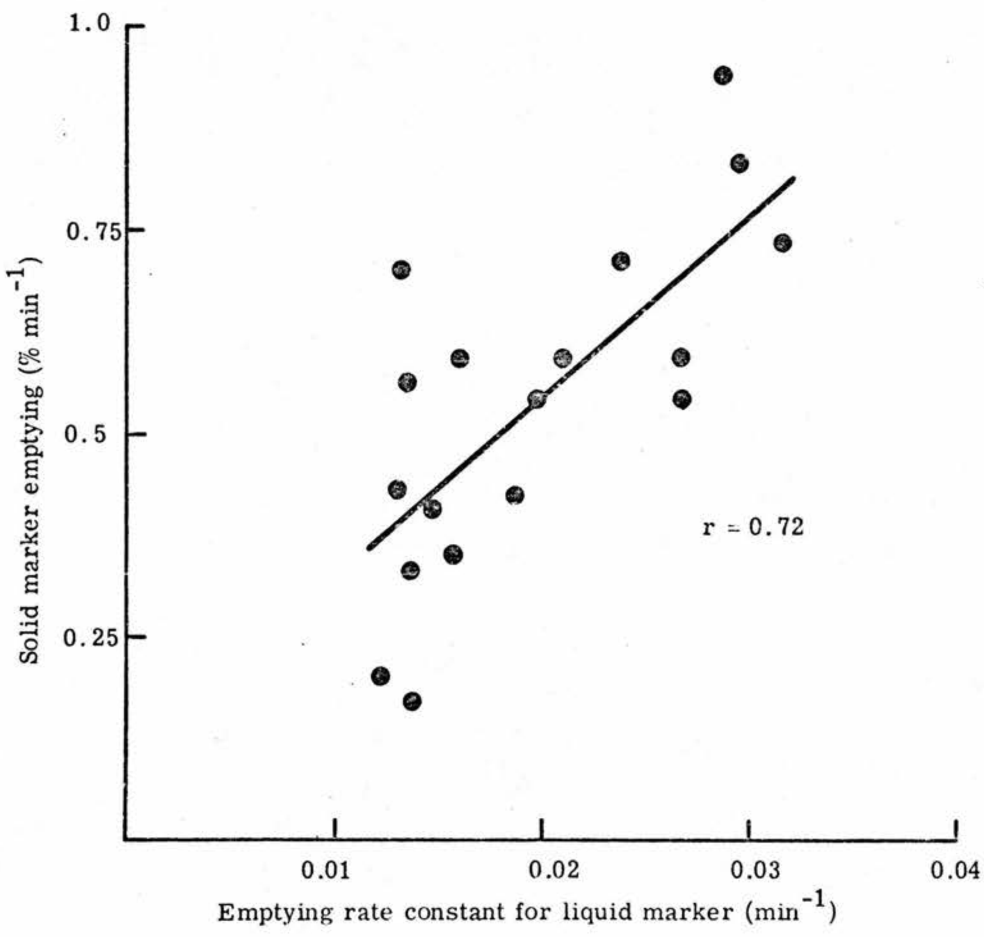
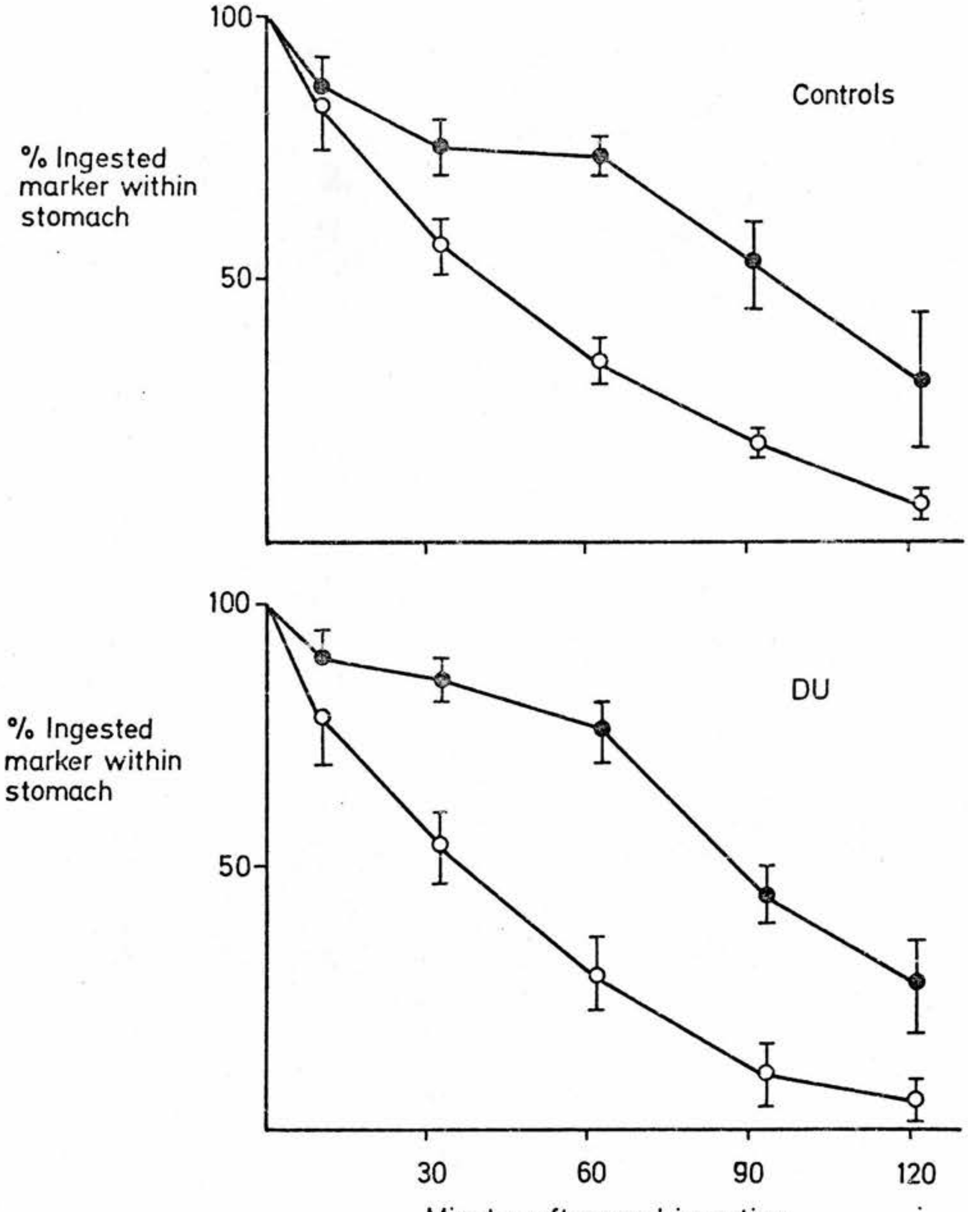

1.0
0.75
0.5
0.25
Solid marker emptying (% min^{-1})
r = 0.72
0.01
0.02
0.03
0.04
Emptying rate constant for liquid marker (min^{-1})

Figure 9

Emptying of liquid (open circles) and solid (closed circles) markers in 5 control subjects and 5 duodenal ulcer patients. Points are means $\pm$ SEM.



100
50
% Ingested marker within stomach
Controls
100
50
% Ingested marker within stomach
DU
30
60
90
120
Minutes after meal ingestion

Results from the patients with partial gastrectomy are presented and discussed in detail in Chapter 5.

Discussion

These results indicate that the basic scintiscanning technique may be extended to provide a measurement of early emptying and to quantitate emptying of solid and liquid markers simultaneously. These two new features are best considered separately.

The simultaneous application of two procedures to measure early emptying of the ^{113m}In was undertaken in attempt to obtain some objective indication of the confidence that should be placed in the results. In most cases, there was acceptable agreement between the two determinations. However, both methods present difficulties. The indirect technique is critically dependent on accurate measurement of the patient's antero-posterior abdominal diameter and in practice the necessary precision was sometimes difficult to achieve. For this reason, it seemed that greater confidence should be placed in the direct determination. However, the direct determination, together with the calculation of excess early fraction requires the assumption that any distinct early phase of emptying is completed within 10 minutes. Such an assumption appears justified by the findings of Clarke & Alexander Williams (1973) and of Colmer et al (1973) but it is possible that in some patients at least, the early phase lasts longer (Cook, Hoschl & Grossman, 1975).

The measurements of early emptying in the control and duodenal ulcer patients showed that during the first 10 minutes, emptying of ^{113m}In occurred at a rate which was on average very similar to the exponential rate operating from 10 minutes onwards. However, there was considerable variation between individuals in the pattern of early emptying and/

and both "slow starters" and "fast starters" were observed in both patient groups. These observations are in accord with the findings made with liquid meals (Hunt & Spurrell, 1951; George, 1968; Clarke & Alexander Williams, 1973; Moberg & Carlberger, 1974) and imply that a distinct early phase of emptying exists for the liquid component of mixed meals as well as for exclusively liquid meals. The same implication may be drawn from the results obtained by Colmer et al (1973).

Two major conclusions can be drawn from the emptying rates and patterns observed with the solid marker in the present study:-

1. There is a marked discrimination between solid and liquid emptying in the intact stomach, with the solid component of a mixed meal emptying more slowly than the liquid.

2. Emptying of the solid marker should be represented as a process linear with time (i.e. a zero order function) rather than by an exponential.

The first of these conclusions was noted by Cannon (1911) and no originality can be claimed for the observation. However, the finding has important implications for the study of "ordinary" mixed meals by scintigraphic methods, since it implies that a complete definition of emptying cannot be gained from the use of only one isotope marker in a meal. Furthermore, since an "ordinary" meal consists of a range of solid components of various sizes, shapes and consistencies, the interpretation placed on measurements made with one type of "solid" marker must be made with care. The paper particles used in these studies, being almost two-dimensional may be emptied differently from three-dimensional particles of solid food. Nevertheless if the gastric contents/

contents after a mixed meal consist of a spectrum of liquid, semi-solid and particulate material with a corresponding spectrum of emptying rates, it seems possible that the ^{99m}Tc labelled paper particles represent a point somewhere towards the "solid" end of the spectrum whereas the ^{113m}In represents a point towards the "liquid" end. The two isotopes may thus be expected to provide an indication of the emptying patterns of solid and liquid components of a meal.

While it is clear that in these studies emptying of the solid marker did not occur as an exponential process and was better represented as a zero order function, the results shown in Figure 9 suggest that the true pattern may be even more complex. However, more detailed mathematical analysis is not appropriate on the basis of only 5 control and 5 duodenal ulcer patient studies performed over the full two-hour period.

This double isotope scintiscanning method provides the means whereby gastric emptying during the early period after meal ingestion may be measured and emptying rates may be determined for the liquid and solid components of a mixed meal. The procedure is not without technical difficulty but it appears to generate results which are acceptably reproducible. The additional complexity appears to be worthwhile since the present observations convincingly confirm the inadequacy of the simple emptying half-time determination as a means of describing emptying of a mixed solid and liquid meal.

SUMMARY

The basic scintiscanning method for measurement of gastric emptying was modified to permit the simultaneous study of liquid and solid components of a test meal. This included the quantitation of early (0-10 min) emptying. The meal consisted of cornflakes, sugar and milk to which ^{113m}In DTPA was added as a liquid phase marker; the solid marker consisted of small squares of plastic-coated filter paper labelled with ^{99m}Tc.

In control and duodenal ulcer patients, liquid emptying was faster than solid emptying and could be represented as a monoexponential process but solid emptying followed a different pattern better represented as linear emptying with time.

Gastric emptying of a mixed solid and liquid meal cannot be fully described unless measurements of early emptying are made and the solid and liquid elements in the meal are both studied.

Further methodological refinements

The double isotope scanning method for gastric emptying measurements is the basis of many of the studies to be described in the following chapters. Although the principles of the method remained unchanged, several practical refinements were gradually introduced to facilitate the measurements, notably the tape recording of scans, with subsequent playback and selection of the "gastric" and "non- gastric abdominal" areas and automatic integration of the recorded counts. A PDP 12 computer was then used to perform the calculations of emptying rates.

After the initial studies already described, no further use was made of the "excess early emptying" measurement. This had been conceived as a means of describing early emptying when there was variation in the time at which the first scan was performed on each subject but it soon became apparent that, with practice, the scanner operator was able to achieve the desired timing consistently. It was then possible to describe emptying during the early phase simply by indicating the percentage of each marker emptied 10 minutes after its ingestion. This was undoubtedly a more realistic and comprehensible expression of early emptying than the abstract "excess early emptying" and was therefore adopted. Emptying during this early period was excluded from the calculations of ^{113m}In emptying half-time and ^{99m}Tc particle emptying rates, which all relate to the period 10-120 minutes after meal ingestion.

One further methodological development was the use of both the anterior and posterior detectors of the scanner to count both isotopes throughout/

throughout the period of study. At first, geometric means of anterior and posterior counts were used as the "accurate" measurements but subsequently, it was found that the arithmetic sum of the anterior and posterior counts was more simply determined and provided a closely similar emptying rate measurement (Tothill, McLoughlin & Heading, 1978). The significance of bilateral count detection in comparison with unilateral count detection is discussed in detail in Chapter 11.

Statistical analysis of results

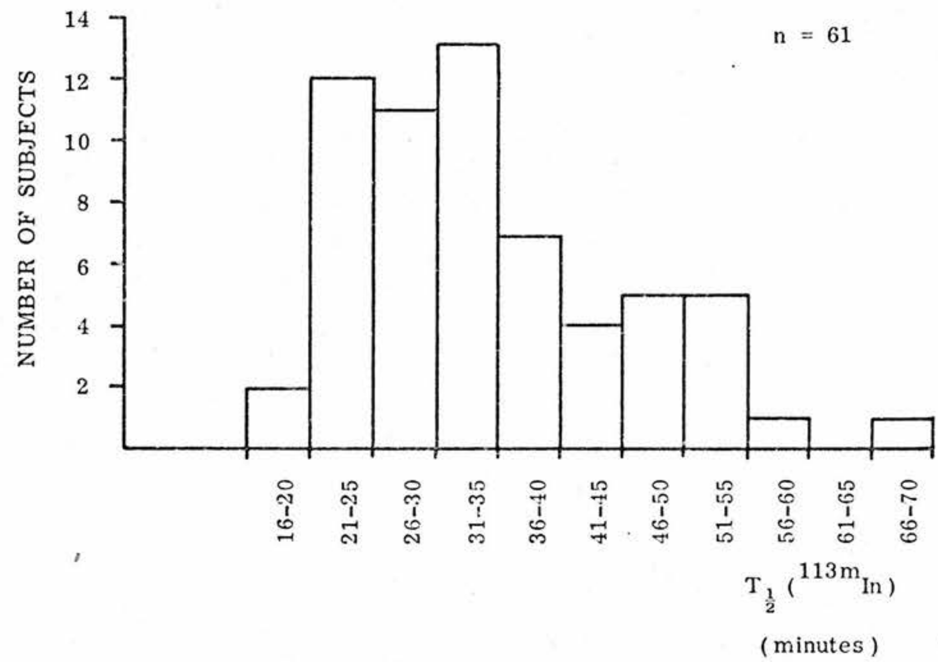
It is appropriate at this point to comment briefly on the statistical procedures adopted in the analysis of results in the following chapters.

Most commonly used statistical tests make some assumptions concerning the nature and distribution of the population samples being analysed. For example, it is well known that the Student t test assumes a normal distribution in the population being studied; it is less well known that the Wilcoxon/Mann Whitney ranking tests assume a) continuous distributions and b) the same population distribution in two samples being compared. The validity of any assumption is necessarily open to question and with many results from biological or clinical investigations, including gastric emptying measurements, it is easy to suggest that because certain assumptions might not be valid, a given statistical analysis is incorrect. If any statistical analysis at all is to be performed, one must hope that a judicious balance of assumption making on the one hand, and commonsense interpretation of results on the other, will represent an optimal compromise.

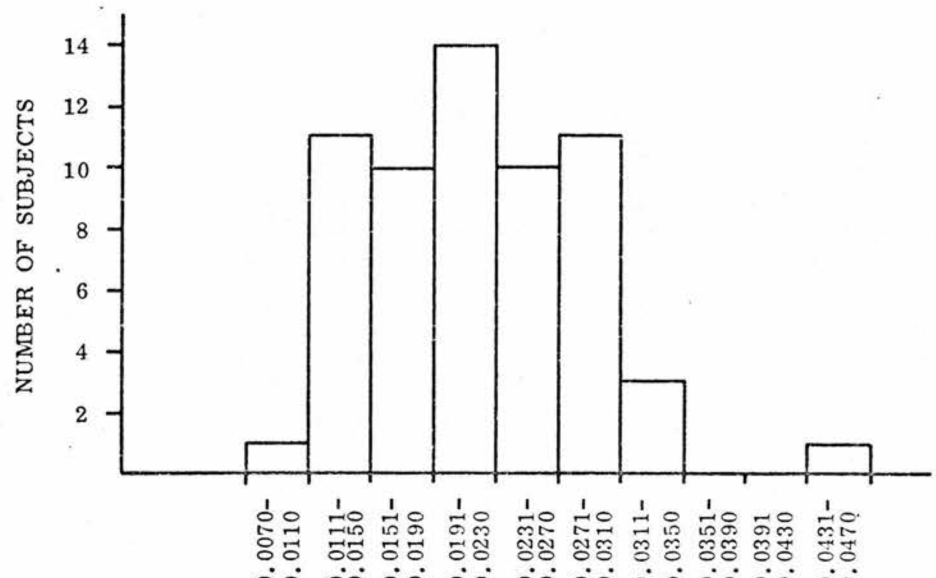
In the absence of any evidence to indicate otherwise, normal distributions have been assumed for most measurements presented in the following chapters, so that standard deviations (or errors of the mean) have been determined and means compared using Student t tests. The ^{113m}In emptying half-times are an important exception. All available results from control subjects (i.e. normal volunteers and patients without gastrointestinal disease participating in studies described in the following chapters, plus some further unpublished results) are shown in Figure 10. It is clear that the emptying half-times are not normally/

Figure 10

Gastric emptying half-times ($T_{\frac{1}{2}}$) and the corresponding emptying rate constants (K) observed in a total of sixty-one healthy subjects and patients without known gastrointestinal disease given the test meal of cornflakes, sugar and milk, labelled with ^{113m}In DTPA.



n = 61
NUMBER OF SUBJECTS
14
12
10
8
6
4
2
16-20
21-25
26-30
31-35
36-40
41-45
46-50
51-55
56-60
61-65
66-70
$T_{\frac{1}{2}}$ (^{113m}In)
(minutes)



NUMBER OF SUBJECTS
14
12
10
8
6
4
2
0.0070-0.0110
0.0111-0.0150
0.0151-0.0190
0.0191-0.0230
0.0231-0.0270
0.0271-0.0310
0.0311-0.0350
0.0351-0.0390
0.0391-0.0430
0.0431-0.0470
K (^{113m}In)
(min^{-1})

normally distributed. However, the distribution of the emptying rate constant ($k = \frac{\ln 2}{T_{\frac{1}{2}}}$) is apparently symmetrical (median = 0.0210, mean = 0.0215 min^{-1}, n = 61) and this may be taken as reasonable evidence for the presumption of a normal distribution. Unfortunately, use of this rate constant lacks the directness of the emptying half-time as an index of emptying. For example, the meaning of an emptying half-time of 30 minutes is immediately apparent, whereas the meaning of an emptying rate constant of 0.023 min^{-1} is not so clear. In the interests of clarity therefore, some results in later chapters are presented as individual or as mean values of emptying half-time and groups are compared using appropriate ranking tests.

To accept unreservedly that ^{113m}In emptying rate constants are normally distributed implies that the convention of using mean $\pm$ 2SD as the "normal range" would be appropriate. The limits of this range, calculated from the 61 control subjects are rate constants corresponding to emptying half-times of 20 and 78 minutes. On a commonsense, perhaps intuitive basis, these values seem too high. In consequence this range has not been adopted as the definition of "normal" and where control values are required in subsequent chapters, the range 16-67 minutes is quoted. Applying distribution free tolerance limits to the 61 observations, there is a probability of 0.95 that 95% of emptying half-times in control subjects will lie within this range.

CHAPTER 4

OBSERVATIONS WITH ^{99m}Tc-LABELLED CHICKEN LIVER

OBSERVATIONS WITH ^{99m}Tc-LABELLED CHICKEN LIVER

When ^{99m}Tc-labelled paper particles were first reported to be emptied from the stomach in an approximately linear manner with time (Heading, Tothill & McLoughlin, 1975), the only previous suggestion of zero order gastric emptying rates for solids had come from a study of antrectomy in dogs (Dozois, Kelly & Code, 1971). Zero order emptying patterns for solids in normal man have now been confirmed by several further investigations (Meyer, MacGregor, Gueller, Martin & Cavalieri, 1976; Grimes & Goddard, 1977; MacGregor, Martin & Meyer, 1977; Guller, Nemec, Kyle & Fridrich, 1977). In addition, further evidence of the nature and magnitude of solid-liquid discrimination during gastric emptying has been presented (MacGregor et al 1977; Malagelada, 1977). Nevertheless an important question remains concerning the interpretation of results obtained with the Perspex-coated paper particles. If these particles are inert and resistent to the grinding action of the gastric antrum, they differ from solid foods which are ground down within the stomach to produce the chyme which normally passes through the pylorus - a fluid containing a fine suspension of solid matter. Inert particles, incapable of being ground to a fine suspension would therefore seem to be a poor model for the solid element in a mixed meal. However, there is also a difficulty if discrete particles of isotopically labelled solid food are used to define the manner in which the stomach handles "solids". They will initially reflect the behaviour of solid particles in the stomach but because such foods are progressively ground down and 'liquified' within the stomach their behaviour will progressively change to reflect the behaviour of liquids. It may be that by using ^{113m}In DTPA as a marker of the liquid component of a meal and the inert ^{99m}Tc-labelled/

^{99m}Tc-labelled paper particles as a solid marker, the extremes of liquid and solid behaviour in a mixed meal can be defined so that the emptying patterns of most natural foods will lie somewhere in between. If this hypothesis could be validated, the use of inert particles to define the manner in which the stomach handles "solids" would be justifiable, provided that the physiological reality of solid food being converted to a more liquid form were not forgotten.

Demonstrations that isotopically labelled foods such as liver (Meyer et al, 1976) and bread (Grimes & Goddard, 1977) are emptied from the stomach in a linear fashion with time indicate that the pattern observed with the paper particles is not an artifact attributable to their artificiality. However, in a comparison of emptying of ^{99m}Tc-labelled paper particles with that of ^{198}Au-labelled liver in 5 normal subjects, the liver was emptied from the stomach more slowly than the paper particles (Guller et al, 1977). This is incompatible with the hypothesis that the emptying pattern of most natural foods will lie between the patterns represented by ^{113m}In DTPA and the ^{99m}Tc-labelled particles in a mixed meal. A study similar to that described by Guller was therefore undertaken to explore the problem further.

Methods

Six normal volunteers each underwent two studies of gastric emptying using a meal of isotopically labelled chicken liver (approximately 20g) and mashed potato (approximately 150g) to which ^{99m}Tc-labelled paper particles had been added. The particles were prepared as described previously; the liver was prepared as described by Meyer et al (1976) except that ^{113m}In sulphur colloid was used in place/

place of ^{99m}Tc sulphur colloid. One hour after i.v. injection of the colloid (3 m Ci) the chicken was killed and the liver removed. This was cooked by boiling for 5 minutes. Checks on the water after cooking revealed no detectable elution of ^{113m}In from the liver.

Approximately half the cooked chicken liver (containing 200-300 µCi ^{113m}In) was cut into cubes, either large (1 x 1 x 1 cm) or small (0.3 x 0.3 x 0.3 cm) and thoroughly mixed with the potato and ^{99m}Tc-labelled particles. The subject was then given the meal together with a hot drink, made up by dissolving 3 'Oxo' cubes in 400ml water. The subjects were asked to consume the drink evenly over the period during which they were eating the solid food but otherwise no specific instructions were given concerning chewing or the speed of eating.

For one study, the subject ate the meal with the larger liver cubes and on the other (usually the following day) he was given the meal with the smaller liver cubes. On each occasion, gastric emptying of the two isotopes was measured as described previously, except that bilateral count detection was used throughout (see page 62). Emptying rates were calculated by linear regression of the ^{99m}Tc and ^{113m}In counts against time.

Results

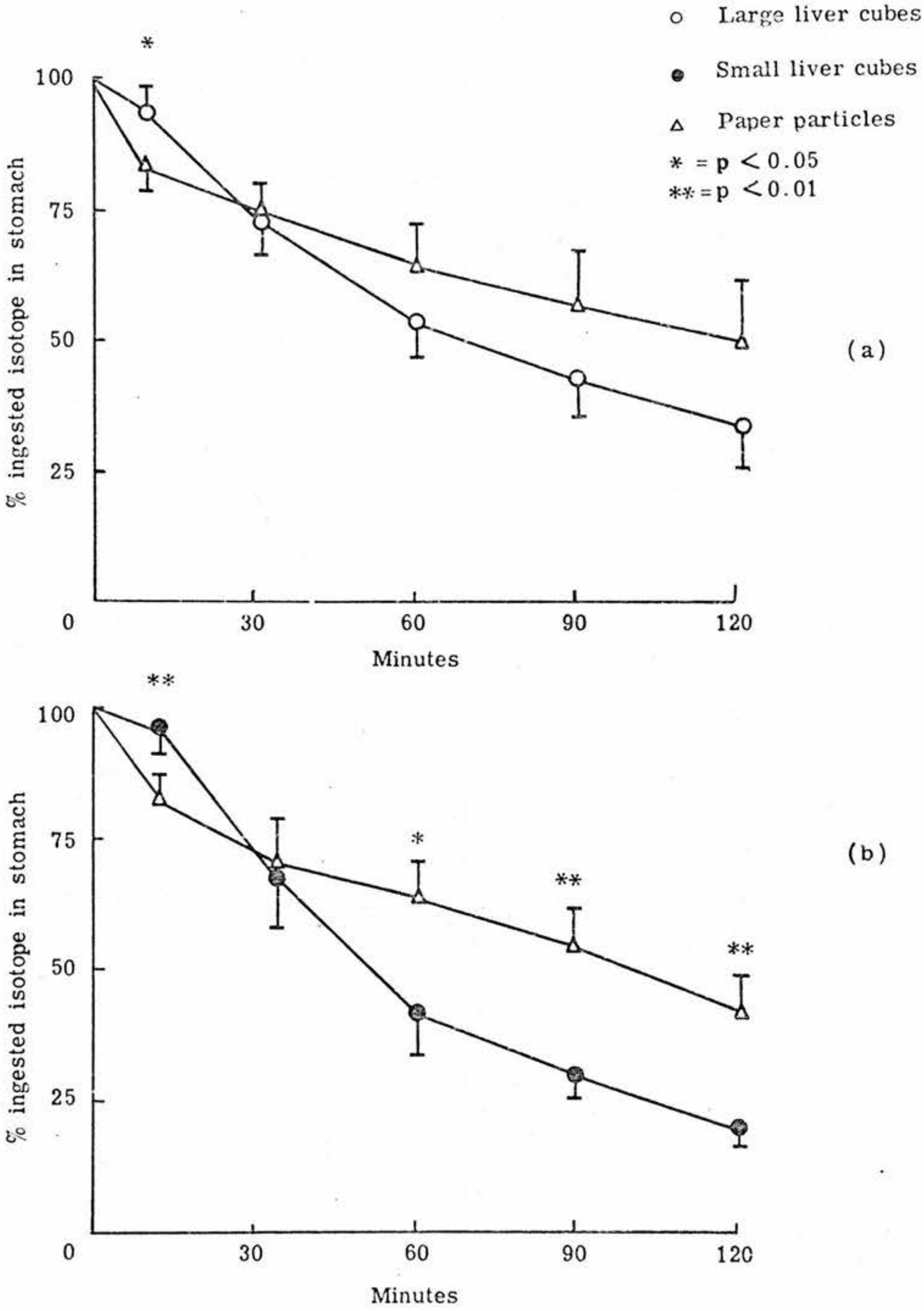
Emptying patterns of the labelled liver and paper particles are shown in Figure 11. Ten minutes after ingestion of the meal, more of the paper particles than liver had been emptied from the stomach, irrespective of the size of the liver cubes ingested (Fig.11, a and b). However, from 10 minutes onwards, emptying rates of the liver were faster than those of the paper particles (Table 8). Comparisons of the amounts of liver emptied at 120 minutes showed that significantly more/

Figure 11

Gastric emptying of ^{113m}In-labelled liver and ^{99m}Tc-labelled paper particles in six normal volunteers. Data are means ± SEM. Paired t tests were used to compare amounts of isotope within the stomach at a given time.

a) Simultaneous study of large liver cubes and paper particles.

b) Simultaneous study of small liver cubes and paper particles.



Large liver cubes
Small liver cubes
Paper particles
* = p < 0.05
** = p < 0.01
% ingested isotope in stomach
100
75
50
25
0
30
60
90
120
Minutes
*
(a)
**
*
**
**
(b)

Large liver cubes 0.58 ± 0.07	Paper particles 0.38 ± 0.11	$p < 0.05$
Small liver cubes 0.73 ± 0.03	Paper particles 0.41 ± 0.05	$p < 0.0025$
$p < 0.05$	NS	

Table 8

Emptying rates (% ingested isotope per minute) of ^{113m}In-labelled liver cubes and ^{99m}Tc-labelled paper particles from 10-120 minutes after meal ingestion in six normal volunteers. Data are means ± SEM, statistical comparisons by paired t tests.

NS = not significant = $p > 0.05$ (one tail) more was emptied when it was given as small rather than large cubes (Fig.12a); comparison of the two measurements made with the paper particles showed highly satisfactory agreement (Fig.12b).

Discussion

These results are consistent with the belief that ingested liver particles are "liquified" in the stomach before being passed through the pylorus. While the number of subjects studied is insufficient to justify detailed mathematical analysis of the emptying curves, the results do show that the liver initially emptied slower and then faster than the paper particles, consistent with the progressive transformation from the solid to a "liquified" form. The fact that the liver emptied more slowly than the paper particles during the first 10 minutes may be attributable to the difference in shape of the two solids - liver cubes as against paper squares - but this explanation remains unproven. However, faster overall emptying of the liver when given as small rather than large cubes, indicates that its "liquifaction" was more rapid with small particles. Ingested particle size is thus an influence on the gastric emptying rate of solid food in man, as in the dog (Hinder & Kelly, 1977; Meyer, Mandiola, Shadchehr & Cohen, 1977).

The present findings differ considerably from the observations described by Guller et al (1977) and there is no obvious methodological explanation for the difference. However, it may be noted that in only one of the 5 patients studied by Guller did gastric emptying of the ingested liver exceed 50% in 3 hours. This suggests that in some unidentified respect, the conditions of study were unusual and that the present results may be more directly relevant to normal gastric function.

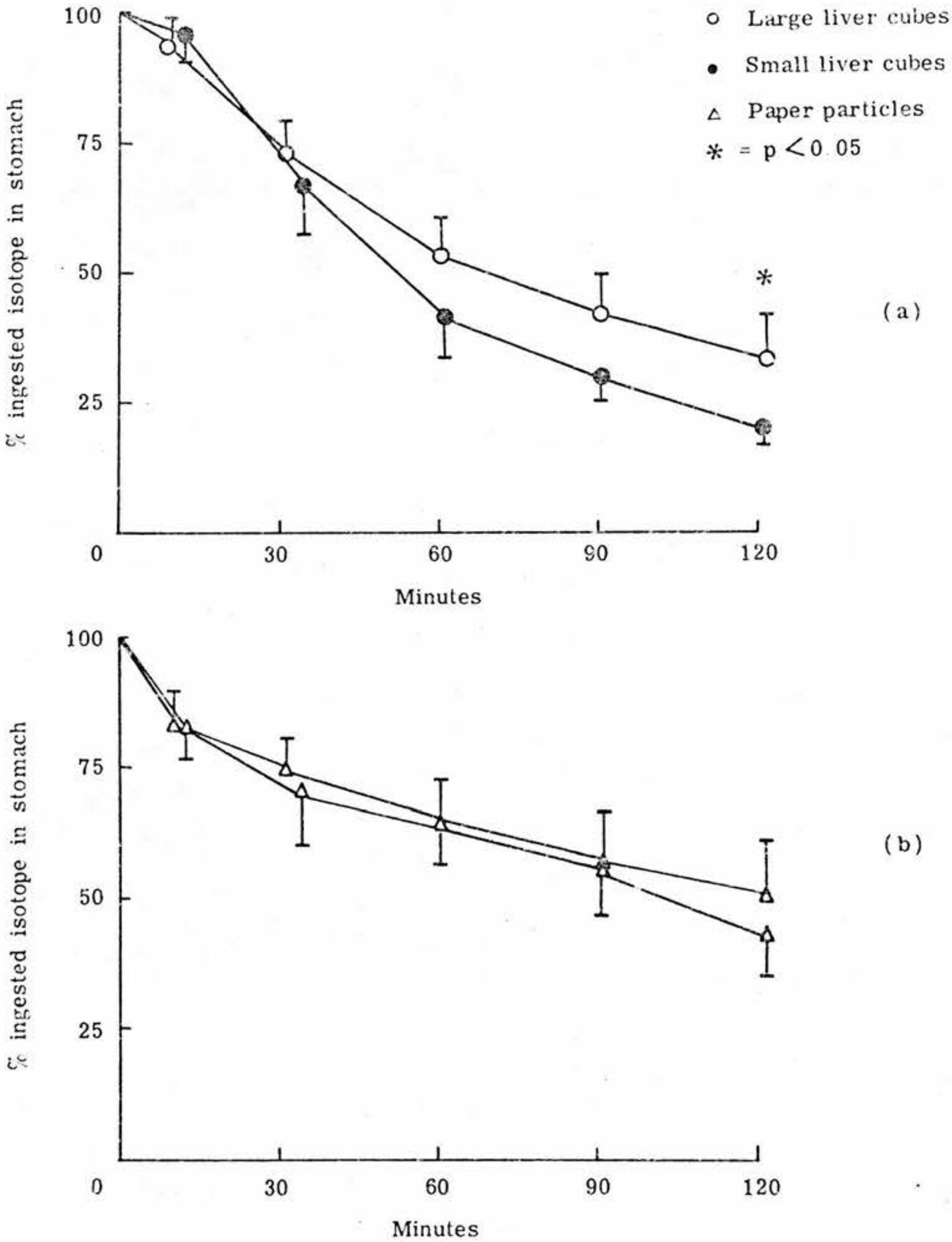
Measurements/

Figure 12

Gastric emptying of ^{113m}In-labelled liver and ^{99m}Tc-labelled paper particles in six normal volunteers. Data are means ± SEM. Paired t tests were used to compare amounts of isotope within the stomach at a given time.

a) Comparison of large and small liver cubes.

b) Comparison of the two studies of paper particles.



o Large liver cubes
• Small liver cubes
△ Paper particles
* = p < 0.05
% ingested isotope in stomach
100
75
50
25
0
30
60
90
120
Minutes
(a)
(b)

Measurements of solid emptying using inert solid particles thus tend to underestimate the emptying rate of solid food, because of the progressive transformation of the latter from solid to liquid form. However, the simultaneous use of the ^{99m}Tc-labelled paper particles and ^{113m}In DTPA would seem to be a reasonable basis for attempts to define the behaviour of solids and liquids in the stomach.

SUMMARY

Gastric emptying of ^{99m}Tc-labelled paper particles was compared with emptying of isotopically-labelled chicken liver in six adult volunteers. The liver tended to empty faster than the particles, and liver fed as small (0.3 cm) cubes emptied faster than liver fed as large (1 cm) cubes. The findings are consistent with the hypothesis that solid foods are ground down and "liquified" by the action of gastric peristalsis before being discharged to the duodenum. Ingested particle size appears to influence the rapidity of this process.

CHAPTER 5

GASTRIC EMPTYING AFTER GASTRIC SURGERY

GASTRIC EMPTYING AFTER GASTRIC SURGERY

The effect of the common gastric operations on gastric emptying has been a subject of continuing interest, earning the attention of many groups of investigators in recent years. The work of Buckler (1967), Madsen & Pedersen (1968), McKelvey (1970), Cowley et al (1972), Wilkinson & Johnston (1973), Hancock et al (1974), Donovan et al (1974), Moberg (1974), Dozois & Kelly (1976), Howlett, Sheiner, Barber, Ward, Perez-Avila & Duthie (1976), MacGregor et al (1977) and Binswanger, Aeberhard, Walther & Vock (1978) is representative.

It seems that a measure of agreement is now emerging in the published reports, following recognition of the fact that earlier conflicting findings were sometimes explained by the difference in emptying patterns of liquids and solids, or by the fact that an emptying rate during the early period after ingestion of a meal may differ from the rate thereafter. Shortly after the development of the double isotope method described in Chapter 3, it was applied to the study of gastric emptying in patients who had undergone gastric surgery. A study of 6 patients with Polya partial gastrectomy was performed first; subsequently an investigation of the effects of vagotomy was undertaken.

Patients and Methods

The double isotope scanning method described in Chapter 3 was used to measure gastric emptying in 10 healthy male volunteers. These subjects formed a control group for comparison with 12 patients with uncomplicated duodenal ulcer and 6 patients who had undergone Polya partial gastrectomy at least six months previously. Studies were then/

then performed in 12 patients who had undergone highly selective (proximal gastric) vagotomy (HSV) and 12 patients who had undergone truncal vagotomy and Heineke Mickulicz pyloroplasty (TV + P). The vagotomy operations had all been performed by one surgeon (Mr. I.B. Macleod) and the emptying measurements were made six months after surgery. Pre and post operative acid secretion data were obtained in 16 of the patients and were consistent with satisfactory vagotomy. These patients were also evaluated clinically and classified according to the Visick (1948) gradings by two assessors working independently. Neither assessor had knowledge of the patient's operation nor of the result of the gastric emptying measurements.

Results

Figure 13 depicts the results obtained in the healthy volunteers and illustrates the differing emptying patterns of the liquid and solid markers. These results are closely similar to those previously observed in a smaller group of control subjects and already shown in Figure 9. In the duodenal ulcer patients (Fig.14) similar emptying patterns were observed, with liquid emptying on average being slightly faster and solid emptying slightly slower than in the normals. The TV + P group (Fig. 15) exhibited greater early emptying (0-10 min.) of both markers than in control subjects although subsequent emptying rates appeared slower. Comparing the HSV group with controls (Fig.16) slightly greater mean emptying of both markers was seen at 10 min., but subsequent emptying rates were almost identical to control rates. The patients with Polya gastrectomies (Fig. 17) showed very rapid early emptying with complete loss of the differentiation between solid and liquid emptying both during the early period and from 10 min. onwards./

Figure 13

Gastric emptying of solid (closed circles) and liquid (open circles) markers in ten normal subjects. Error bars are $\pm$ SEM.

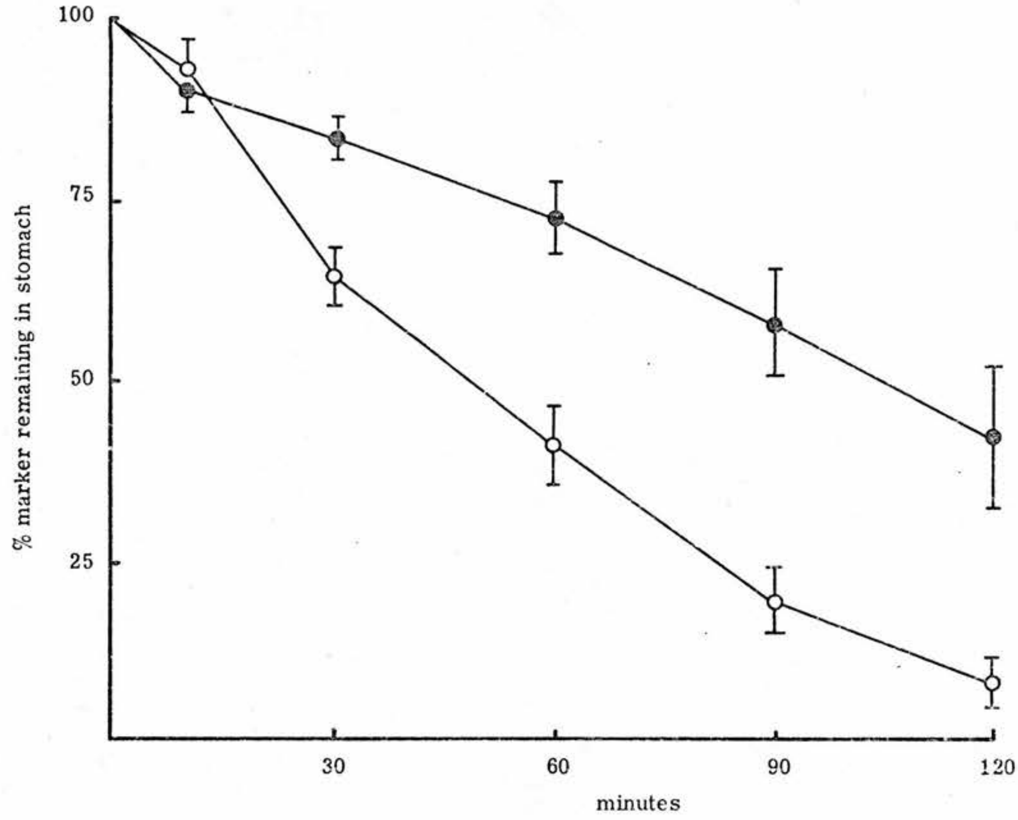
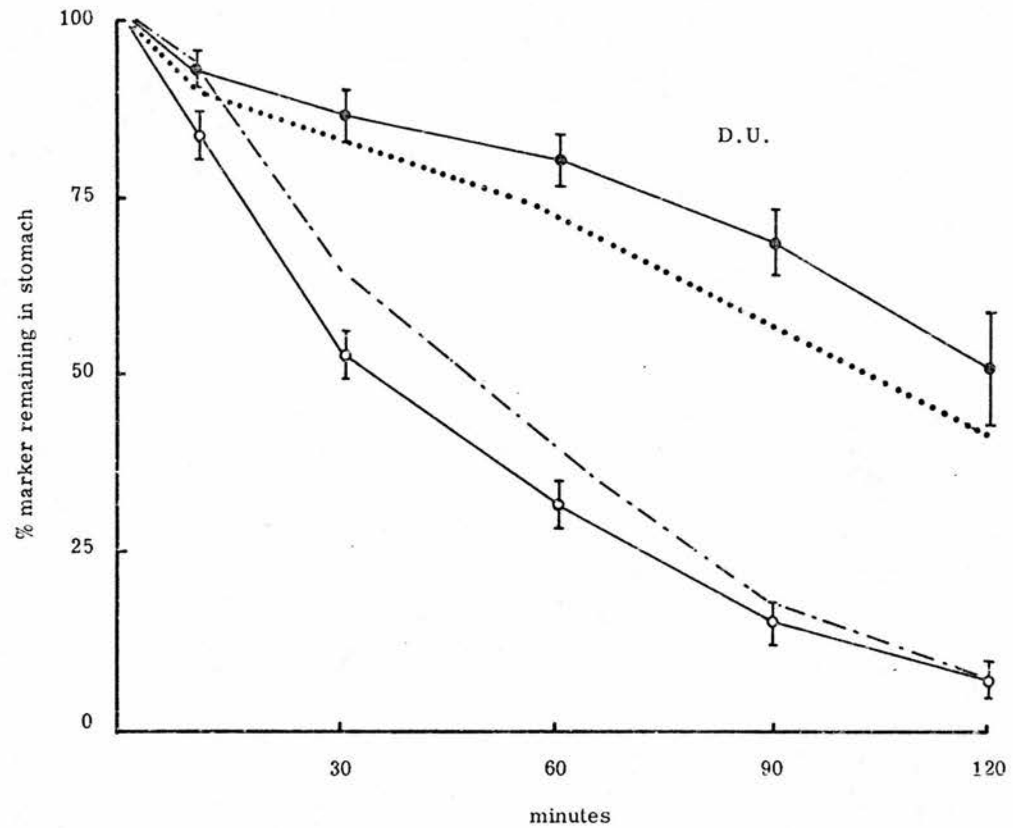

100
75
50
25
% marker remaining in stomach
30
60
90
120
minutes

Figure 14

Gastric emptying of solid (closed circles) and liquid (open circles) markers in twelve duodenal ulcer patients. Error bars are ± SEM. Broken lines represent emptying in normal subjects shown in Figure 13.



D.U.
100
75
50
25
0
% marker remaining in stomach
30
60
90
120
minutes

Figure 15

Gastric emptying in twelve patients with truncal vagotomy and pyloroplasty. Symbols as for Figure 14.

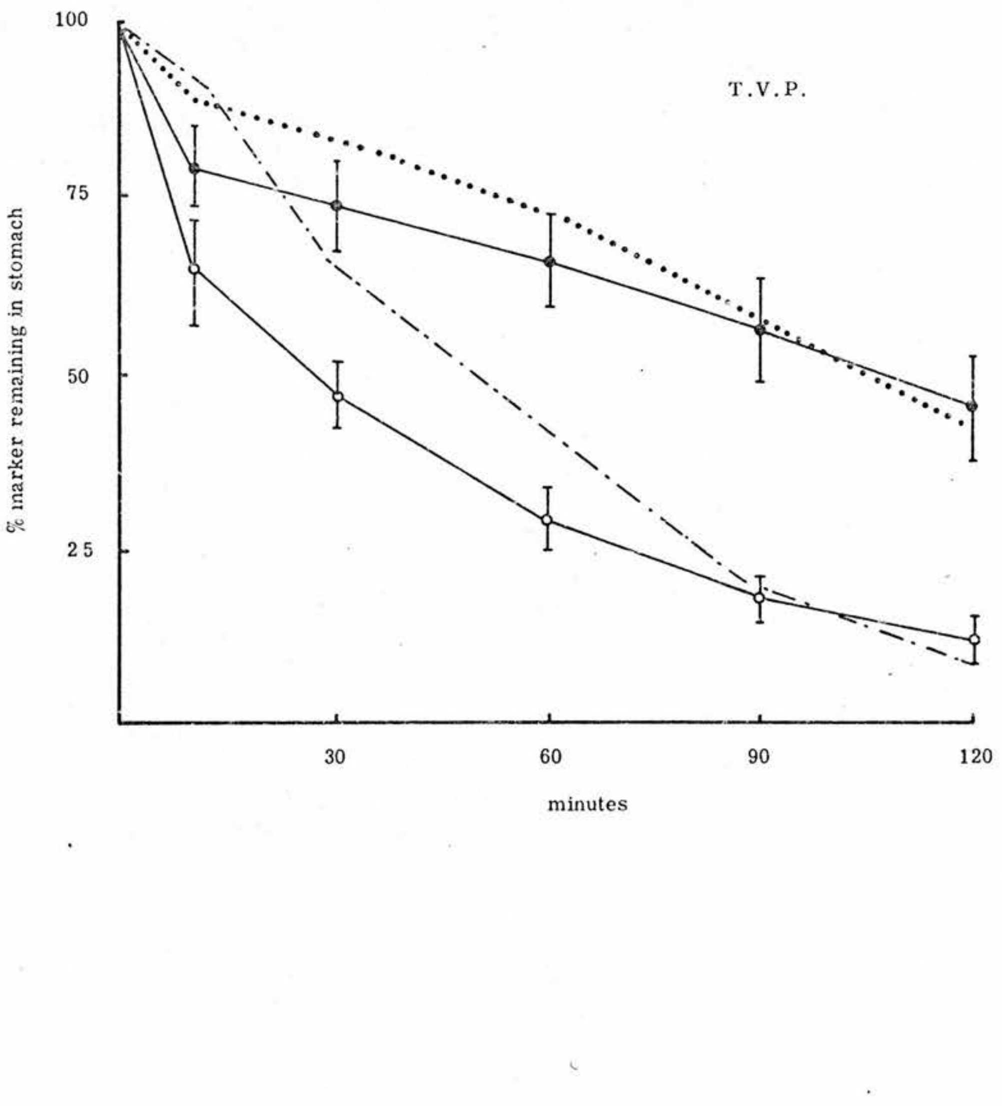

T.V.P.
100
75
50
25
% marker remaining in stomach
30
60
90
120
minutes

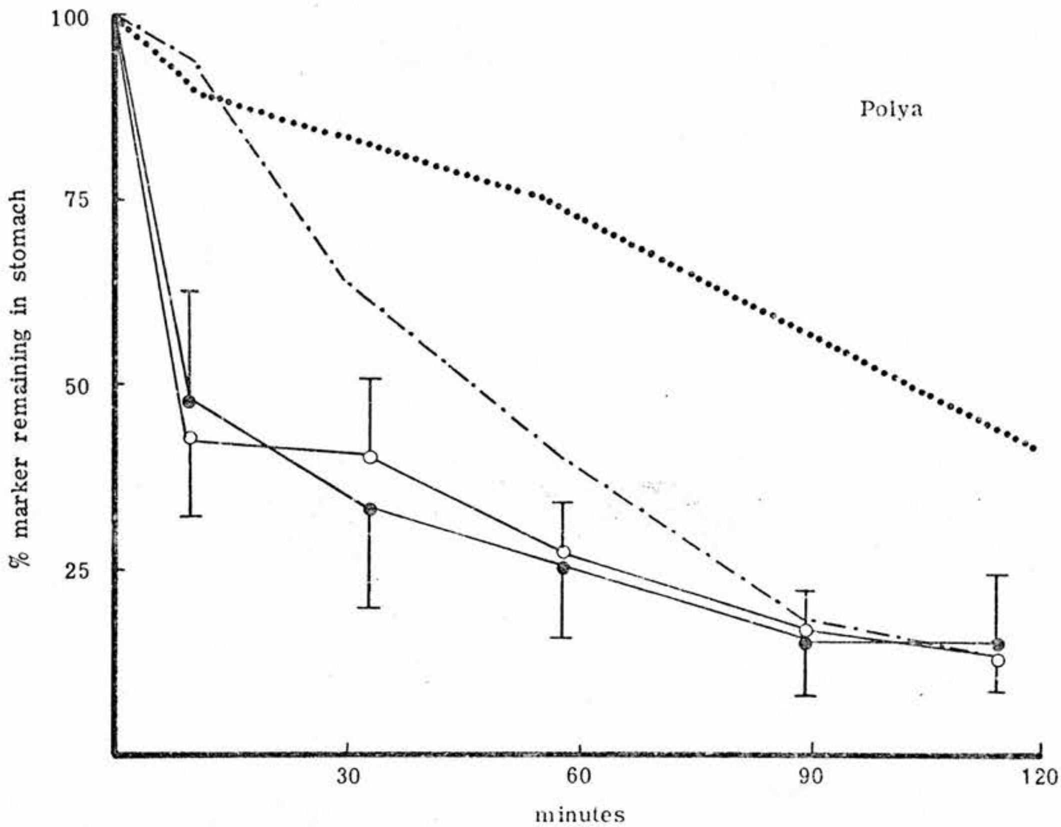
Figure 16

Gastric emptying in twelve patients with highly selective vagotomy. Symbols as for Figure 14.

100
75
50
25
0
% marker remaining in stomach
H.S.V.
30
60
90
120
minutes

Figure 17

Gastric emptying in six patients with a Polya partial gastrectomy. Symbols as for Figure 14.


Polya
100
75
50
25
% marker remaining in stomach
30
60
90
120
minutes

onwards.

Statistical comparisons of the controls with each of the four patient groups were performed using Student's t test in respect of the amounts of marker emptied at 10 min. and the 10-120 min. emptying rates. First order emptying rates were calculated for ^{113m}In and zero order rates for ^{99m}Tc as described in Chapter 3. Significant differences from controls were identified in respect of rapid early emptying of the liquid marker in TV + P patients ($p < 0.05$) and rapid early emptying of both markers in the Polya gastrectomy patients ($p < 0.01$).

The relationship of early emptying to symptoms of diarrhoea and/or post prandial nausea and epigastric fullness in the HSV and TV + P patients is shown in Figure 18. The patients with symptoms were sufficiently affected to warrant classification as Visick grade III or IV in the opinion of the two assessors working independently. A clear association between rapid early emptying and the occurrence of symptoms was identified in the TV + P patients ($p < 0.01$; two sample rank test) but two HSV patients with normal early emptying were also symptomatic.

Figure 19 shows the emptying result recorded from the patient with the greatest incapacity from post operative symptoms, who was classified as Visick grade IV due to post prandial epigastric discomfort and diarrhoea. In addition to very rapid early emptying of both markers, this TV + P patient had lost all solid liquid differentiation. His emptying pattern was therefore similar to that seen in the Polya gastrectomy patients. Clearly this is an atypical pattern for a TV + P patient, implying that TV + P does not normally lead to loss of differential emptying between solids and liquids.

Discussion/

Figure 18

Early gastric emptying of the liquid marker in HSV and TV + P patients with and without post-operative symptoms.

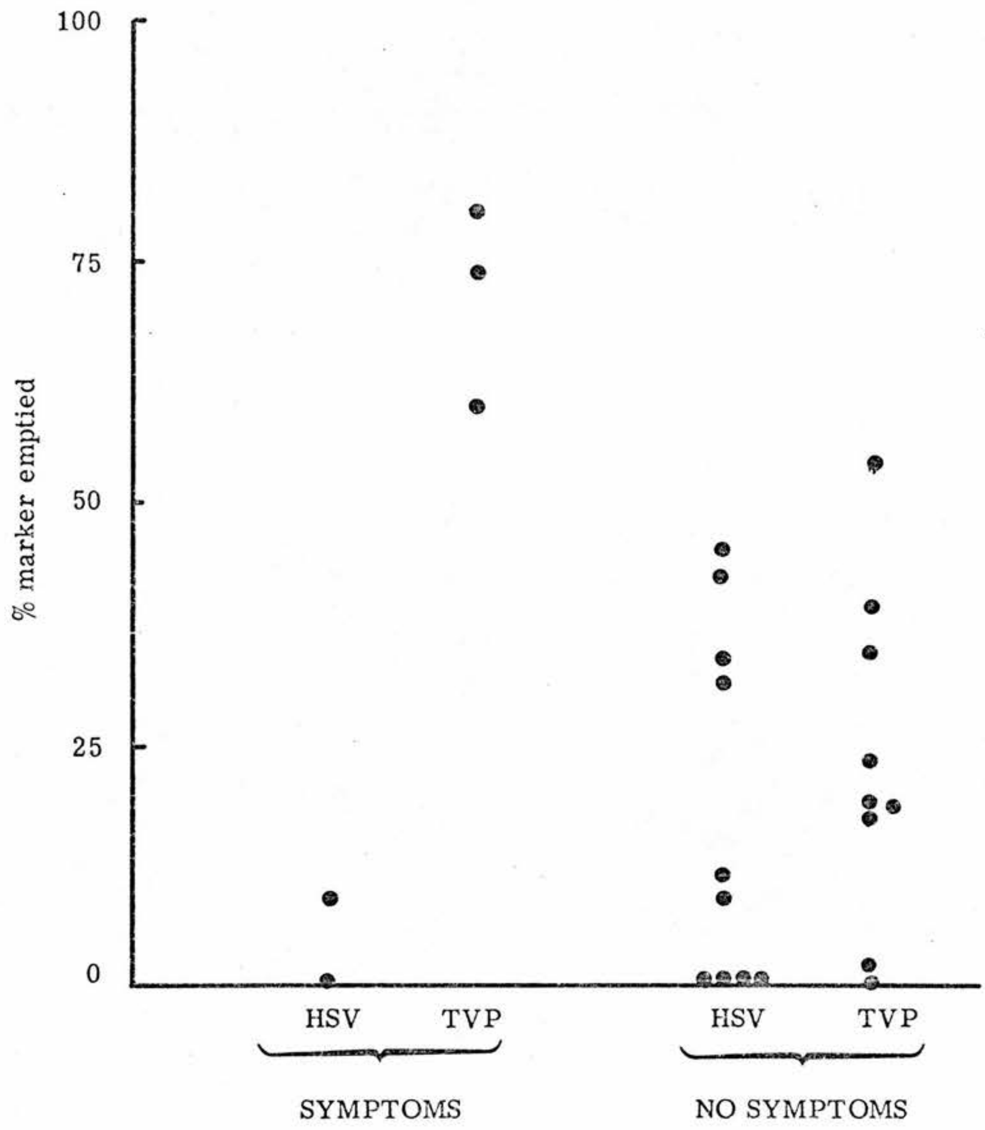
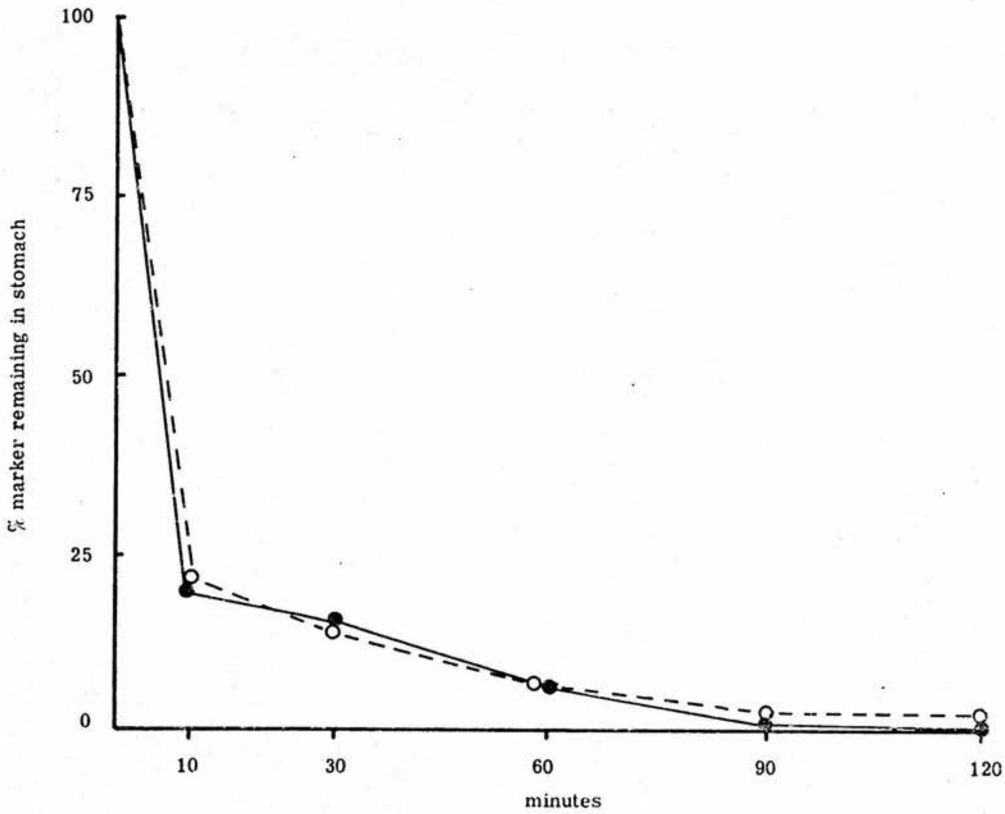

100
75
50
25
0
% marker emptied
HSV
TVP
HSV
TVP
SYMPTOMS
NO SYMPTOMS

Figure 19

Gastric emptying of solid (closed circles) and liquid (open circles) markers in one TV + P patient with severe diarrhoea and post-prandial abdominal discomfort.



100
75
50
25
0
% marker remaining in stomach
10
30
60
90
120
minutes

Discussion

During the past ten years, many studies of the effects of gastric surgery on gastric emptying have been conducted using a variety of test meals and measurement techniques. At first the importance of some of these methodological differences was not fully appreciated, so that apparently conflicting results went unexplained. More recently, adequate appreciation of the importance of distinguishing solid and liquid emptying and of recognising the existence of the early period of emptying have rendered the experimental findings more comprehensible. However, the double isotope scanning method presents a means whereby these aspects of gastric emptying may be studied simultaneously and previously this has not been possible.

Duodenal ulcer

Consideration of the emptying rates and patterns in duodenal ulcer patients is a desirable preliminary to examination of the findings in patients who have undergone gastric surgery, since most of the operations were carried out because of duodenal ulceration. In fact, no statistically significant differences between the patients with duodenal ulcer and the controls were observed. This finding is at variance with the commonly held belief that gastric emptying in duodenal patients is faster than normal (Cooke, 1975) but is nevertheless in line with other recent studies. This subject is discussed in greater detail in Chapter 7.

TV + P

Investigations using liquid test meals have consistently found that TV + P patients exhibit rapid early emptying (Madsen & Pedersen, 1968/

1968; McKelvey, 1970; Hall & Read, 1970; Clarke & Alexander-Williams, 1973; MacGregor, Parent & Meyer, 1977) and there seems to be no doubt that the abnormality is due partly to the vagotomy and partly to the pyloroplasty (Clarke & Alexander-Williams, 1973; Gleysteen, Burdeshaw & Hallenbeck, 1976). In contrast, conflicting results are reported from studies using scintigraphic methods to measure emptying of mixed solid and liquid meals. Colmer et al (1973) observed rapid early emptying in their TV + P patients but no such abnormality was observed in three other studies (Hancock et al, 1974; Howlett et al, 1976; Sheiner, Thompson, Hamilton & Quinlan, 1977). This uncertainty concerning the behaviour of a mixed meal is particularly unsatisfactory because it leaves doubt about whether rapid early emptying occurs when an ordinary meal is ingested under ordinary circumstances. The present results demonstrate clearly that the TV + P group exhibited rapid early emptying of the liquid phase marker whilst early emptying of the solid marker was less obviously accelerated and the difference from normal did not attain statistical significance. Thus rapid early emptying is not a phenomenon restricted to liquid test meals but liquids appear to be more markedly affected than solids.

Between 10 and 120 minutes after ingestion of the meal, emptying of both the solid and liquid markers tended to be slower in the TV + P group than in the controls, although the differences were not statistically significant. However, this slowing was probably real - in a previous study of a larger group of TV + P patients, emptying of the liquid phase marker was significantly slower than in DU patients (Heading, Tothill, McLoughlin & Shearman, 1975). Other published studies have shown delayed emptying rates in TV + P patients in the early months after operation, with the subsequent progressive return towards/

towards normal. The present results are thus in accord with the findings described by others.

A feature of the TV + P results depicted in Figure 15 is the preservation of differential emptying of the two markers. Clearly the discriminating process is not dependent on vagal or pyloric integrity.

Highly Selective Vagotomy

The operation of highly selective vagotomy was developed in the hope that preservation of the vagal innervation of the antrum would obviate the need for a drainage procedure such as pyloroplasty and that a more normal pattern of gastric emptying would result in a reduced likelihood of post operative stasis, dumping and diarrhoea. The present results are consistent with other investigations which suggest that this expectation is justified. The absence of a statistically significant increase in early emptying is in agreement with the findings of Howlett et al (1976) who used a "solid" test meal although rapid early emptying was noted "in some patients" by Guerts, Winkers & Wittebol (1977), also using a mixed solid and liquid meal. In contrast, rapid early emptying has been consistently observed in HSV patients studied with liquid test meals, although the abnormality is less than after TV + P (Clarke & Alexander-Williams, 1973; Donovan et al, 1974; Berger, Ceder, Hamfelt & Meurling, 1976; Faxen, Berger, Kewenter & Kock, 1977). Thus the situation after HSV differs only in degree from that after TV + P. After both operations, rapid early emptying can be demonstrated under appropriate test circumstances.

No abnormality of emptying in the 10 – 120 minute period was found in/

in the HSV patients. This is also in accord with observations reported by others.

Polya partial gastrectomy

The results shown in Figure 17 are strikingly different from those obtained in the other groups of patients. Very rapid early emptying of both the liquid and solid markers indicates that vagotomy is not the only procedure leading to "gastric incontinence" and the complete loss of all differentiation between solid and liquid emptying implies that this differentiation is normally effected by the gastric antrum. These findings have been confirmed by MacGregor et al (1977) and by Kroop, Long, Alavi & Hansell (1979). The latter group noted that the precipitate emptying of solid food from the stomach is only seen when a moderate amount of liquid is ingested at the same time.

Post vagotomy dumping and diarrhoea

The assessment of post operative symptoms, which was confined to the HSV and TV + P groups of patients, is of interest because there has been dispute about the association of such symptoms with rapid early gastric emptying (Colmer et al, 1973; Alexander-Williams, Donovan, Gunn, Brown & Harding, 1973; Howlett et al, 1976; Sheiner et al, 1977; Moir, 1979). The present results support this association in respect of the TV + P patients. Of course there is still uncertainty about the manner in which rapid early emptying might lead to the symptomatology of which the patients complain. However, the present results and the findings of others suggest that there would be merit in searching for pharmacological or surgical means of reducing rapid early emptying as a potential treatment for these symptomatic patients.

The/

The following conclusions may thus be drawn from these studies of post gastric surgery patients.

1. When the reservoir function of the stomach is compromised by vagotomy, loss of the pylorus leads to rapid early gastric emptying. Polya partial gastrectomy also produces rapid early emptying.

2. In TV + P patients there is an association of post operative dumping and/or diarrhoea with rapid gastric early emptying.

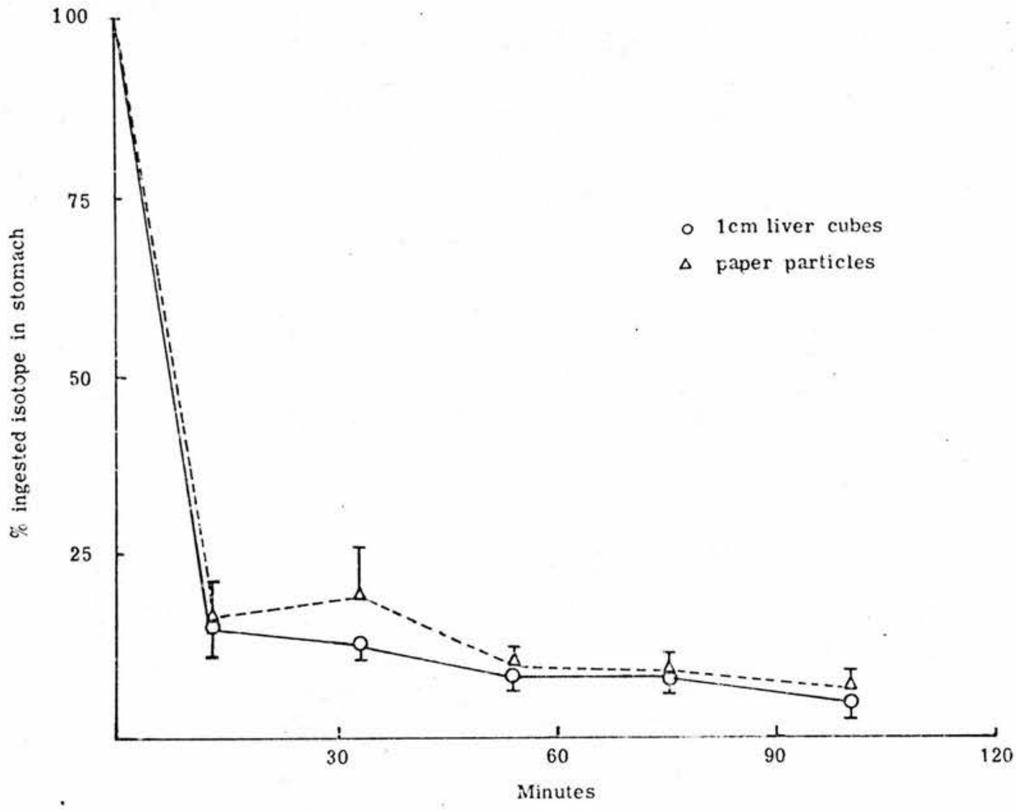
3. The normal differentiation of solid and liquid emptying is probably a function of the antrum. Differentiation is not usually compromised by TV + P but may be impaired in the occasional patient.

Further studies of post gastric surgery patients

The studies of surgical patients described so far have been interpreted on the assumption that emptying of the ^{99m}Tc-labelled particles provides an indication of the behaviour of other solid particles, including food. The observations presented in Chapter 4 provide a substantial justification of this assumption, but relate only to the normal stomach. It therefore seemed desirable to check the behaviour of the ^{99m}Tc-labelled paper particles against that of ^{113m}In-labelled liver in at least one "abnormal" group of patients. The methods were as described in Chapter 4 - the comparison of ^{99m}Tc-labelled paper particles with ^{113m}In-labelled liver cubes (1 x 1 x 1 cm.) being carried out in 6 patients, selected because they suffered diarrhoea thought to be due to their previous gastric surgery. The results are shown in Figure 20 and demonstrate that in these patients the two markers behaved/

Figure 20

Gastric emptying of isotopically labelled liver cubes and Perspex coated paper particles in six patients with diarrhoea due to previous gastric surgery.
Error bars are $\pm$ SEM.


100
75
50
25
% ingested isotope in stomach
30
60
90
120
Minutes
1cm liver cubes
paper particles

behaved identically. The validity of the ^{99m}Tc-labelled particles is thus confirmed in this group, in whom the emptying pattern was notably different from that in normal subjects (cf Figure 11)

Gastric emptying of isotopically labelled liver has been studied in TV + P and partial gastrectomy patients (MacGregor et al 1977) and the findings correspond to the present observations. However, an investigation in which isotopically labelled liver was fed to dogs is of interest, in that although the grinding function of the normal stomach was shown to be impaired by antrectomy, the abnormality was very much greater if reconstruction was effected by end to side gastroduodenostomy than by end to end Billroth 1 type anastomosis (Meyer, Thomson, Cohen, Shadchehr & Mandiola, 1979). Surprisingly, the pattern with Billroth 1 gastrectomy was close to normal, whereas the abnormal pattern seen with the end to side reconstruction was also observed after TV + P. These observations seem inconsistent with the concept that grinding of solid food is an antral function.

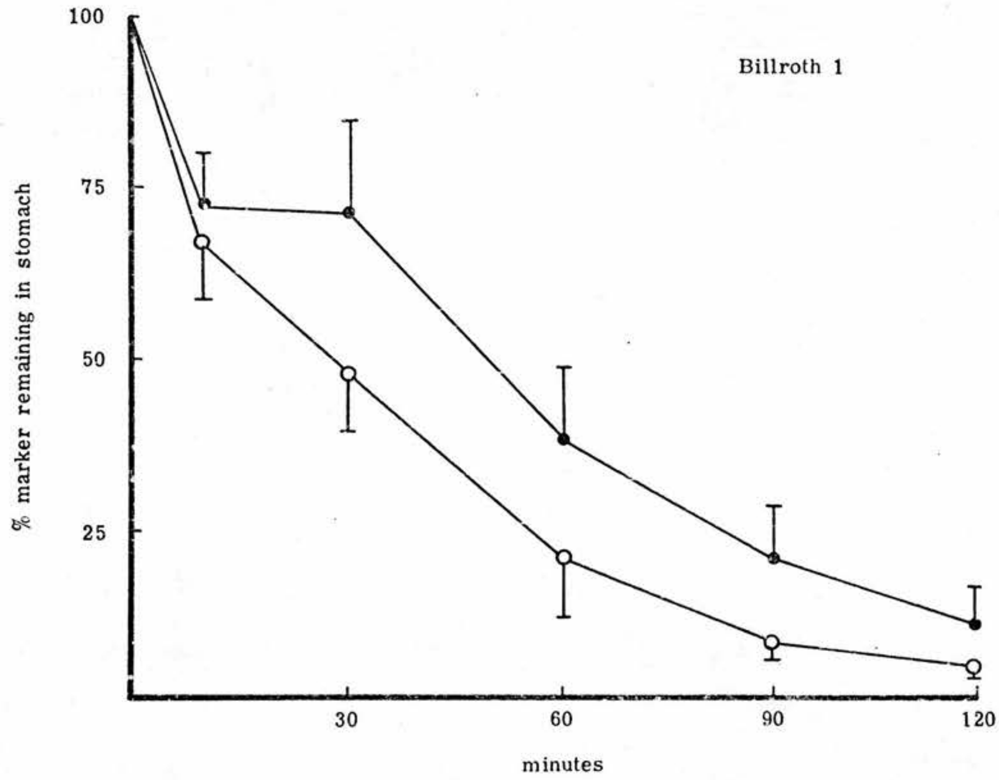
The corresponding comparisons are difficult to make in man, not least because of the possibility that patients who have undergone Billroth 1 gastrectomy may, on average, have undergone a lesser resection than those with a Polya gastrectomy. In the dog studies described by Meyer et al, the antrectomy had been a standardised procedure. Despite this constraint on the interpretation of studies in man, a limited investigation of Billroth 1 gastrectomy patients seemed warranted.

The results obtained from 6 patients with Billroth 1 gastrectomy are shown in Figure 21. Although the overall emptying pattern appears less deranged than that of the Polya patients (Fig. 17) no statistically significant/

Figure 21

Gastric emptying of solid (closed circles) and liquid (open circles) markers in six patients with Billroth 1 partial gastrectomy.

Error bars are ± SEM.



100
75
50
25
Billroth 1
% marker remaining in stomach
30
60
90
120
minutes

significant separation of the two markers occurred. It therefore seems reasonable to maintain that in man, solid-liquid differentiation is an antral function and that the emptying pattern after partial gastrectomy is determined mainly by the resection and not by nature of the reconstruction.

Attempts to minimise rapid early emptying

Evidence linking rapid early emptying with the occurrence of dumping or diarrhoea after gastric surgery raises the possibility that correction of the early emptying abnormality might be an effective approach to treatment of these conditions. The partial success of other measures such as the use of cholestyramine to treat post vagotomy diarrhoea (Allan & Russell, 1977) or a glycoside hydrolase inhibitor to treat dumping (McLoughlin, Buchanan & Alam,1979) is not incompatible with the hypothesis that rapid early emptying is a prime cause of these clinical symdromes and that in consequence, a reduction in this early emptying would be worthwhile. Medical and surgical approaches to the problem are possible.

A medical approach

The primary cause of rapid early emptying in the post vagotomy patient is presumably loss of the adaptive relaxation reflex mediated by the vagus (Jahnberg, 1977). Because the neurotransmitter of the responsible vagal efferent neurones is unknown, there is presently no good basis for suggesting a form of drug therapy that would substitute directly for the loss. However, the possibility of an indirect approach arises with the Ca^{2+} antagonist, nifedipine (Adalat).

Nifedipine interferes with the Ca^{2+} activation of ATP ase mediating smooth/

smooth muscle contraction (Fleckenstein, Grun, Byon, Doring & Tritthart, 1975). Contractile tone in the muscle is thereby reduced. Because of the effects of nifedipine on arteriolar smooth muscle and on the heart, the drug has been widely used in the treatment of angina pectoris but it also affects oesophageal smooth muscle, diminishing the force of peristaltic contraction and reducing lower oesophageal sphincter pressure (Blackwell, Holt & Heading, 1980). The possibility that nifedipine would also cause relaxation of gastric smooth muscle and thus diminish rapid early emptying seemed sufficiently likely to justify a small study. Five control subjects and six patients who had undergone gastric surgery were therefore examined. The latter group comprised patients with truncal vagotomy and pyloroplasty (2), truncal vagotomy and gastroenterostomy (1), Billroth 1 gastrectomy (1) and Polya gastrectomy (1). All had undergone their surgery more than 8 years previously.

The double isotope scanning method was used to measure gastric emptying rates as previously described. Each subject underwent two studies, which were usually carried out on successive days. On one occasion, the subject was given 2 x 10mg nifedipine tablets 20 minutes before the meal and on the other occasion was given two placebo tablets. The order of the two investigations was randomised.

The results are given in Table 9 and show that the administration of nifedipine tablets had no perceptible effect on any aspect of gastric emptying. In particular, the magnitude of early emptying was unaffected in both the control and post surgical patients thus indicating that despite the theoretical possibilities, the drug has no potential as a means of diminishing excessively rapid early emptying in patients with dumping or diarrhoea.

	Control Group (5)				Post-Gastric Surgery Group (6)			
Study	% liquid marker emptied in 10 min.	$T\frac{1}{2}$ liquid marker (min)	% solid marker emptied in 10 min.	% solid marker emptied per min.	% liquid marker emptied in 10 min.	$T\frac{1}{2}$ liquid marker (min)	% solid marker emptied in 10 min.	% solid marker emptied per min
Placebo	11.8 ± 3.1	39.5	6.5 ± 1.8	0.31 ± 0.1	31.4 ± 10.6	42.7	31.3 ± 10.9	0.63 ± 0.17
Nifedipine (20 mg)	15.0 ± 5.8	43.0	9.9 ± 2.8	0.28 ± 0.13	34.8 ± 11.7	46.0	34.4 ± 9.4	0.54 ± 0.13

Table 9

Gastric emptying rates following placebo or nifedipine.

$T_{\frac{1}{2}}$ values are means; other results are means ± SEM.

A surgical approach

A different approach to the problem of rapid early emptying after gastric surgery comes from taking note of the importance of the pyloroplasty in contributing to the magnitude of the abnormality in TV + P patients. Perhaps excessively rapid early emptying could be diminished surgically by refashioning a pyloroplasty or by an analogous reconstruction procedure on the gastrojejunal anastomosis of a Polya gastrectomy. Clearly such reconstructions would call for fine judgement in view of the obvious consequences of narrowing the gastric outlet too much. No formal study of re-operation on symptomatic patients has been conducted as part of the present work, but two cases are worthy of brief comment.

Case 1

A 58-year old man presented with an 18-month history of diarrhoea which had begun two weeks after he had undergone vagotomy and pyloroplasty for a prepyloric gastric ulcer. His diarrhoea consisted of loose bowel motions of variable frequency, but usually occurring three or four times daily. From his point of view, the extreme urgency associated with defaecation was the principal problem. Comprehensive clinical assessment and investigation had identified no abnormality other than the gastric surgery to account for the diarrhoea. He had responded inadequately to medical treatment.

Pyloric reconstruction was therefore carried out by Mr. I.B. Macleod - the pyloroplasty being incised transversely and resewn longitudinally. The patient made an uncomplicated recovery after operation and subsequently suffered bowel symptoms which were much less troublesome. Although some looseness persisted, there was a marked reduction in urgency. Four months after operation the patient was requiring no anti-diarrhoeal/

anti-diarrhoeal medication.

Pre and post operative gastric emptying results are shown in Figure 22. Extremely rapid early emptying occurred pre-operatively; this was reduced after pyloric reconstruction, although it was still much larger than in the average TV + P patient (shown in Fig. 15). However, it seems that the operation was partially successful in reducing the rapid early gastric emptying and that the reduction was associated with amelioration of the patient's diarrhoea.

Case 2

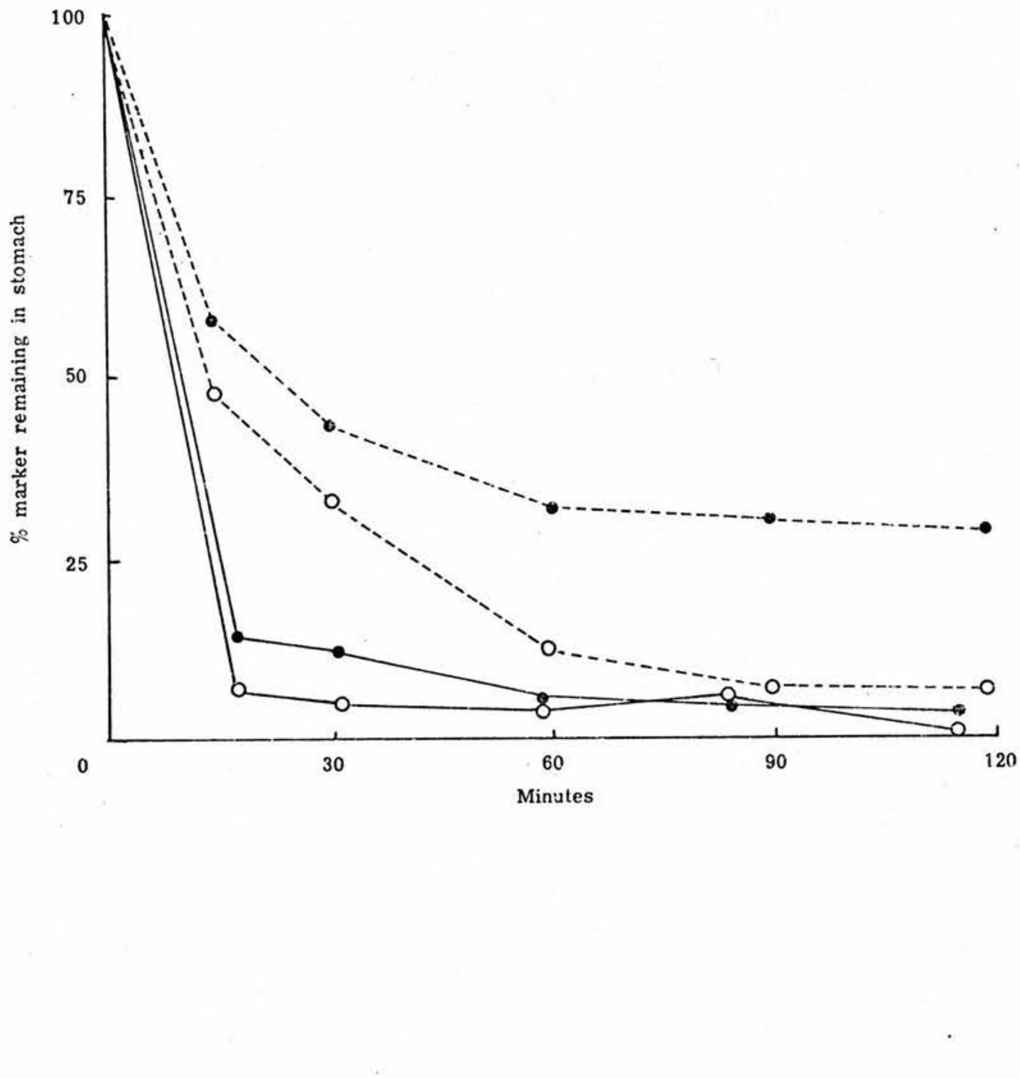
A 52-year old man had suffered diarrhoea and some bile vomiting since vagotomy and pyloroplasty for a duodenal ulcer three years previously. Again, all investigations failed to identify any cause except the previous surgery. The diarrhoea was of sufficient frequency and urgency to prevent him working (he was a bus driver) and had not responded to medical treatment.

Pyloric reconstruction was carried out by Mr. D.C. Carter using a procedure similar to that described for Case 1. There was no subsequent improvement in the patient's symptoms. Gastric emptying studies before and after surgery showed no reduction in the excessively rapid early emptying.

Thus it appears that this type of surgical approach to the correction of rapid early emptying may sometimes be successful, but not always. Further studies are necessary.

Figure 22

Gastric emptying of solid (closed circles) and liquid (open circles) markers in one TV + P patient studied before (solid lines) and after (broken lines) pyloric reconstruction.


100
75
50
25
0
30
60
90
120
Minutes
% marker remaining in stomach

SUMMARY

The double isotope scanning method was used to study gastric emptying in groups of patients who had undergone gastric surgery, in an attempt to define the emptying abnormalities produced by different operations. Accelerated early gastric emptying occurred after partial gastrectomy (Polya or Billroth 1) and after truncal vagotomy and pyloroplasty but was not observed in patients with highly selective vagotomy. Gastric antral function appeared to be the basis for the differential between solid and liquid emptying since differentiation was lost in the patients with partial gastrectomy but was usually preserved after vagotomy and pyloroplasty.

Post operative dumping and/or diarrhoea in the patients with vagotomy and pyloroplasty was associated with extremely rapid early emptying. Retardation of early gastric emptying would seem to be worth pursuing as a basis for treatment of these syndromes.

CHAPTER 6

GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY

GASTRIC EMPTYING IN DIABETIC AUTONOMIC NEUROPATHY

The occurrence of delayed gastric emptying as a complication of diabetes was first described by Rundles (1945) and became more widely recognised when Kassander (1958) introduced the descriptive term gastroparesis diabeticorum. The condition seems to be rare, with a reported incidence of less than 1 in 1,000 diabetics (Zitomer, Gramm & Kozak, 1968) but when it does occur, the symptoms of abdominal distension, nausea and vomiting may cause the patient considerable distress and diabetic control is often difficult to maintain (Campbell & Conway, 1960). The delay in gastric emptying has been attributed to vagal neuropathy, occurring as part of a more generalised autonomic neuropathy. However, Scarpello, Barber, Hague, Cullen & Sladen (1976), using a gamma camera method to study emptying of a mixed solid and liquid meal, could find no difference between control subjects and diabetic patients with or without neuropathy. These observations are at variance with those of earlier investigators who found emptying of liquid meals to be slower in diabetics than in controls. (Dotevall, 1961; Aylett, 1965).

A study of gastric emptying in diabetic patients was therefore initiated. In addition to the measurement of emptying rates in diabetics with and without autonomic neuropathy, an attempt was made in two subjects to assess the value of metoclopramide in the treatment of diabetic gastric stasis.

Methods

Twelve male diabetic patients were studied. Six patients had clinical features of autonomic neuropathy (patients 1-6, Table 10) and were/

Patient No.	Age (years)	Duration of diabetes (years)	Clinical manifestations of autonomic neuropathy					
			Postprandial epigastric fullness and nausea	Postural hypotension	Impotence	Diarrhoea	Sweating * abnormalities	Hypoglycaemic unawareness
1	52	11	+	+	+	+	-	-
2	47	23	-	+	+	-	+	-
3	64	3	+	+	+	-	+	+
4	54	18	-	+	+	-	+	+
5	33	17	+	+	+	+	+	+
6	63	11	-	+	+	-	-	-

* Patients 2, 4 and 5 had reduced sweating in the legs and patient 3 had gustatory sweating.

Table 10 Details of six patients with diabetic autonomic neuropathy.

were all shown to have abnormal cardiovascular reflexes - namely an impaired heart rate response to the Valsalva manoeuvre, an abnormal blood pressure response to sustained hand grip and a postural fall in systolic blood pressure of at least 30mm Hg. These abnormalities constitute objective evidence of autonomic neuropathy (Clarke, Ewing & Campbell, 1979). Patients 1, 3 and 5 had symptoms suggestive of gastric stasis with intermittent nausea and a feeling of fullness after meals, whereas patients 2, 4 and 6 had no gastrointestinal symptoms. The other six diabetic patients (patients 7-12) had no clinical evidence of autonomic neuropathy, had normal cardiovascular reflexes and had no gastrointestinal symptoms. All the diabetic patients were receiving treatment with insulin, apart from patients 2 and 10 who were receiving chlorpropamide; no diabetic was receiving a biguanide. The two groups of diabetics were matched for mean age and duration of diabetes.

One week before the gastric emptying study, all the diabetic patients underwent a conventional barium study of the upper alimentary tract. The radiologist (Dr. T.A.S. Buist) was not told which patients had autonomic neuropathy.

Gastric emptying rates were measured using the meal of cornflakes, sugar and milk containing ^{113m}In DTPA and the ^{99m}Tc-labelled paper particles. Because this study of diabetic patients was carried out while the double isotope method was being developed, some of the measurements of ^{99m}Tc emptying were restricted to the period 30-120 minutes after meal ingestion (See Chapter 3).

The effect of metoclopramide (Maxolon) on gastric emptying was assessed in two diabetics (patients 1 and 5) who were found to have gastric stasis. The third patient with stasis (patient 3) became unwell/

unwell and was not available for further study. Six weeks after the first measurement on patients 1 and 5, the emptying measurements were repeated with intravenous administration of 10mg metoclopramide 5 minutes before meal ingestion. After a further week, the patients started oral metoclopramide 10mg three times daily before meals, which was continued for two weeks. A third emptying study was then performed; on this occasion the patients were given one 10mg metoclopramide tablet 20 minutes before the meal.

Gastric emptying measurements were also performed on 20 non-diabetic patients without known gastrointestinal disease. These formed a control group with which the diabetics could be compared.

Results

The radiological examination revealed abnormal oesophageal motility with prominent tertiary contractions in four of the six diabetics with autonomic neuropathy (patients 1, 2, 4 and 5). However, only one patient (patient 5) was considered to have delayed gastric emptying. No abnormality was noted in the other two patients with autonomic neuropathy, nor in the six diabetic patients without neuropathy.

The gastric emptying half-times for the ^{113m}In marker are shown in Table 11. All six diabetics without autonomic neuropathy had normal emptying rates as did three of the diabetics with autonomic neuropathy. However, the other three (patients 1, 3 and 5) exhibited gastric stasis with emptying half-times greater than 100 minutes. These three patients were the ones in whom gastric stasis had been suspected clinically, although only in patient 5 had delayed emptying been recognised on barium examination.

In/

Patient No.	^{113m}In Emptying $T_{\frac{1}{2}}$ (minutes)
1	106
2	52
3	103
4	51
5	205
6	26
7	52
8	41
9	41
10	42
11	20
12	47
Control range	16-67

Table 11

Gastric emptying half-times ($T_{\frac{1}{2}}$) in diabetic patients with autonomic neuropathy (numbers 1-6), without autonomic neuropathy (numbers 7-12) and in non-diabetic controls.

The control range is explained on page 65.

In the nine diabetic patients without stasis and in the twenty controls, the emptying patterns of the two markers were compared (Fig.23). For the reasons already mentioned and described in full in Chapter 3, this comparison was first made from the second scan onwards and thus the results in Figure 23 begin at approximately 30 minutes after meal ingestion. In the control group, a difference in emptying of the two markers was clearly seen, with the ^{99m}Tc-labelled particles emptying more slowly than the ^{113m}In. In the diabetics, however, the patterns of solid and liquid marker emptying were much more alike and the difference between them was not statistically significant.

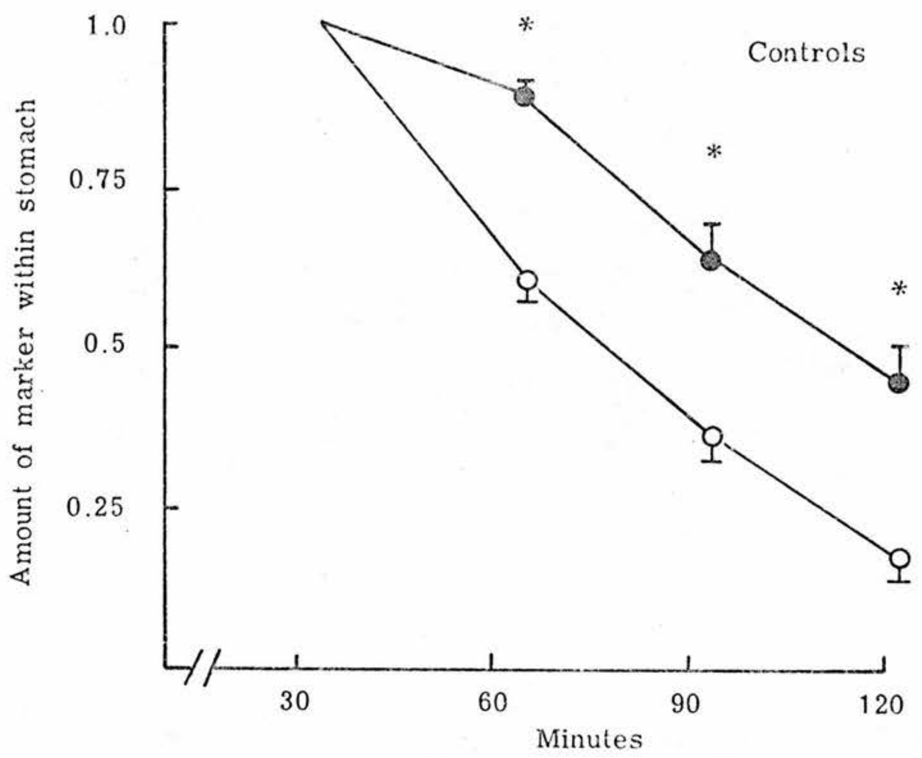
In four of the nine diabetics without stasis (patients 6, 8, 11 and 12) and in six of the controls, measurements were made over the full two hour time period. These results are shown in Figure 24. Differentiation between the two markers was again obvious in the control subjects, whereas it was much less obvious in the diabetics and did not attain statistical significance.

Early emptying of the ^{113m}In was measured in the nine diabetic patients without stasis and in fourteen non-diabetic controls. In both groups, an average of just under 25% of the ingested isotope had emptied from the stomach in approximately 12 minutes. In the three patients with gastric stasis, no measurable emptying occurred during this early period.

The effect of metoclopramide on gastric emptying in the two patients with gastric stasis is summarised in Table 12. Both intravenous and oral administration of the drug restored the emptying half-time of the ^{113m}In to within the control range and emptying of the ^{99m}Tc-labelled particles was also accelerated, apparently to normal. Both patients/

Figure 23

Gastric emptying of solid (closed circles) and liquid (open circles) markers during the period between the second and final scans in nine diabetic and twenty control subjects. The amount of each marker within the stomach at the second scan was arbitrarily defined as 1.0; subsequent points are means $\pm$ SEM. Significant solid-liquid differences are indicated: * = $p < 0.001$ (paired t test).


1.0
0.75
0.5
0.25
Amount of marker within stomach
Controls
*
*
*
30
60
90
120
Minutes

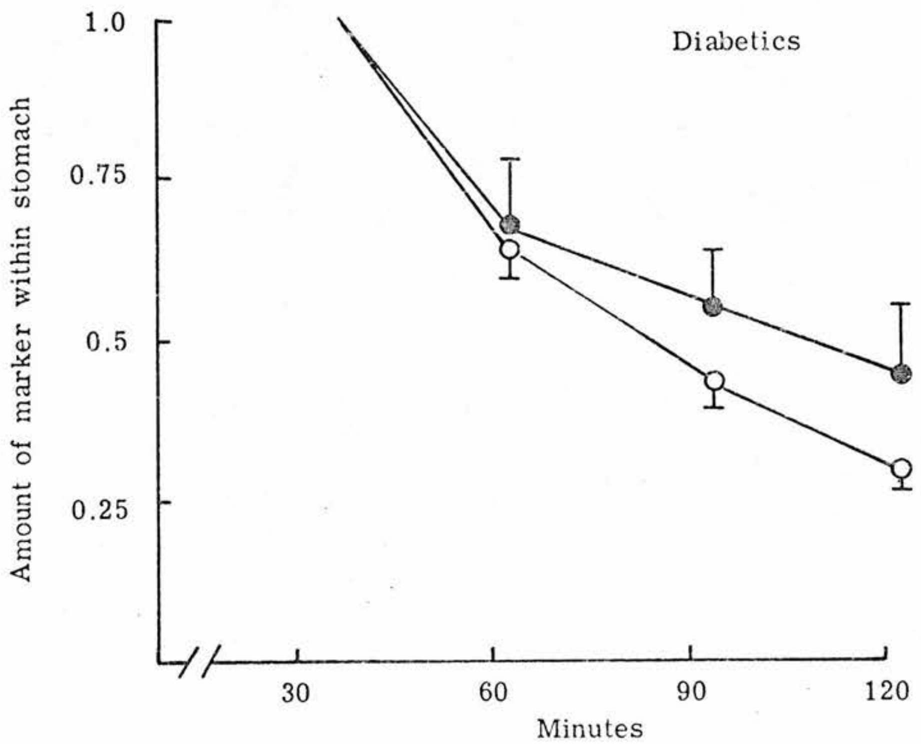
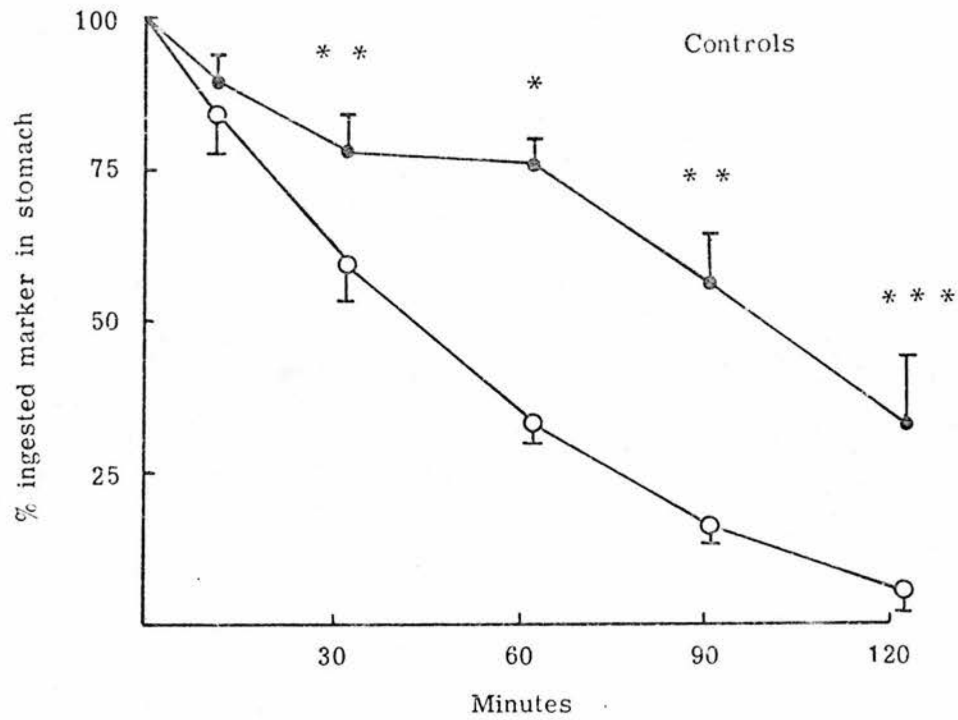
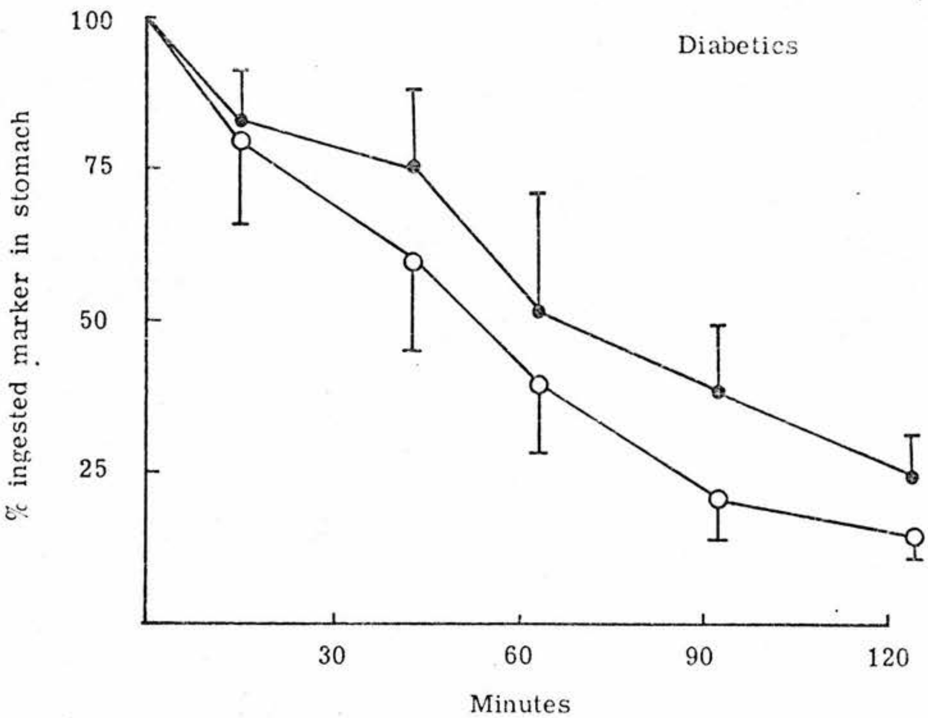

1.0
0.75
0.5
0.25
Amount of marker within stomach
Diabetics
30
60
90
120
Minutes

Figure 24

Gastric emptying of solid (closed circles) and liquid (open circles) markers over the two-hour period in four diabetic and six control subjects. Error bars show 1 SEM. Significant solid-liquid differences are indicated: * = $p < 0.001$, ** = $p < 0.01$, *** = $p < 0.05$ (paired t test).



100
75
50
25
% ingested marker in stomach
Controls
* *
*
* *
* * *
30
60
90
120
Minutes



100
75
50
25
% ingested marker in stomach
Diabetics
30
60
90
120
Minutes

Patient	Emptying $T_{\frac{1}{2}}$ for ^{113m}In (min.)			^{99m}Tc emptied in 2h (% amount ingested)		
	Without metoclopramide	After i/v metoclopramide	After oral metoclopramide	Without metoclopramide	After i/v metoclopramide	After oral metoclopramide
1	106	38	40	0	48	48
5	205	22	46	0	100	60
	Control range 16 - 67 (see page 65)			55 ± 20 (mean $\pm$ SD, n = 12)		

Table 12 Effect of metoclopramide on gastric emptying in two diabetic patients with gastric stasis.

patients reported improvement in their upper abdominal discomfort and nausea during the two-week period of oral metoclopramide therapy.

Discussion

Gastric stasis in diabetic patients is believed to be similar to that seen after vagotomy (Kassander, 1958) and has been attributed to a vagal neuropathy (Wooten & Meriwether, 1961). However, perhaps because of the relative rarity of the condition, it has received little formal study. Conventional radiological examination with barium shows atony and dilatation of the stomach in affected patients, with delayed emptying despite a widely patent pylorus (Zitomer et al, 1968). Such patients may suffer postprandial nausea and upper abdominal distension or, alternatively, may be entirely asymptomatic (Clarke et al, 1979). Although vagal denervation of the stomach is thought to be the basis of the disorder, surgical 'drainage' procedures such as pyloroplasty or antrectomy are thought not to be helpful (Wooten & Meriwether, 1961; Wheelock & Marble, 1971).

Previous studies of gastric emptying in diabetic patients have concluded that emptying in diabetics is slower than normal (Dotevall, 1961; Aylett, 1965). However, liquid test meals were used in these studies and the patients were unselected as regards autonomic neuropathy. The conclusions seem incompatible with the findings of the only substantial study of diabetic patients using a solid meal, in which no abnormality of gastric emptying was observed in patients with or without autonomic neuropathy (Scarpello et al, 1976).

In the present study, in which patients with and without autonomic neuropathy were matched for age, sex and duration of diabetes, gastric stasis was only observed in patients with autonomic neuropathy. As in/

in previous studies of diabetes, radiological abnormalities of oesophageal motility were seen in some patients and were again limited to those with autonomic neuropathy. None of the patients had symptoms of oesophageal dysfunction but in all three patients with symptoms suggesting gastric stasis, delayed gastric emptying was confirmed by the scintigraphic method although it was demonstrable radiologically in only one. This implies that the barium examination is an insensitive approach to the detection of gastric stasis in diabetic patients.

Loss of normal vagal innervation of the proximal stomach may result in accelerated early gastric emptying, as discussed in Chapter 5. Impairment of receptive relaxation in diabetic subjects has been described (Liavig & Tonjum, 1971) but in the present study, there was no evidence of rapid early emptying in any of the diabetic patients. An unexpected finding was the impairment of solid-liquid differentiation in the patients without stasis. This abnormality cannot simply be attributed to loss of vagal integrity, since solid-liquid differentiation is preserved in most patients with truncal vagotomy and pyloroplasty (Chapter 5). The observation in these asymptomatic diabetic patients without gastric stasis therefore implies that they have some abnormality of antral function which is not merely a manifestation of an unrecognised vagal neuropathy. Whatever the explanation, it may be noted that the impairment of solid-liquid differentiation results in an acceleration of solid emptying, particularly during the first 60 minutes after ingestion of the meal. This may account for the discrepancy between the observations of Scarpello et al (1976) made with the solid meal and those of the earlier workers using liquid meals.

The findings in the two patients with gastric stasis who received treatment/

treatment with metoclopramide, suggest that the drug is of considerable potential benefit. There are only three previous reports which refer briefly to the use of metoclopramide in this condition and all agree that the drug is useful (Brownlee & Kroopf, 1974; Berkowitz, Metzger & Sturdevant, 1976; Longstreth, Malagelada & Kelly, 1977). In non-diabetic subjects, metoclopramide is known to increase the strength of gastric contractions and to accelerate emptying (Schulze-Delrieu, 1979). Metoclopramide has also been shown to reduce gastric stasis resulting from surgical vagotomy (Hancock, Bowen-Jones, Dixon, Dymock & Cowley, 1974; Metzger, Cano & Sturdevant, 1976). In the present study, intravenous and oral metoclopramide both restored solid and liquid emptying to that seen in control subjects and both patients noted a reduction of symptoms during the two weeks of therapy. These preliminary results suggested that oral metoclopramide may be helpful in the clinical management of gastric stasis in diabetic patients.

Further studies with metoclopramide

The possibility that metoclopramide might provide effective therapy for gastric stasis in diabetic patients seemed to be of sufficient practical importance to merit further attention. A double blind crossover trial of metoclopramide and placebo was therefore undertaken in six further patients with autonomic neuropathy, selected because they suffered gastrointestinal symptoms thought to be due to their autonomic neuropathy. Five of the six had been reported as showing delayed gastric emptying on barium meal examinations performed during the previous three months.

Gastric emptying measurements were performed as for the initial study of diabetic patients, except that emptying of both markers was measured from the time of meal ingestion in all patients. Emptying measurements were performed at the time of entry to the trial, after six weeks on placebo (one tablet three times daily) and after six weeks on metoclopramide (1 x 10mg tablet three times daily). The periods of placebo and metoclopramide treatment were consecutive, the order being randomised, and the patients took their medication as usual on the days of the gastric emptying measurements. Throughout the study, the subjects assessed their own symptoms of nausea and vomiting, each being graded on a 0-5 scale of increasing severity. Symptoms were recorded daily for two weeks before entry to the study and daily during the periods of treatment.

Results

Gastric emptying half-times for the ^{113m}In marker in the meal are given in Table 13. Only two of the six patients (patients A and E) exhibited gastric stasis at the time of entry to the study. Emptying in/

Patient	Gastric emptying $T_{\frac{1}{2}}$ for ^{113m}In (min.)			^{99m}Tc emptied in 2h (% amount ingested)		
	before assessment	on placebo	on metoclopramide	before treatment	on placebo	on metoclopramide
A	96	35	45	62	26	68
B	49	48	42	20	3	14
C	34	36	42	65	73	36
D	41	33	34	34	89	37
E	149	52	46	24	3	2
F	61	48	50	25	11	23

Controls 16 - 67 (see page 65)

Controls - 55 $\pm$ 20 (mean $\pm$ SD, n = 12)

Table 13 Effect of metoclopramide therapy on gastric emptying in six diabetic subjects with gastrointestinal symptoms thought to be due to autonomic neuropathy.

in the other four patients was within the control range as defined on page 65. However, all six patients exhibited normal ^{113m}In emptying at the end of their periods of treatment with placebo and with metoclopramide. There was no evidence that the emptying rate during metoclopramide therapy was different from that on placebo, so that no claim that metoclopramide accelerated gastric emptying could be made.

The measurement of ^{99m}Tc-labelled particle emptying likewise showed no evidence of an acceleration during the period of treatment with the active drug (Table 13). None of the patients showed abnormal delay of ^{99m}Tc emptying in all three studies (defining abnormal as lying outside the range mean $\pm$ 2SD in controls), but patients B and E did so on two of the three occasions and patient F on one occasion.

Despite the apparent lack of effect on emptying, the patients' own assessments of therapy were of interest. Two suffered no nausea or vomiting immediately before or at any time during the trial (patients E and F) although both had done so previously. The other four patients all scored their symptoms as being reduced or abolished on metoclopramide in comparison with pre-treatment or on placebo therapy. On being asked specifically whether they preferred the first or second of their trial medications, five patients indicated a definite preference for the period of metoclopramide treatment and the sixth declared a marginal preference for it.

Discussion

This study of metoclopramide was undertaken in an attempt to evaluate its possible use in diabetic patients with gastric stasis. However, since the results show that none of the patients exhibited delayed gastric emptying consistently, no judgement about the effect of the/

the drug in diabetic gastric stasis can be made. It is of interest that the patients' symptoms did not provide a good guide to the presence of stasis. Although this is contrary to the impression gained from the study of the initial twelve patients, most previous investigations have concluded that delayed gastric emptying and the presence of symptoms correlate poorly.

Day to day and month to month variation in symptoms is well recognised in patients with diabetic gastric stasis (Feldman & Fordtran, 1978), and the present results suggest that similar variation occurs in the gastric stasis itself. Such variation presents obvious difficulties for studies of drug treatment of the disorder. However, there is perhaps a particular problem with this group of patients that is relevant to the design of future studies - namely the possible duration of the so-called "carry over" effect of the active drug. If the occurrence of gastric stasis in individual diabetic patients is variable, it is possible that therapy which successfully treats the condition may be followed by a period of time during which emptying may be normal without the patient receiving any therapy whatsoever. Thus in a crossover trial, the state of affairs during a period of placebo therapy which follows active treatment may differ from that during placebo therapy which precedes active treatment. However, if a crossover study is conducted such that demonstrable gastric stasis is a condition of entry and the period of placebo treatment then precedes active treatment in all cases, an inherent bias in favour of the active treatment is created. Thus it would seem that a satisfactory trial of treatment for gastric stasis in diabetic patients requires a straightforward, non-crossover comparison of placebo and active treatment. Unfortunately, such a design would require a greater number/

number of patients with this relatively rare disorder.

A further aspect of the present study which merits a brief comment is the consistent patient preference for the active drug compared with the placebo. It is possible that this merely reflects the central anti-emetic effect of metoclopramide. Nevertheless, since the investigation was undertaken to assess the effect of the drug in this group of patients, it should be noted that they were unanimously of the opinion that it was beneficial. The dissociation already noted between the presence of symptoms and the existence of gastric stasis should not detract from the simple and clinically relevant observation that all the patients felt better on the active medication.

SUMMARY

The double isotope scanning method was used to study gastric emptying in diabetic patients with and without autonomic neuropathy. In the initial investigation, three of six patients with autonomic neuropathy were found to have gastric stasis, though this had been detected by barium examination in only one. The differentiation between solid and liquid emptying appeared to be reduced in the diabetic patients without gastric stasis, suggesting an abnormality of antral function which cannot be explained by vagal denervation alone.

In a subsequent study of metoclopramide therapy in diabetic patients, symptoms were found to be a poor guide to the presence of gastric stasis. Stasis itself was variable and the gastric emptying patterns showed no consistent change after 6 weeks of metoclopramide administration. Despite this, all the patients claimed symptom relief, implying that the benefits of metoclopramide must be attributed to something other than its action on gastric motility.

CHAPTER 7

EFFECTS OF HISTAMINE H_2 RECEPTOR BLOCKADE ON GASTRIC EMPTYING

EFFECTS OF HISTAMINE H_2 RECEPTOR BLOCKADE ON GASTRIC EMPTYING

Metiamide was the first histamine H_2 antagonist to become available for comprehensive study in man and in due course, evidence of its efficacy as an inhibitor of gastric acid secretion and as an ulcer healing agent came from many investigators (Editorial, Lancet, 1974; Multicentre trial, 1975). During the initial evaluation of the drug for human use, it seemed desirable that a study of its effect on gastric emptying should be undertaken. An earlier histamine H_2 antagonist - burimamide - had been found to inhibit gastric contractions in the rat (Ridley, Groves, Schlosser & Massenberg, 1973) and although no such effect was produced by metiamide in these animals, the possibility that metiamide might inhibit gastric contractility in man had obvious relevance to its anticipated use in patients with peptic ulcer. A study of the effect of metiamide on gastric emptying in duodenal ulcer patients was therefore undertaken.

The study was performed in 24 patients (20 males and 4 females, mean age 44 years, range 19-69 years) divided into three groups. All patients had radiologically proven duodenal ulcers without evidence of pyloric stenosis, and patients who had undergone previous surgery or who were taking drugs likely to influence gastrointestinal motility were excluded. Gastric emptying rates were measured using the meal of cornflakes, sugar and milk labelled with ^{113m}In DTPA. Only the emptying half-times were determined. Two measurements were undertaken on successive days, one being preceded by the administration of metiamide.

A pilot study was undertaken on six patients, primarily to establish the/

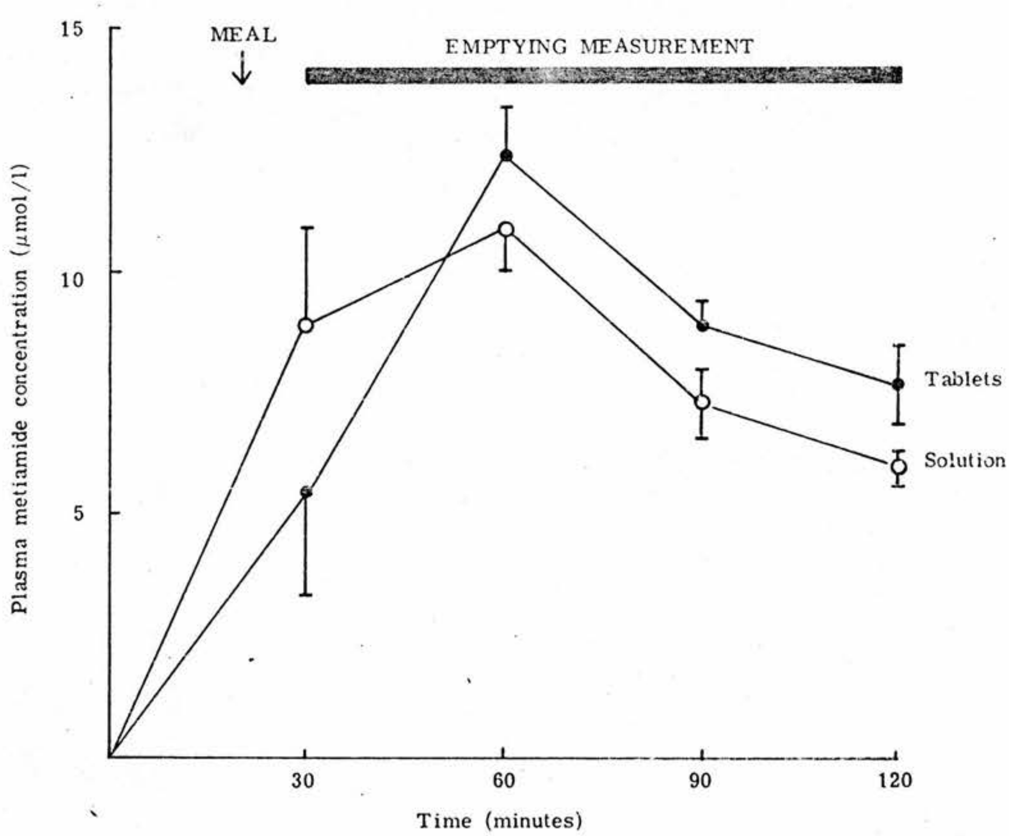
the time of absorption of the drug in relation to the emptying measurement. The control test was carried out on the first day without prior administration of placebo. On the following day, 400mg metiamide (4 x 100mg tablets) labelled with tritium (0.25 μCi/mg) were given with 40ml water 20 minutes before the meal. Venous blood samples were taken at intervals after administration of the metiamide to assess its absorption. ^3H metiamide concentrations in plasma were determined by liquid scintillation counting after octanol extraction (Hesselbo, 1973) and converted to plasma metiamide concentrations on the basis of the known specific radioactivity of the administered drug.

The plasma metiamide concentrations in this group of patients are shown in Figure 25. The concentration peaked approximately 60 minutes after tablet ingestion and the gastric emptying measurements were performed approximately 30-120 minutes after tablet ingestion. Gastric emptying was therefore assessed while the mean plasma metiamide concentrations were not less than 5μmol/l. Acid secretion studies indicate that these levels achieve effective histamine H_2 blockade (Carter, Forrest, Werner, Heading, Park & Shearman, 1974; Richardson, Bailey, Walsh & Fordtran, 1975).

The gastric emptying results in the pilot group are shown in Table 14. There is no statistically significant difference between the control and metiamide results but the trend towards slower emptying with metiamide was considered sufficient to justify a more controlled investigation. However, before performing a fully controlled study, a further six patients were studied using metiamide solution instead of tablets to exclude the possibility that the trend seen in the pilot group was due to a constituent of the metiamide tablets other than metiamide/

Figure 25

Plasma metiamide concentrations in six duodenal ulcer patients given metiamide as 4 x 100mg tablets and six patients given 400mg metiamide in solution. Values are means $\pm$ SEM.



15
10
5
MEAL
EMPTYING MEASUREMENT
Plasma metiamide concentration (μmol/l)
Tablets
Solution
30
60
90
120
Time (minutes)

	Patient No.	Control	Metiamide	Difference	P *
Pilot group	1	20	32	+ 12	
	2	70	104	+ 34	
	3	40	67	+ 27	
	4	21	51	+ 30	> 0.05
	5	29	24	- 5	
	6	85	58	- 27	
Group 1	1	36	59	+ 23	
	2	40	51	+ 11	
	3	54	51	- 3	< 0.05
	4	26	34	+ 8	
	5	85	91	+ 6	
	6	43	136	+ 93	
Group 2	1	27	26	- 1	
	2	29	33	+ 4	
	3	24	38	+ 14	
	4	86	80	- 6	
	5	43	67	+ 24	
	6	29	39	+ 10	< 0.05
	7	38	41	+ 3	
	8	44	62	+ 18	
	9	38	30	- 8	
	10	54	64	+ 10	
	11	56	66	+ 10	
	12	28	35	+ 7	

Table 14 Effect of metiamide (400mg) on gastric emptying half-times (min) in duodenal ulcer patients.

* Significance of differences using the signed ranks test (one tail).

metiamide itself. The tablets were known to contain a small quantity (approximately 10mg) of potassium stearate. Thus in six further patients (designated Group 1) 400mg ^3H metiamide was given in 40 ml saline (30 mmol/l NaCl) or 40ml saline was given alone. The order of administration of metiamide solution or saline was randomised, but the procedures were otherwise identical to those used in the pilot study.

The plasma metiamide levels in these Group 1 patients were similar to the levels seen after tablet administration (Fig. 25). However, in these patients, gastric emptying was significantly slower after metiamide than placebo (Table 14). Thus a controlled assessment of the effect of metiamide tablets on gastric emptying was required and appropriate placebo tablets were prepared.

Two gastric emptying tests were carried out on a further group of twelve duodenal ulcer patients (designated Group 2). On one occasion, the patients received 4 x 100mg metiamide tablets, and on the other occasion were given 4 placebo tablets. The order of administration was randomised. The placebo and active tablets had an identical appearance and, apart from the content of metiamide, had the same composition. No blood samples were taken from these patients.

The gastric emptying results in the Group 2 patients are also shown in Table 14. Emptying rates were slower with metiamide than with placebo in nine of the twelve patients, a difference which was statistically significant at the 5% level.

Thus gastric emptying was apparently slowed by metiamide. The magnitude/

magnitude of the effect was small, with an average increase in emptying half-time of only 7 minutes and it seemed unlikely that this could have any clinical importance. Nevertheless, why should metiamide slow emptying at all? Apart from the possibility of a primary action of the drug on gastric motility, secondary effects might arise as a consequence of the suppression of gastric secretion. However, a suppression of acid output might be expected to accelerate rather than retard the emptying rate, since intraduodenal acid is a well recognised inhibitor of emptying (Cooke, 1975). Gastric emptying is known to be slowed by gastrin (Hunt & Ramsbottom, 1967) and in a series of experiments performed in parallel with the present study of gastric emptying, metiamide was found to enhance the serum gastrin response to food (Forrest, Heading, Park, Carter, Lennon, Lidgard et al, 1976). However, since the studies of gastric emptying and gastrin response to food were performed in different subjects, the relationship between emptying rate changes and changes in gastrin response to food could not be assessed. Attention was directed to the possibility of a relationship in subsequent work with cimetidine.

CIMETIDINE

The development of agranulocytosis in two patients undergoing treatment with metiamide (Forrest, Shearman, Spence & Celestin, 1975) led to cessation of all clinical trials. Shortly afterwards, clinical evaluation of the related compound, cimetidine, began. In view of the observations already made with metiamide, an investigation of the effect of cimetidine on gastric emptying was undertaken as part of this evaluation.

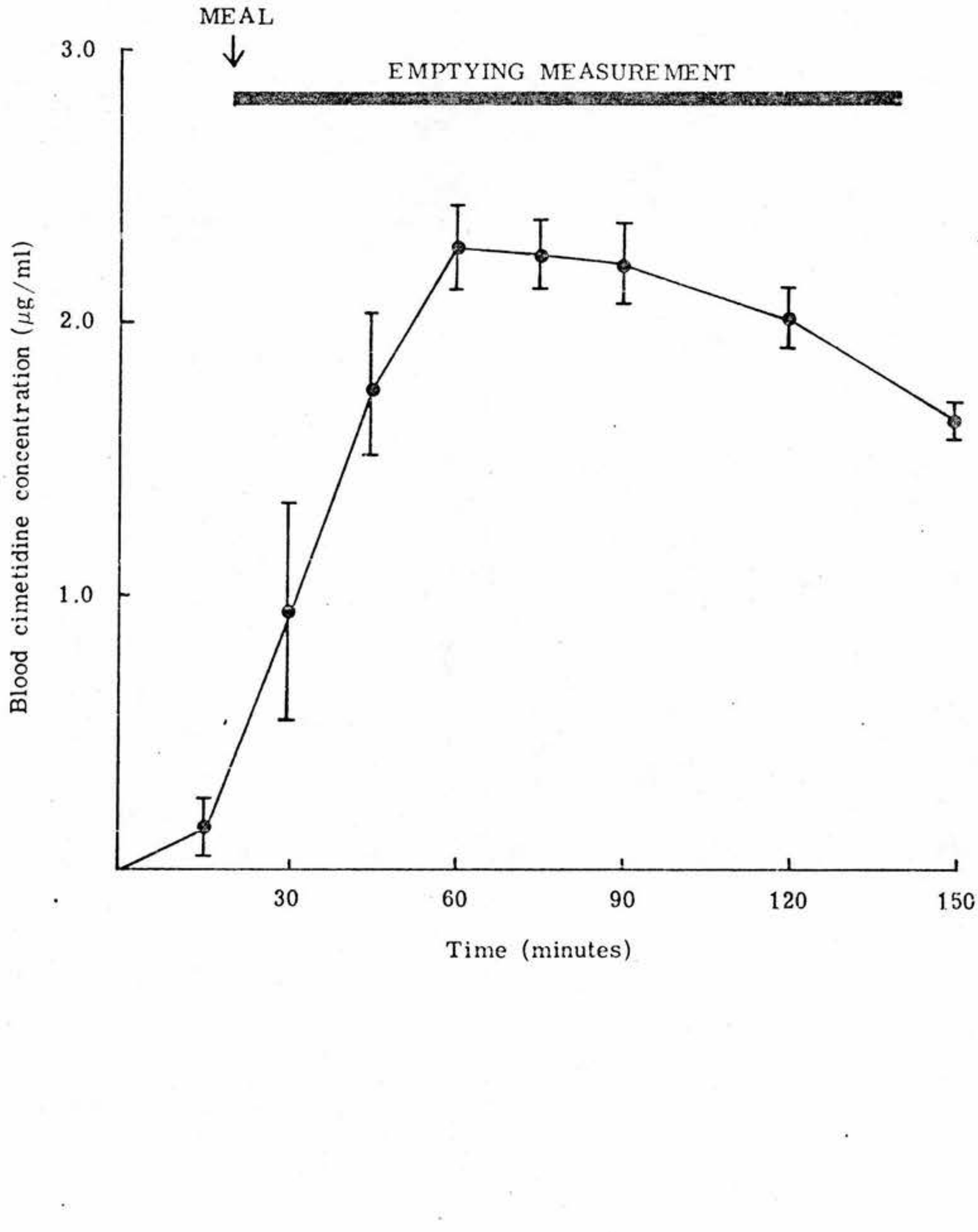
Gastric emptying rates were measured on two occasions in ten healthy male volunteers (age range 25-35) using the double isotope method described in Chapter 3. On one occasion, 400mg cimetidine (2 x 200mg tablets) were given with 40ml water 20 minutes before the meal; on the other occasion, the subjects were given two placebo tablets with the same volume of water. The order of administration was randomised. In nine of the ten subjects, serial venous blood samples were taken up to 180 minutes after administration of the drug, for determination of blood cimetidine and serus gastrin concentrations. The blood cimetidine levels were measured by courtesy of Smith, Kline & French Laboratories Ltd., the serum gastrin concentrations by courtesy of Dr. G.P. Lidgard, Regional Hormone Laboratory, Edinburgh.

The mean blood cimetidine concentrations after ingestion of the drug are shown in Figure 26. During the period of the emptying measurement, the mean concentrations ranged from approximately 0.4 µg/l at the time of meal ingestion to approximately 2.3 µg/l 40 minutes later. These levels are sufficient to produce substantial histamine H_2 receptor blockade (Richardson, Walsh & Hicks, 1976; Carter, Forrest, Logan/

Figure 26

Whole blood cimetidine concentrations after administration of 2 x 200 mg cimetidine tablets to ten healthy volunteers.

Values are means ± SEM.



MEAL
EMPTYING MEASUREMENT
3.0
2.0
1.0
Blood cimetidine concentration (μg/ml)
30
60
90
120
150
Time (minutes)

Logan, Ansell, Lidgard, Heading et al, 1976).

The overall emptying patterns for the ^{113m}In and ^{99m}Tc markers in the meal are shown in Figure 27. Paired statistical analyses of the individual emptying rates revealed no statistically significant differences between the cimetidine and placebo tests for either marker. However, the mean emptying rate of the ^{99m}Tc-labelled particles was slightly faster with cimetidine (0.54) than with placebo (0.45% min^{-1}).

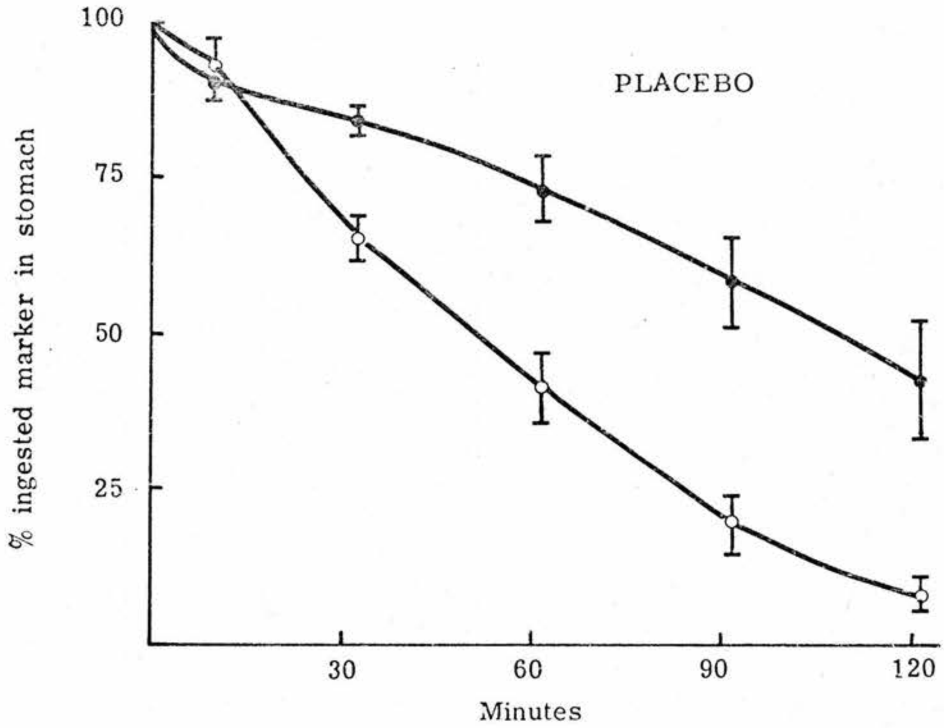
The effect of cimetidine on the serum gastrin response to the meal is shown in Figure 28. Because the absolute concentrations were not normally distributed, the values were normalised by expressing each gastrin concentration as a percentage of the corresponding basal level observed on the day of the cimetidine study. Comparison of serum gastrin responses to the meal following cimetidine and placebo demonstrated no differences in the first 70 minutes after the meal, but thereafter, greater increases occurred with cimetidine. The individual values for the integrated gastrin response (IGR) during the period of the emptying measurement were also greater with cimetidine than with placebo ($p < 0.01$; paired t test). However, comparison of the individual placebo-cimetidine differences in IGR with the corresponding differences in solid or liquid marker emptying rates revealed no apparent relationships. Thus individual changes in emptying rates could not be attributed to changes in the gastrin response to food.

Discussion

Why should cimetidine not affect gastric emptying when metiamide appeared to do so? Both drugs were given in doses sufficient to produce substantial suppression of gastric acid secretion and thus any modifications of normal physiological responses to food caused by this suppression/

Figure 27

Gastric emptying of solid (closed circles) and liquid (open circles) markers in ten healthy volunteers given cimetidine (400mg) or placebo tablets 20 minutes before the test meal. Values are means ± SEM.


PLACEBO
% ingested marker in stomach
100
75
50
25
30
60
90
120
Minutes

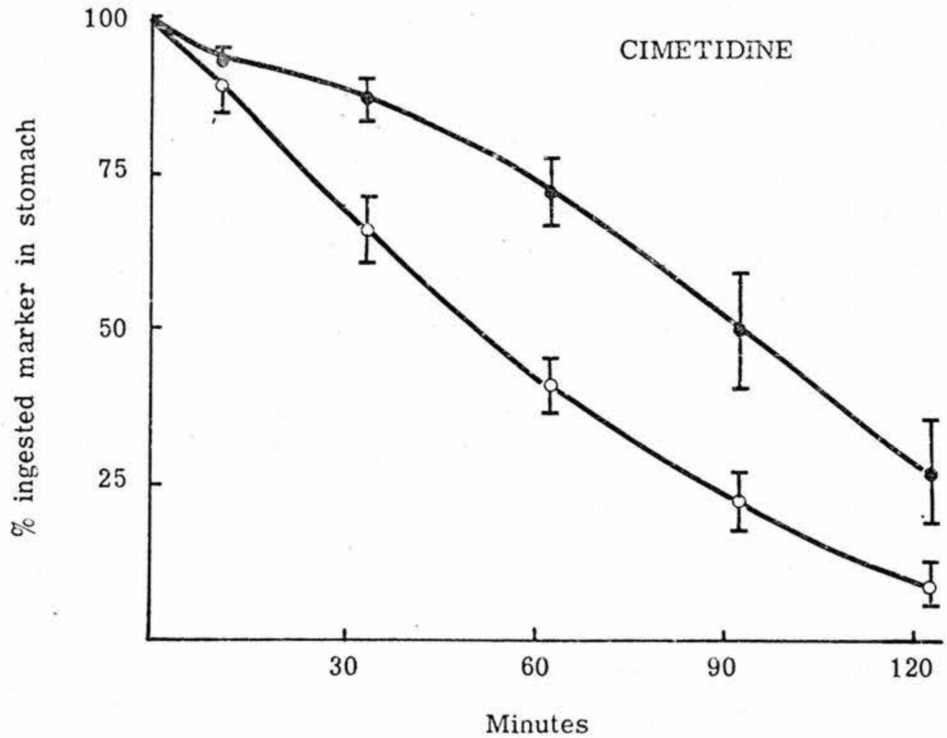
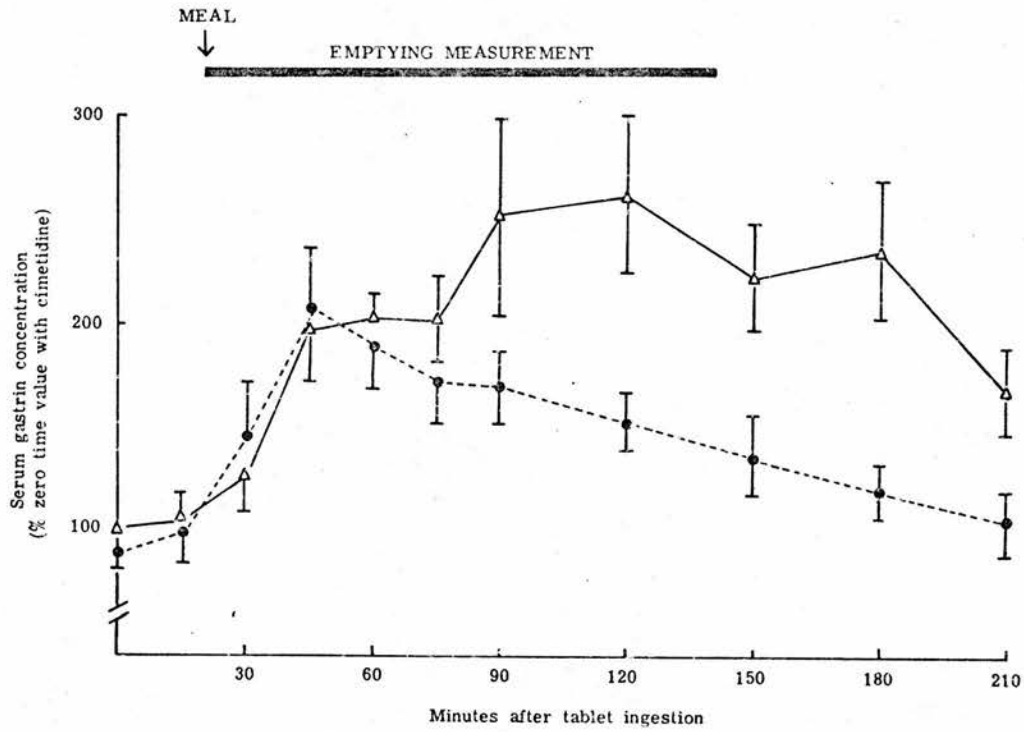

CIMETIDINE
% ingested marker in stomach
100
75
50
25
30
60
90
120
Minutes

Figure 28

Effect of cimetidine on serum gastrin response to the test meal. Points are means $\pm$ SEM; closed circles indicate the placebo study, triangles the cimetidine study.



MEAL
EMPTYING MEASUREMENT
Serum gastrin concentration
(% zero time value with cimetidine)
300
200
100
30
60
90
120
150
180
210
Minutes after tablet ingestion

suppression were presumably similar with the two drugs. Since there is no obvious reason to reject the observations made with metiamide, one must conclude either that the drugs differ or that the investigations have failed to detect the effect of cimetidine on emptying. At present, there is no satisfactory basis for choice between these possibilities.

Other studies of cimetidine and gastric emptying in man have unanimously concluded that the drug has no effect on the emptying rate of a test meal (Richardson et al, 1976; Moberg, Carlberger, Gilljam & Befritz, 1977; Longstreth, Go & Malagelada, 1977; Deering & Malagelada, 1977). There is also no effect on isolated guinea pig stomach muscle (Gerner, Haffner & Norstein, 1979). However, in the rhesus monkey, emptying is apparently inhibited by cimetidine and accelerated by the highly specific histamine H_2 agonist, dimaprit, (dimethylaminopropylisothiourea) (Dubois, Nompleggi, Myers & Castell, 1978). Thus despite the agreement between the published studies in man, it is still possible that H_2 blockade has a small effect on gastric emptying.

Effect of long-term cimetidine

The demonstration that a single dose of cimetidine produces no perceptible alteration in gastric emptying does not imply that long term administration of the drug is without effect. To establish the consequences of long term treatment, gastric emptying measurements were undertaken in sixteen duodenal ulcer patients before, during and after therapy lasting seven months or more. For these studies, a substantial meal of high energy density was used in preference to the cornflakes, sugar and milk meal, so as to provide a greater test of the physiological mechanisms involved in regulation of gastric emptying.

Sixteen patients with endoscopically proven duodenal ulcers were studied./

studied. After fasting overnight, they were given a meal consisting of Carnation breakfast food, milk, biscuits and cheese (50g protein, 55g carbohydrate and 40g fat in a volume of 230ml; 3.4 kcal/ml) to which ^{113m}In DTPA and the ^{99m}Tc-labelled paper particles had been added. Gastric emptying of the two isotopes was then measured as previously described.

The initial studies were performed before therapy was given. Thereafter the patients received cimetidine, 1 or 2g/day for four or eight weeks until there was endoscopic evidence of ulcer healing. Maintenance therapy with the drug was then begun at a dose of 600mg bd and three months later, the emptying studies were repeated. For this measurement, the patients were instructed to take their normal morning dose of cimetidine. The course of maintenance therapy lasted six months and further emptying measurements were performed at least five days after last dose of the drug. All patients were shown to be free of duodenal ulceration at this time.

Results

The emptying rates observed in these patients are given in Table 15 and are shown graphically in Figure 29. Although the mean emptying rate of ^{113m}In increased progressively between the first and third measurements, there was no change that could be directly attributed to the effect of cimetidine. However, in contrast, emptying rates of the ^{99m}Tc-labelled particles were similar before and after cimetidine therapy but the emptying rate during therapy was notably faster.

Discussion

In interpreting these observations, it is obviously important to

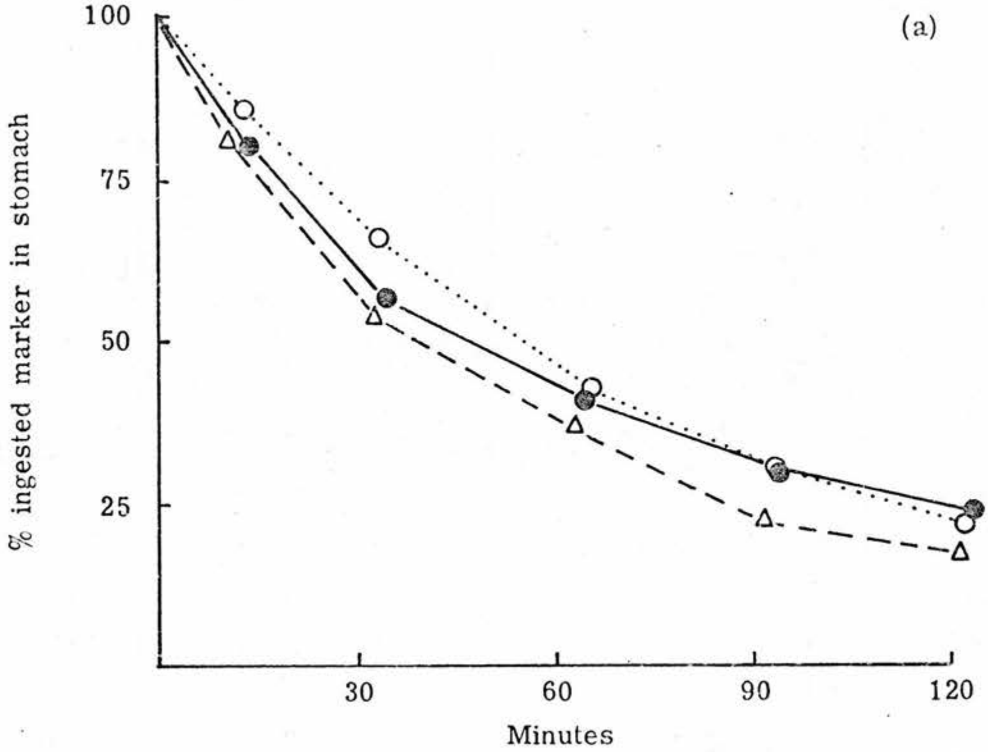
	Before therapy	During therapy	After six months therapy
^{113m}In emptying rate constant (min^{-1})	0.0111 $\pm$ 0.0007	0.0121 $\pm$ 0.0007	0.0144 $\pm$ 0.0010
	←—— NS ——→		
	←——————	$p < 0.05$	——————→
		←— $p < 0.05$	——→
^{113m}In emptied by first scan (% ingested dose)	19.4 $\pm$ 2.5	13.7 $\pm$ 3.0	18.4 $\pm$ 4.4
	←—— NS ——→		
	←——————	NS	——————→
		←—— NS	——→
^{99m}Tc emptying rate (% min^{-1})	0.15 $\pm$ 0.03	0.28 $\pm$ 0.05	0.17 $\pm$ 0.04
	←— $p < 0.01$ ——→		
	←——————	NS	——————→
		←—— $p < 0.01$	——→

Table 15 Effect of long term cimetidine therapy on gastric emptying in 16 duodenal ulcer patients given a high energy density meal containing ^{113m}In DTPA and ^{99m}Tc-labelled paper particles. Data are means $\pm$ 1 SEM; significance of differences was determined by paired t tests. NS = not significant = $p > 0.05$.

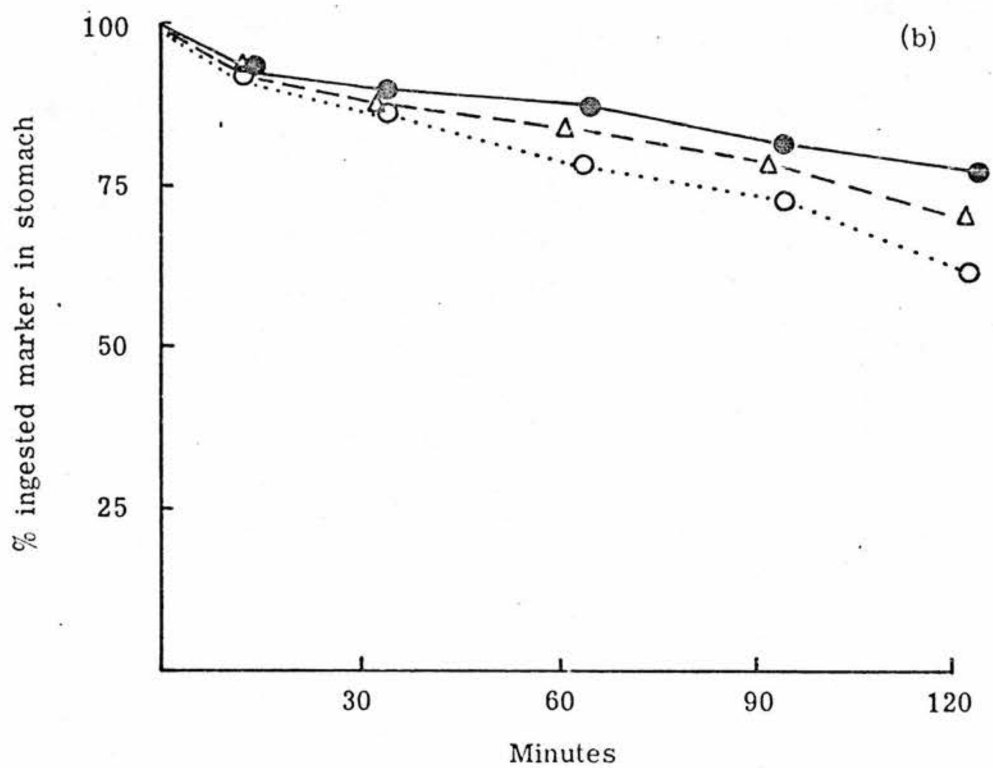
Figure 29

Gastric emptying of (a) liquid and (b) solid markers in sixteen duodenal ulcer patients studied using a high energy density meal before (closed circles), during (open circles) and after completion (triangles) of at least 7 months cimetidine therapy.

Points are means; error bars omitted for clarity.



(a)
% ingested marker in stomach
100
75
50
25
30
60
90
120
Minutes



(b)
% ingested marker in stomach
100
75
50
25
30
60
90
120
Minutes

distinguish changes in emptying due to cimetidine from changes occurring as a result of duodenal ulcer healing. The changes in emptying rate of the ^{99m}Tc-labelled particles appear to be the simplest to interpret, in that the acceleration in emptying rate during therapy seems to be directly or indirectly due to the drug. The fact that a similar change (though not statistically significant) was observed in the single dose studies with cimetidine (Fig. 27) gives support to this suggestion. However, the observations do not provide an explanation for the increase in ^{99m}Tc-labelled particle emptying rate, other than suggesting that cimetidine is the cause. The drug may have modified the gastric antral contraction in such a way that accelerated emptying of particles occurred. Alternatively, the acceleration may have resulted from the suppression of gastric secretion by the drug. Circumstantial evidence favouring the second explanation is shown in Figure 30. Emptying patterns in the duodenal ulcer patients during and after cimetidine therapy (i.e. with and without suppression of gastric secretion) bear a relationship to each other which is similar to the relationship between emptying rates in pernicious anaemia patients and controls. Of course this superficial resemblance does not prove that the effect of cimetidine on particle emptying is a result of suppressed gastric secretion, but it seems a plausible suggestion.

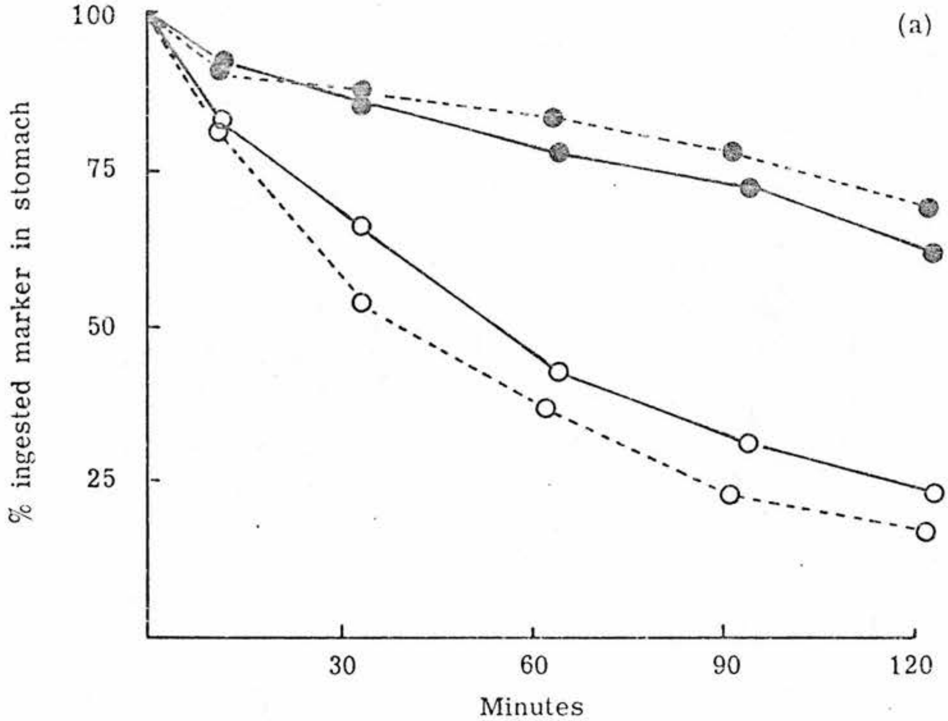
The changes in ^{113m}In emptying rate are of interest in that no statistically significant change occurred between the first and second studies, despite the fact that duodenal ulcer healing had been achieved by the second, and cimetidine therapy was being given at that time. However, there was a statistically significant increase in emptying rate between the second and third measurements and also between the first and third, indicating that emptying rates after cessation of

Figure 30

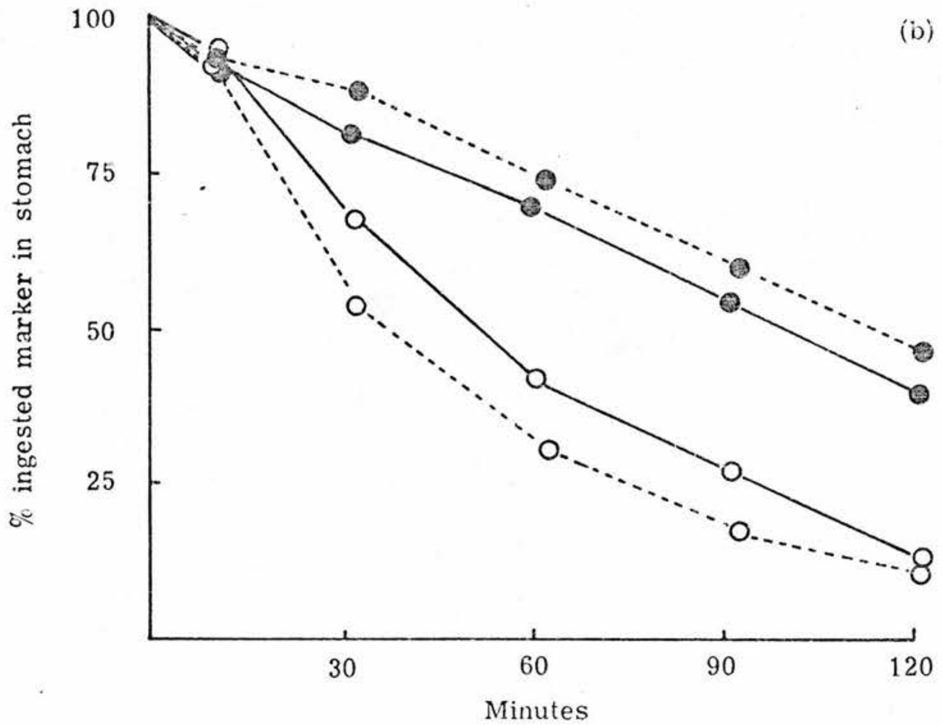
a) Gastric emptying in sixteen duodenal ulcer patients studied using a high energy density meal during (solid lines) and after (broken lines) cimetidine therapy.

b) Gastric emptying in twelve patients with pernicious anaemia (solid lines) and twelve control subjects (broken lines) studied using a meal of cornflakes, sugar and milk.

Solid and liquid markers are represented by closed and open circles respectively; error bars omitted for clarity.



100
75
50
25
% ingested marker in stomach
(a)
30
60
90
120
Minutes



100
75
50
25
% ingested marker in stomach
(b)
30
60
90
120
Minutes

therapy were faster than before and during treatment. Since the patients' duodenal ulcers had healed at the second and third studies, the obvious interpretation of the difference between these two measurements must be that cimetidine inhibited ^{113m}In emptying. Similarly, the difference between the first and third measurements implies that ulcer healing tended to increase ^{113m}In emptying rates. Thus the absence of statistically significant differences between the first and second emptying measurements in these patients may conceal the opposing influences of cimetidine (inhibition) and ulcer healing (acceleration) on the ^{113m}In emptying rate. A trend towards acceleration of gastric emptying with healing of duodenal ulceration has also been described by Miyaoka, Misaki, Sasaki, Kimoto & Kawai (1977).

These conclusions are somewhat controversial and certainly further experimental evidence will be required to justify their assertion with any confidence. Equally certainly, any effects of the histamine H_2 receptor antagonists on gastric emptying in man are small and have no importance in relation to the clinical usage of the drugs in the treatment of peptic ulceration.

A note on gastric emptying in duodenal ulcer

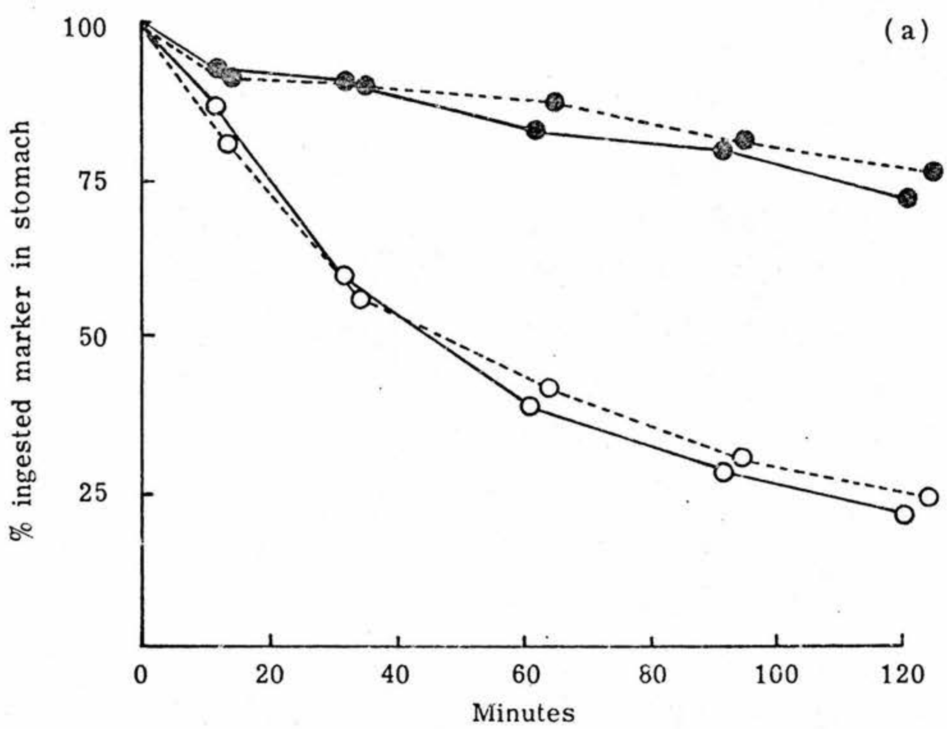
The studies of emptying in duodenal ulcer patients treated with cimetidine were undertaken primarily to study the effects of long term administration of the drug. However, the results obtained with the high energy density meal deserve comparison with equivalent measurements performed on normal subjects in an attempt to assess the possibility that a fundamental abnormality of gastric emptying exists in duodenal ulcer subjects. Stubbs & Hunt (1975) have presented evidence that rapid emptying occurs in duodenal ulcer subjects given meals of high energy density, whereas a lesser abnormality is seen with meals of lower energy density.

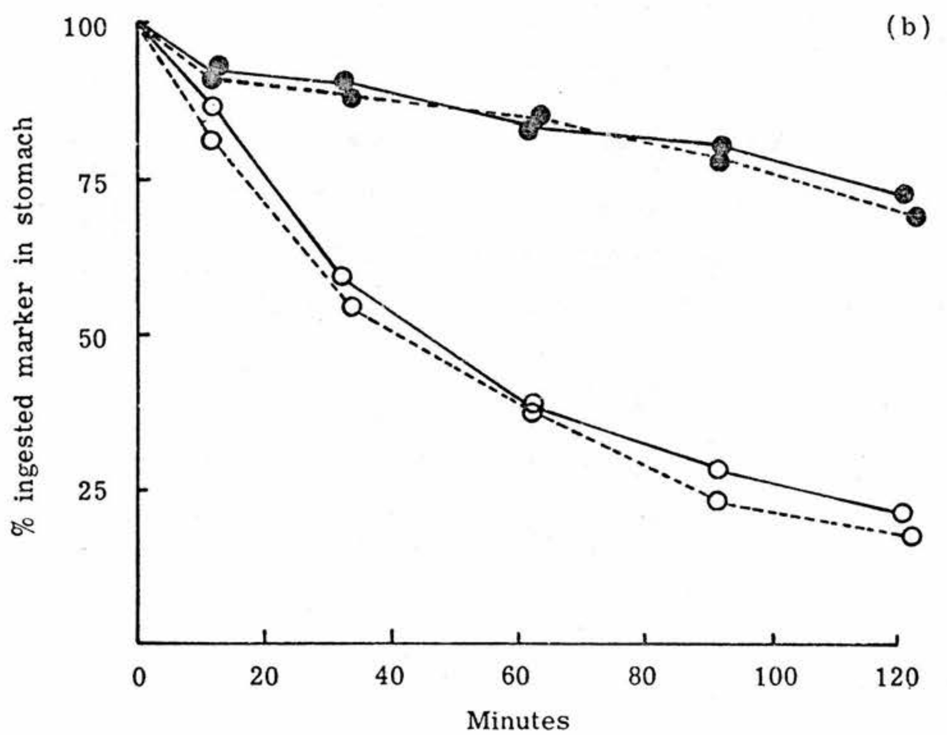
Gastric emptying measurements were therefore performed on twelve control patients without known gastrointestinal disease, using the high energy density meal already described. The results are shown in Figure 31. No statistically significant differences between the control and duodenal ulcer patients were identified. In particular, the results from control subjects and from the healed duodenal ulcer patients (Fig. 31b) were remarkably similar, suggesting that the increase in ^{113m}In emptying rate previously noted in association with ulcer healing should be regarded as a return towards the normal.

These observations provide no evidence of abnormally fast gastric emptying in duodenal ulcer patients as suggested by Griffith et al (1968), Fordtran & Walsh (1973) and by Stubbs & Hunt (1975). However, it may be noted that Howlett et al (1976) found no difference between emptying rates in control and duodenal ulcer subjects until the data was subjected to complex mathematical analysis and Malagelada, Longstreth/

Figure 31

Gastric emptying studied using a high energy density meal in twelve control subjects (solid lines) and sixteen duodenal ulcer patients (broken lines) before (a) and after (b) ulcer healing. Solid and liquid markers are represented by closed and open circles respectively; error bars omitted for clarity.


(a)
100
75
50
25
% ingested marker in stomach
0
20
40
60
80
100
120
Minutes


(b)
100
75
50
25
% ingested marker in stomach
0
20
40
60
80
100
120
Minutes

Longstreth, Deering, Summerskill & Go (1977) found no difference in gastric emptying rates during the first two hours after administration of a test meal. Thus despite some suggestions that gastric emptying in duodenal ulcer patients is abnormally rapid, the present results are in agreement with those of other recent investigations. It is possible that differences between duodenal ulcer subjects and normals may be detected during the later stages of emptying after a meal (Malagelada et al, 1977), but there would now seem to be good reason to reject the simplistic notion that emptying in duodenal ulcer patients is faster than normal.

SUMMARY

Gastric emptying studies were undertaken with the histamine H_2 receptor antagonists, metiamide and cimetidine. Metiamide (400mg) was found to have a small but statistically significant retarding effect on gastric emptying in duodenal ulcer patients, but cimetidine (400mg) produced no perceptible change of emptying in healthy subjects. In a subsequent investigation of long term cimetidine therapy in duodenal ulcer patients, the results suggested that cimetidine slightly retarded gastric emptying of ^{113m}In in the test meal, while ulcer healing produced a slight acceleration. A totally different response was seen with the ^{99m}Tc-labelled particles, which showed accelerated emptying when the patients were taking cimetidine. This may be a consequence of reduced gastric secretion.

No abnormality of gastric emptying in duodenal ulcer patients was identified.

CHAPTER 8

GASTRIC EMPTYING REGULATES ABSORPTION RATE OF ORALLY ADMINISTERED DRUGS

GASTRIC EMPTYING REGULATES ABSORPTION RATE OF ORALLY ADMINISTERED DRUGS

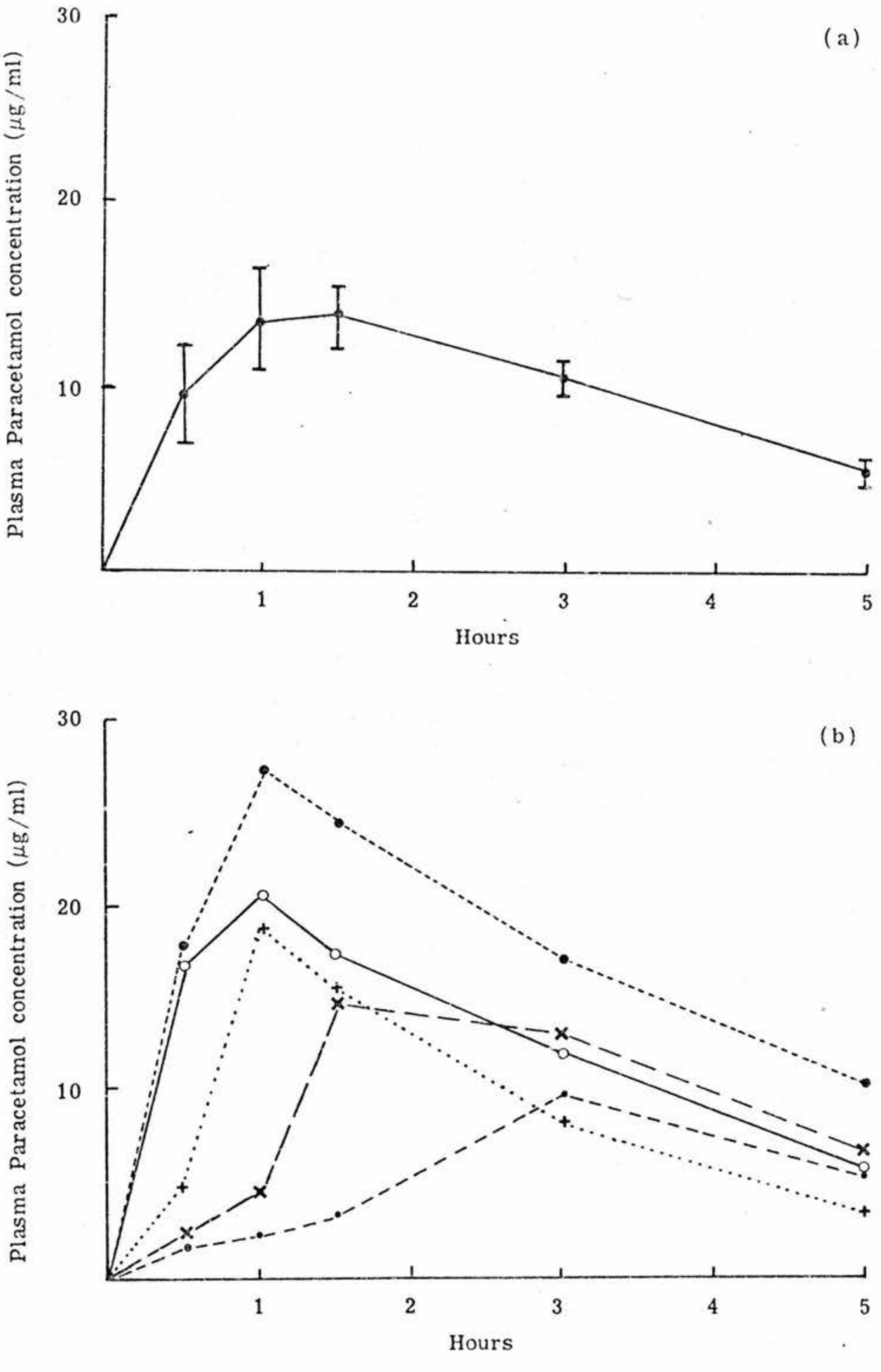
There is often considerable individual variation in the rate at which orally administered drugs are absorbed in man. Unfortunately, the conventional plot of plasma concentration against time after ingestion of a drug does not usually make clear the magnitude of this individual variation, as illustrated for absorption of paracetamol in Figure 32 (data by courtesy of Dr. J. Nimmo). Inspection of the mean plasma paracetamol concentrations obtained from a group of ten subjects (Fig.32a) does not readily reveal the fact that there was a difference of almost 15-fold between the lowest and highest concentrations observed 60 minutes after tablet ingestion (Fig. 32b). If individual variation of this magnitude occurs in normal volunteers studied under standard conditions, it seems likely that variation will be even greater in patients given medication for therapeutic reasons. In the clinical situation, the effects of variable conditions of administration, of disease and of other drugs will be added to the causes of variation in absorption in healthy subjects.

In experimental animals, drug absorption is known to be modified by factors such as intestinal motility, the rate of gastric emptying, splanchnic blood flow and the volume, composition and pH of alimentary secretions (Levine, 1970). However, there have been relatively few studies in which these potential influences have been investigated in man. An attempt was therefore made to assess the possibility that individual differences in paracetamol absorption rate such as those shown in Figure 32 were explained by individual differences in gastric emptying. In the first part of the study, the relationship between paracetamol absorption and gastric emptying was assessed in a group of hospital/

Figure 32

a) Plasma paracetamol concentrations in ten healthy volunteers given 3 x 500mg paracetamol tablets. Values are means ± SEM.

b) Plasma paracetamol concentrations in five of the ten subjects.



30
20
10
(a)
Plasma Paracetamol concentration (µg/ml)
1
2
3
4
5
Hours
30
20
10
(b)
Plasma Paracetamol concentration (µg/ml)
1
2
3
4
5
Hours

hospital patients. When the results suggested that there was a relationship between them, further studies were conducted to see if the pharmacological modification of gastric emptying led to the predicted changes in paracetamol absorption.

Relationship between gastric emptying and paracetamol absorption: Methods

Fourteen convalescent hospital patients were studied. Two patients had previously undergone truncal vagotomy and pyloroplasty for peptic ulcer and another had a duodenal ulcer with pyloric stenosis. None of the patients had clinical evidence of malabsorption nor any known cardiac, renal or hepatic disease. All medication was withheld during the period of the study.

Following an overnight fast, the patients were given 1.5g paracetamol (as 3 x 500mg "Panadol" tablets) with 50ml water. Fluids were withheld for two hours and food and tobacco for three hours. Venous blood samples were obtained at 0, 0.5, 1, 1.5, 3, 5 and 8 hours and, in twelve patients, urine was collected for 0-4 and 4-24 hours. Plasma and urine were stored frozen until the time of analysis. Total unchanged and conjugated paracetamol in urine and unchanged paracetamol in plasma were estimated by gas liquid chromatography (Prescott 1971a, 1971b).

In all patients, gastric emptying rates were measured within six days of the paracetamol absorption study using the standard meal of cornflakes, sugar and milk containing ^{113m}In DTPA, as described in Chapter 1. Gastric emptying rates were expressed as half-times.

Results

The maximum plasma paracetamol concentrations varied from 7.4 to 37.0 µg/ml /

37.0 μg/ml and the time taken to reach peak concentrations ranged from 30 to 180 minutes after tablet ingestion. Statistically significant correlations were established for both the peak concentration and the time of peak with the gastric emptying half-times ($r = -0.77$ and $+ 0.76$ respectively, $p < 0.005$; Fig. 33 and 34). Thus rapid gastric emptying was associated with a high and early peak plasma paracetamol concentration, whereas peak concentrations were low and occurred late when emptying was slow.

Urinary recoveries of paracetamol and its conjugates are given in Table 16. Significant correlations between urinary recovery and gastric emptying half-time were identified both for the period 0-4 hours and for the period 0-24 hours after tablet ingestion. Thus slow gastric emptying was apparently associated with reduced absorption of paracetamol.

Pharmacological modification of gastric emptying:

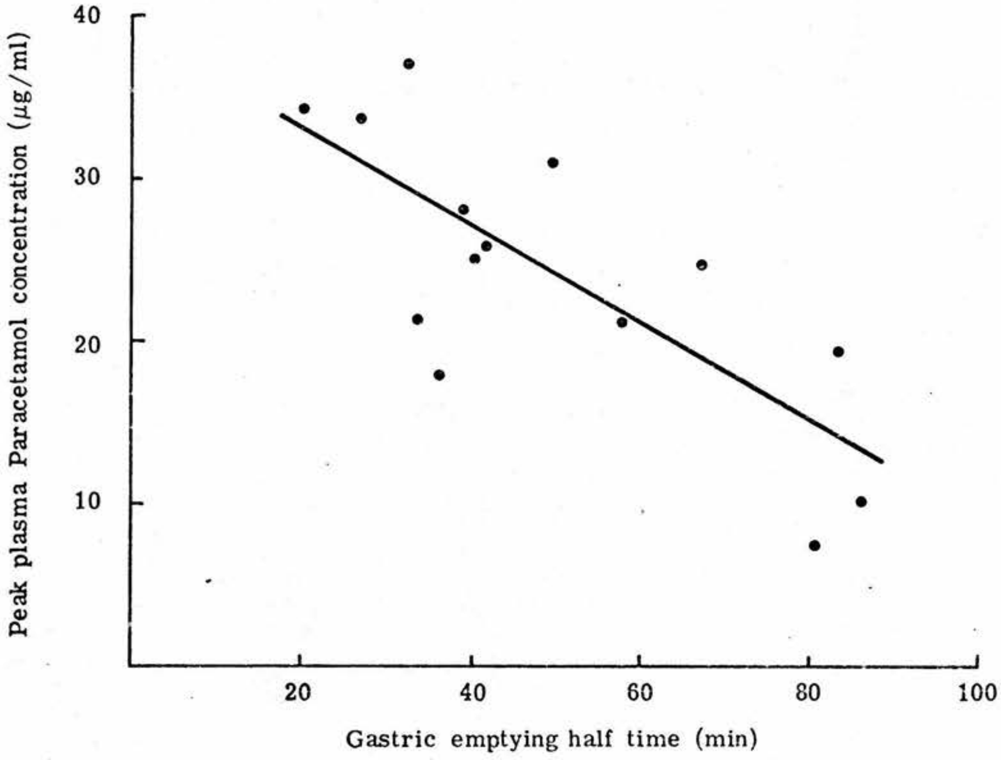
Methods

Using the procedure described above, paracetamol absorption was assessed in five healthy volunteers who were known to be consistently slow absorbers of the drug. The study was then repeated in each subject at least one week later, but on this occasion 10mg metoclopramide was given intravenously at the time the paracetamol was taken.

In six convalescent hospital patients, gastric emptying and paracetamol absorption were measured simultaneously. The patients were given 3 x 500mg "Panadol" tablets together with 400ml water containing 200 μCi ^{113m}In DTPA. Gastric emptying was measured as previously described and the emptying half-time calculated. At least 48 hours later, the whole procedure was repeated with an intravenous injection of 30mg propantheline being given 15 minutes before the paracetamol tablets/

Figure 33

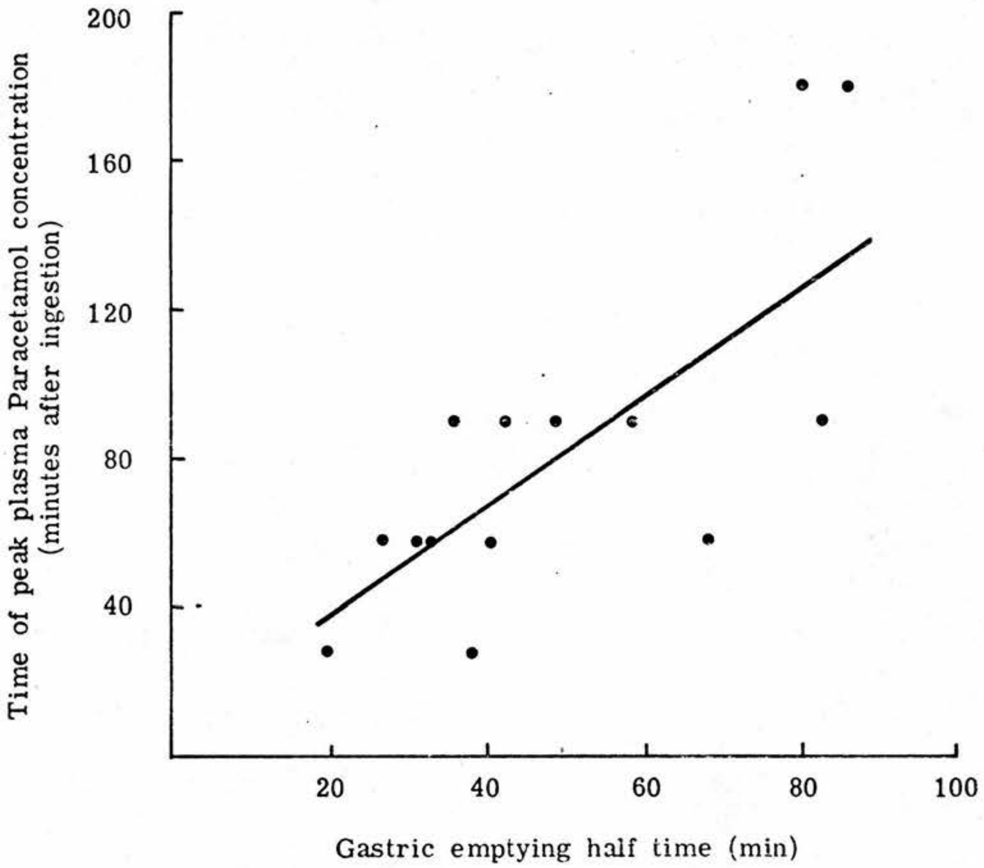
Correlation of the peak plasma paracetamol concentration and the gastric emptying half-time in fourteen patients. ($r = -0.77$)



Peak plasma Paracetamol concentration (μg/ml)
40
30
20
10
20
40
60
80
100
Gastric emptying half time (min)

Figure 34

Correlation of the time of the peak plasma paracetamol concentration and the gastric emptying half-time in fourteen patients. (r = 0.76)


200
160
120
80
40
Time of peak plasma Paracetamol concentration
(minutes after ingestion)
20
40
60
80
100
Gastric emptying half time (min)

Patient	Gastric emptying half-time (min)	Unchanged paracetamol in urine (mg)	Total unchanged and conjugated paracetamol in urine (mg)	
		0-4 h	0-4 h	0-24 h
1	42	9.5	333	1019
2	34	13.3	373	-
3	68	4.8	384	1168
4	37	12.8	567	1161
5	20	24.9	522	1236
6	59	-	178	890
7	81	1.3	61	881
8	39	37.5	390	1114
9	26	8.1	254	1316
10	84	6.7	281	-
11	86	4.9	247	964
12	41	14.1	386	1134
Correlation with gastric emptying half-time	r	-0.59	-0.62	-0.73
	p	<0.05	<0.05	<0.01

Table 16 Gastric emptying and paracetamol recovery in twelve patients.

tablets. One patient underwent a third study in which an intravenous injection of metoclopramide was given at the time of paracetamol ingestion.

Samples of venous blood and urine were obtained for estimation of paracetamol content, as described above.

Results

Effect of propantheline

Propantheline decreased the rate of gastric emptying in all six patients, increasing the mean emptying half-time from 25 to 152 minutes ($p < 0.05$, signed ranks test; Table 17). The mean time to reach maximum plasma concentrations of paracetamol was correspondingly increased from 70 to 160 minutes and the mean maximum concentration was reduced from 26.3 to 17.5 µg/ml. These differences were all statistically significant ($p < 0.005$, paired t tests). There was no difference in the amount of total unchanged and conjugated paracetamol excreted in the urine in 24 hours but propantheline administration was association with a significant reduction in excretion in the 0 to 12 hour period ($p < 0.05$).

Effect of metoclopramide

Maximum plasma concentrations of unchanged paracetamol were higher and appeared earlier after metoclopramide than in the control study in each of the five volunteers. The mean time taken to reach maximum plasma concentration was reduced from 120 to 48 minutes ($p < 0.05$) and was associated with an increase in mean maximum concentration from 12.5 to 20.5 µg/ml ($p < 0.05$, one-tail test) (Table 18). Metoclopramide had no effect on the urinary excretion of paracetamol.

The plasma concentrations of paracetamol in the one patient studied with/

	Gastric emptying half-time (min)	Maximum plasma concentration of unchanged paracetamol (ug/ml)	Time of peak plasma concentration (min after ingestion)	Urinary excretion of unchanged plus conjugated paracetamol	
				0-12 h (mg)	0-24 h (mg)
Control	25	26 ± 4	70 ± 10	880 ± 83	1009 ± 75
After propantheline	152	18 ± 5	160 ± 13	536 ± 73	1014 ± 107

Table 17 Effect of propantheline on gastric emptying and paracetamol absorption in six patients.

Mean emptying half-times are given; other results are means ± SEM.

	Maximum plasma concentration of unchanged paracetamol (µg/ml)	Time of peak plasma concentration (min after ingestion)	Urinary excretion of unchanged plus conjugated paracetamol	
			0-12 h (mg)	0-24 h (mg)
Control	13 ± 6	120 ± 25	1066 ± 17	1175 ± 27
After metoclopramide	21 ± 4	48 ± 12	1016 ± 23	1116 ± 18

Table 18 Effect of metcclopramide on paracetamol absorption in five selected healthy volunteers.

Data are means ± SEM.

with both propantheline and metoclopramide are shown in Figure 35. In comparison with the control study, paracetamol absorption was apparently accelerated by metoclopramide and delayed by propantheline.

Discussion

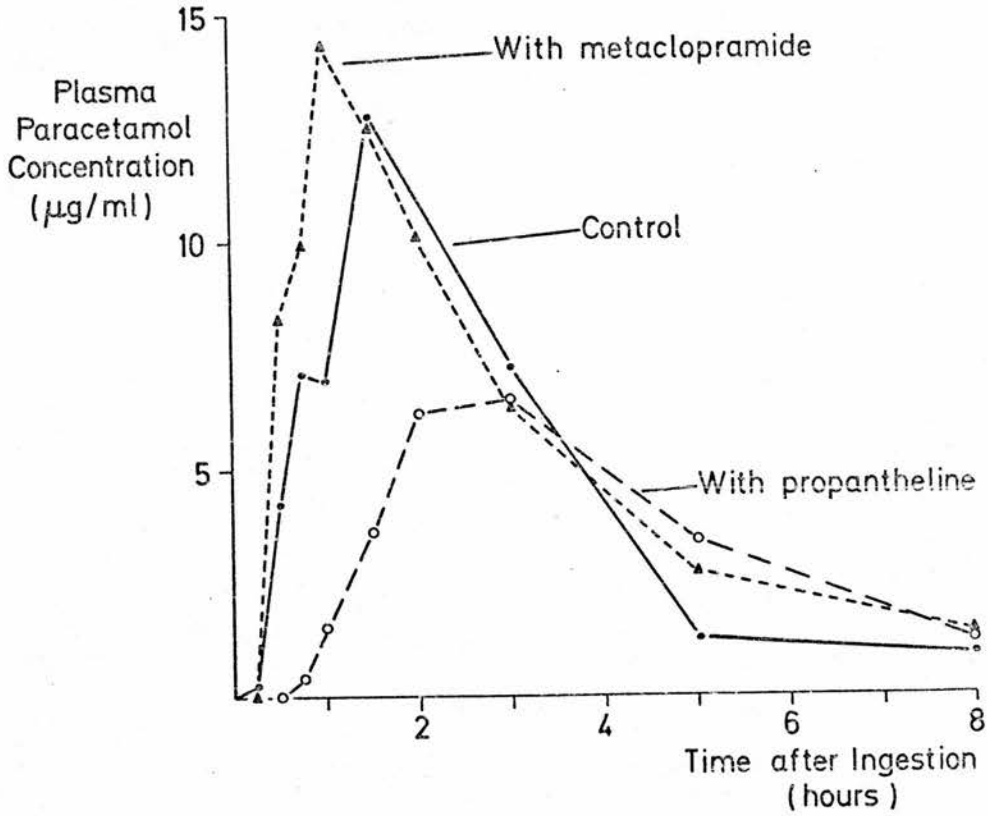
These results suggest that differences in gastric emptying rate are responsible for much of the previously noted individual variation in paracetamol absorption. A clear association between emptying rate and paracetamol absorption rate was observed in the group of convalescent patients and the anticipated changes in paracetamol absorption were seen when gastric emptying was accelerated and retarded by metoclopramide and propantheline respectively. Although gastric emptying measurements were not made in the metoclopramide study, the effect of this drug on emptying is well established (Schulze-Delrieu, 1979).

Paracetamol is a weakly acidic drug with pK_a of 9.5. It is therefore un-ionised both at intragastric and at intrajejunal pH and, according to classical drug absorption theory (Schanker, Shore, Brodie & Hogben, 1957) should be absorbed readily at both sites. In fact the present results suggest that absorption of paracetamol is dependent on delivery of the drug to the small intestine, and that gastric absorption is minimal. Similar "aberrations" from classical theory are recognised for other weakly acidic molecules such as aspirin (Siurala, Mustala & Jussila, 1969) and warfarin (Kekki, Pyorala, Mustala, Salmi, Jussila & Siurala, 1971) and the predominance of small intestinal over gastric absorption is also recognised for ethanol (Magnussen, 1968). Thus it seems likely that gastric emptying is an important factor in determining absorption rate of most orally ingested substances.

Although the present findings present a clear message with respect to/

Figure 35

Effects of propantheline and metoclopramide on paracetamol absorption in one subject.


15
Plasma
Paracetamol
Concentration
(μg/ml)
10
5
With metaclopramide
Control
With propantheline
2
4
6
8
Time after Ingestion
(hours)

to the rate of paracetamol absorption, the results relating to total absorption of the drug are inconclusive. The first study suggested that slow absorption of the drug was associated with reduced total absorption (as reflected by 24 hour urinary recovery) but the finding was not confirmed by the studies with propantheline and metoclopramide. This is clearly a point of potential practical importance which can only be clarified by further investigation.

The importance of gastric emptying as a major determinant of drug absorption rate is now generally accepted (Rawlins, 1980) in contrast with the position in 1973 when these observations with paracetamol were first reported (Heading, Nimmo, Prescott & Tothill, 1973; Nimmo, Heading, Tothill & Prescott, 1973). There is therefore some irony in the fact that although the conclusions drawn from these studies are now known to be correct, they are not entirely justified by the observations made. In order to simulate closely the conditions under which patients are usually given medication, most of the subjects in these studies were given paracetamol tablets with a small volume of water. No consideration was given to the behaviour of the stomach in response to small ingested volumes and to the possible variations in tablet disintegration and dissolution that might have influence on the results. It is therefore not possible to refute the perfectly reasonable hypothesis that the observed effects of metoclopramide and propantheline on paracetamol absorption were due to increased and decreased disintegration and dissolution of paracetamol within the stomach rather than a result of altered gastric emptying.

A second limitation of the study was the use of the gastric emptying half-time as the only index of emptying. Observations described in Chapters 3 and 5 have demonstrated its inadequacies. However/

However, this problem may be less serious than it might at first appear since "excess early emptying" in the combined results from a group of normal subjects is small (see Table 6). Thus the emptying half-time provides a reasonably satisfactory index of the mean emptying rate in such a group, although it does not describe individual patterns in which fast or slow early emptying occurs.

The existence of a relationship between paracetamol absorption and gastric emptying was more satisfactorily established in subsequent studies using paracetamol in solution (see Chapters 9 and 10) and it therefore seems that the conclusions drawn from the present investigation were probably correct. Gastric emptying thus appears to be a major determinant of absorption rate when paracetamol is given in tablet form under conditions corresponding to those in which it is taken by patients.

The possibility that metoclopramide may be used as a means of accelerating analgesic absorption has some therapeutic relevance. A combination of aspirin and metoclopramide ("Migravess", Miles Laboratories) is currently being promoted for the treatment of migraine, on the basis that the metoclopramide facilitates speedy absorption of the analgesic.

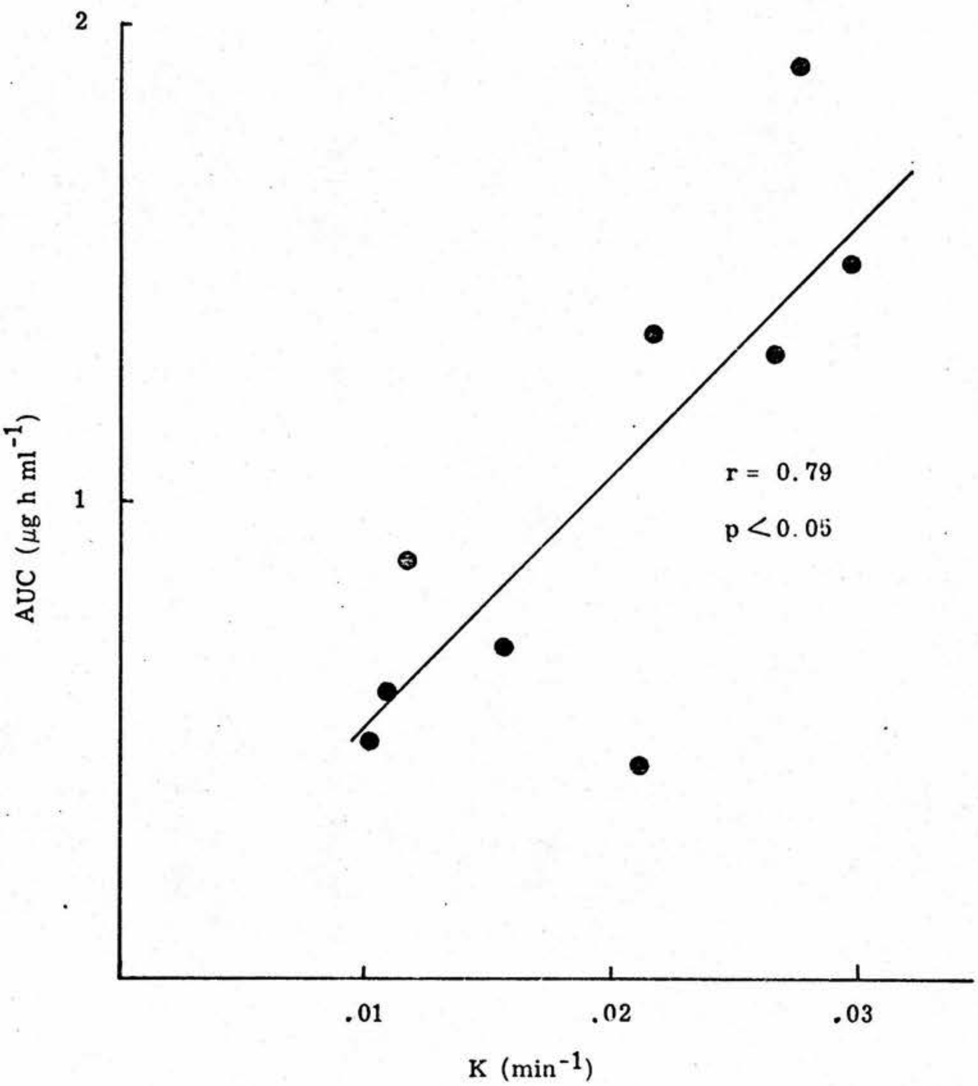
Gastric emptying and cimetidine absorption

The measurements of gastric emptying after cimetidine administration described in Chapter 7 provided an opportunity to study the relationship between gastric emptying rate and the rate of absorption of the drug. In an attempt to find a more satisfactory mathematical expression of the relationship, the area under the blood cimetidine concentration-time curve between 0 and 1 hour was compared with the first order rate constant for emptying of the ^{113m}In in the meal.

The results are presented in Figure 36. In the nine subjects studied, there was a significant positive correlation between the two variables ($r = 0.79$, $p < 0.05$) inplying that for cimetidine, as for paracetamol, individual variation in gastric emptying is an important cause of individual variation in the rate of drug absorption.

Figure 36

Correlation of the area under the blood cimetidine concentration - time curve (0 - 1 hour) (AUC) and the rate constant for gastric emptying (K) in nine healthy subjects.



2
1
AUC (μg h ml-1)
r = 0.79
p < 0.05
.01
.02
.03
K (min-1)

SUMMARY

Measurements of gastric emptying and of paracetamol absorption after tablet administration were undertaken to investigate the relationship between them. Significant correlations between indices of drug absorption rate and gastric emptying rate were observed, and pharmacological modification of gastric emptying by propantheline and by metoclopramide produced the expected changes in paracetamol absorption. Although gastric emptying apparently influenced the rate of drug absorption, it had no clear effect on the completeness of absorption, as judged from 24 hour urinary recoveries of the drug.

Gastric emptying appears to be an important regulator of the rate of absorption of orally administered paracetamol. It seems likely that individual variation in emptying is responsible for much of the individual variation in absorption of the drug.

CHAPTER 9

EFFECTS OF NARCOTIC ANALGESICS ON GASTRIC EMPTYING

EFFECTS OF NARCOTIC ANALGESICS ON GASTRIC EMPTYING

In a study of obstetric patients, Nimmo, Wilson & Prescott (1975) observed that the absorption of orally administered paracetamol by women in labour was markedly retarded in those who had been given narcotic analgesics. The investigation had been undertaken with the intention of using paracetamol absorption to provide an indirect indication of gastric emptying rate and, to explain the findings, it was suggested that the narcotic drugs were themselves inhibitors of gastric emptying. This proposal was of interest for two principal reasons. Firstly, inhibition of gastric emptying and drug absorption had not previously been generally appreciated as a consequence of narcotic administration and such an action on drug absorption might be of clinical importance. Secondly, delayed gastric emptying in women in labour might predispose to regurgitation of gastric contents during induction of anaesthesia. Since regurgitation and pulmonary aspiration of gastric secretion is a major hazard of obstetric anaesthesia (Report on Confidential Inquiries into Maternal Deaths, 1972), there is obvious importance in an observation suggesting that much of the predisposition is iatrogenic.

Nimmo et al (1975) did not provide proof that narcotic drugs inhibited gastric emptying and paracetamol absorption because they were unable to distinguish between effects due to narcotic administration and effects resulting from the increasing distress of labour, which was the reason the narcotic drugs were given to their patients. Because of this uncertainty, it seemed desirable to study directly the effects of narcotic analgesics on gastric emptying and drug absorption. However, women in an advanced stage of labour are hardly suitable for gastric emptying studies under the rectilinear scanner or a gamma camera and there/

there are similar practical and ethical constraints on the study of other patients who are sufficiently ill to require narcotic analgesia. A satisfactory answer to the question about narcotic effects on gastric emptying therefore required studies of volunteers.

Methods

Gastric emptying and paracetamol absorption were measured simultaneously in eight adult male volunteers. After fasting overnight, each subject drank 400ml paracetamol solution (20 mg/kg) in orange juice, which also contained 300 μCi ^{113m}In DTPA. The drink was consumed within two minutes. Gastric emptying was measured by sequential scintiscanning as previously described and included a measurement of emptying between ingestion of the drink and performance of the first scan, using the "indirect method" described in Chapter 3. Gastric emptying results were expressed as the time taken to empty 50% of ingested solution from the stomach and also as the amount emptied in one hour.

Serial blood samples were taken up to eight hours after ingestion for assessment of paracetamol absorption. The plasma was stored frozen and the concentration of unchanged paracetamol was measured by gas liquid chromatography as previously. Urine collections were obtained from 0-4 and 4-24 hours, and the total unchanged and conjugated paracetamol in each sample was also determined.

No food, drink or tobacco were permitted for four hours after ingestion of the solution and the subjects remained supine throughout this period. Each subject was studied on two occasions at least seven days apart. On one occasion an intramuscular injection of pethidine (150mg) or diamorphine (10mg) was given 30 minutes before the paracetamol and/

and on the other occasion, the subjects received a placebo injection of 0.9% w/v NaCl solution. Four subjects were given pethidine and four received diamorphine. The order of narcotic and placebo administration was randomised and the subjects were not told beforehand which injection they would receive. However, following administration of the active drug, all subjects developed typical narcotic effects such as light-headedness or drowsiness and were thus aware of the treatment they had been given.

The administration of highly addictive narcotic drugs, even in single doses, to volunteer medical staff inevitably prompts concern about the possibility of addiction. In accordance with the recommendations of the local Advisory Ethical Committee, the participating subjects were interviewed before the study and again afterwards by a senior physician nominated by the Committee, in order to identify any excessive risks or problems. None were encountered.

Results

Gastric emptying occurred rapidly in all the control studies following placebo injection. The time for 50% emptying of the ingested solution ranged from 4 to 22 minutes (mean 11.9 minutes) (Table 19). Paracetamol absorption was correspondingly rapid with a mean peak plasma concentration of 20.0 μg/ml occurring 22 minutes after ingestion (Table 20).

After pethidine, the mean time for 50% emptying of the ingested solution was prolonged to 89.5 minutes (Table 19). The mean peak plasma paracetamol concentration was correspondingly reduced and delayed to 13.8 μg/ml at 114 minutes (Table 20). The effects of pethidine on gastric emptying in paracetamol absorption in one subject are shown in Figure/

	Time to 50% emptying of ingested solution (min)	p
Control (n = 8)	11.9	-
Pethidine (n = 4)	89.5	< 0.01
Diamorphine (n = 4)	> 130	< 0.01

Table 19 Effect of pethidine and diamorphine on gastric emptying. Times are means; p values relate to comparison of pethidine or diamorphine results with controls using the Mann-Whitney U test.

	Peak plasma paracetamol concentration (μg/ml)	p	Time of peak (min after ingestion)	p
Control (n = 8)	20.0 ± 1.8	-	22 ± 3.1	
Pethidine (n = 4)	13.8 ± 3.9	< 0.05	114 ± 36	< 0.05
Diamorphine (n = 4)	5.2 ± 1.5	< 0.05	142 ± 72	< 0.01

Table 20 Effect of pethidine and diamorphine on paracetamol absorption. Data are means ± SEM. p values relate to comparisons of pethidine or diamorphine results with controls using paired t tests.

Figure 37.

Diamorphine completely inhibited gastric emptying for more than 90 minutes in three of the four subjects and none achieved 50% emptying within two hours (Table 19). The mean peak plasma paracetamol concentration was only 5.2 ug/ml and was not reached until 142 minutes after ingestion. An example of the effects of diamorphine on gastric emptying in paracetamol absorption in one subject is shown in Figure 38.

The mean plasma paracetamol concentration-time curves are shown in Figure 39. These show that the inhibition of absorption was greater and more prolonged with diamorphine than with pethidine, in accord with the gastric emptying measurements.

The mean recovery of paracetamol from urine at 4 hours was reduced after narcotic administration. The mean percentage of ingested dose recovered in the 0-4 hour urine collection was 37.1% in the controls, 24.9% after pethidine and 13.1% after diamorphine. However, these values were not significantly different. The total amount of paracetamol appearing in the urine in 24 hours was unaffected by narcotic administration. The mean recovery was 77.2% of the administered dose in the control studies and 75.3% after the narcotics.

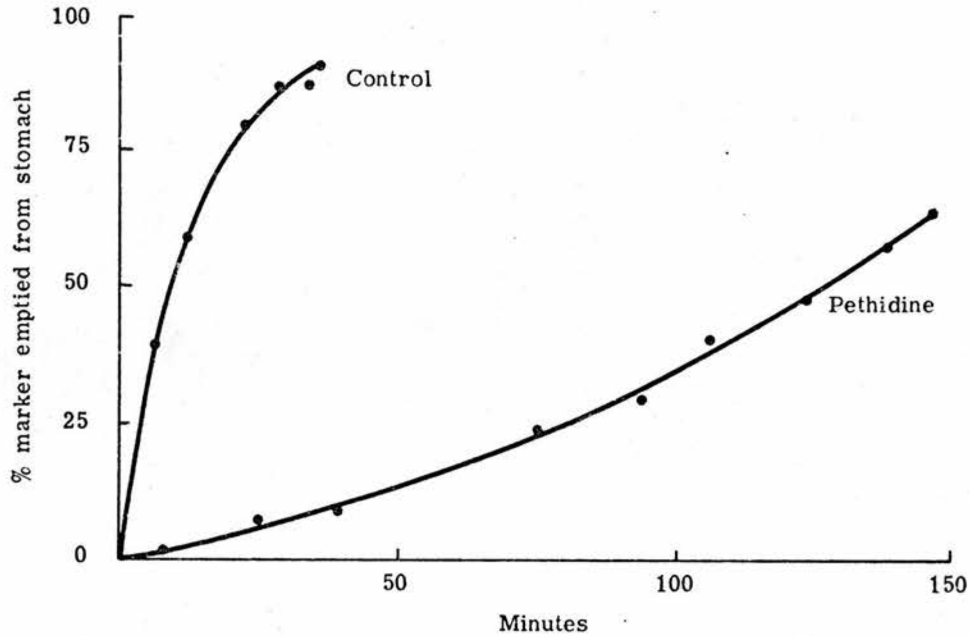
The area under the plasma concentration-time curve at one hour was plotted against the percentage of ingested solution emptied from the stomach at one hour for each subject. A highly significant positive correlation was obtained ($r = 0.94$, $p < 0.001$; Fig.40).

Discussion

These results are further evidence of a close relationship between gastric emptying and paracetamol absorption rate. In particular, they/

Figure 37

Effect of 150mg pethidine on gastric emptying and plasma paracetamol concentrations following ingestion of paracetamol solution by a healthy subject.


100
75
50
25
0
% marker emptied from stomach
Control
Pethidine
50
100
150
Minutes

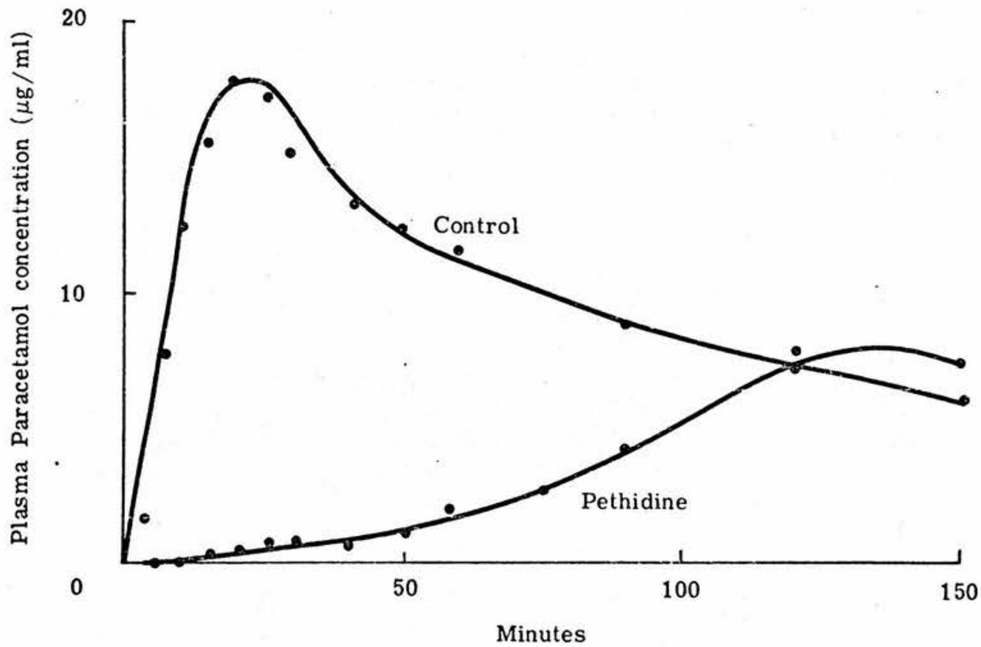
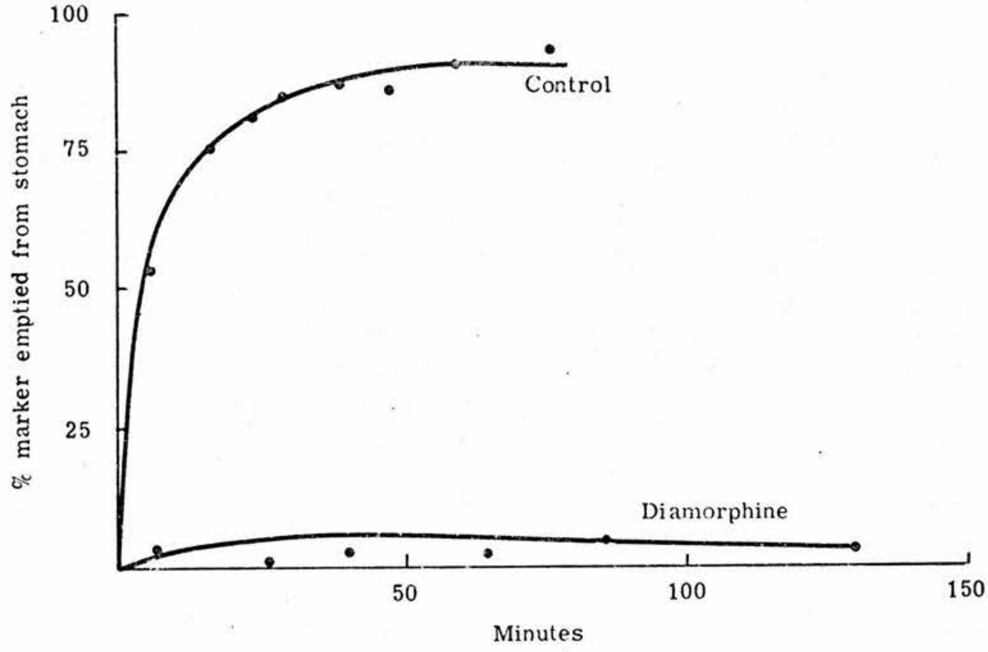

20
10
0
Plasma Paracetamol concentration (μg/ml)
Control
Pethidine
50
100
150
Minutes

Figure 38

Effect of 10mg diamorphine on gastric emptying and plasma paracetamol concentrations following ingestion of paracetamol solution by a healthy subject.


100
75
50
25
% marker emptied from stomach
Control
Diamorphine
50
100
150
Minutes

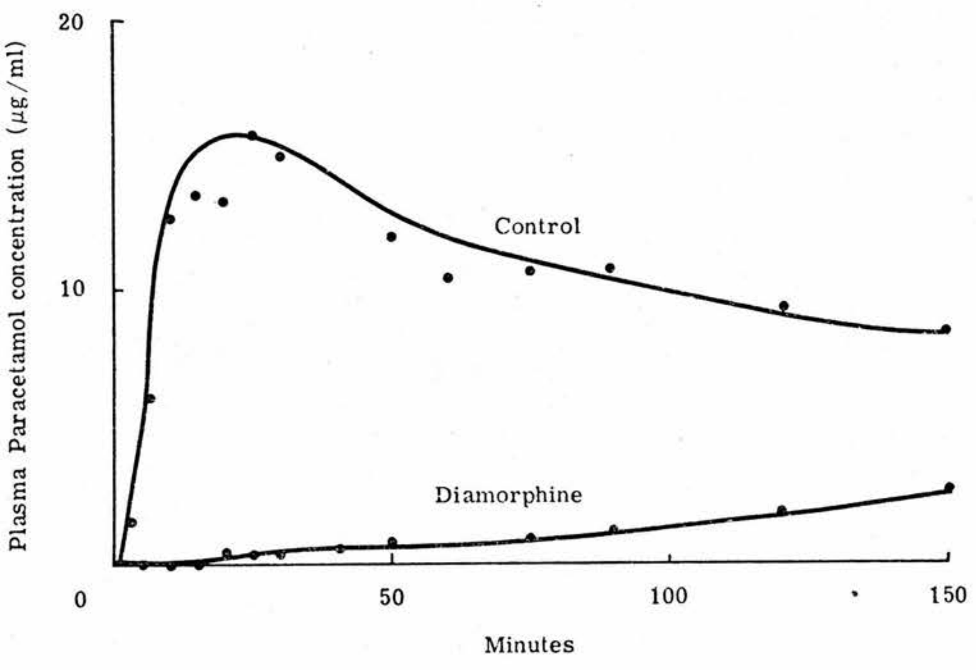
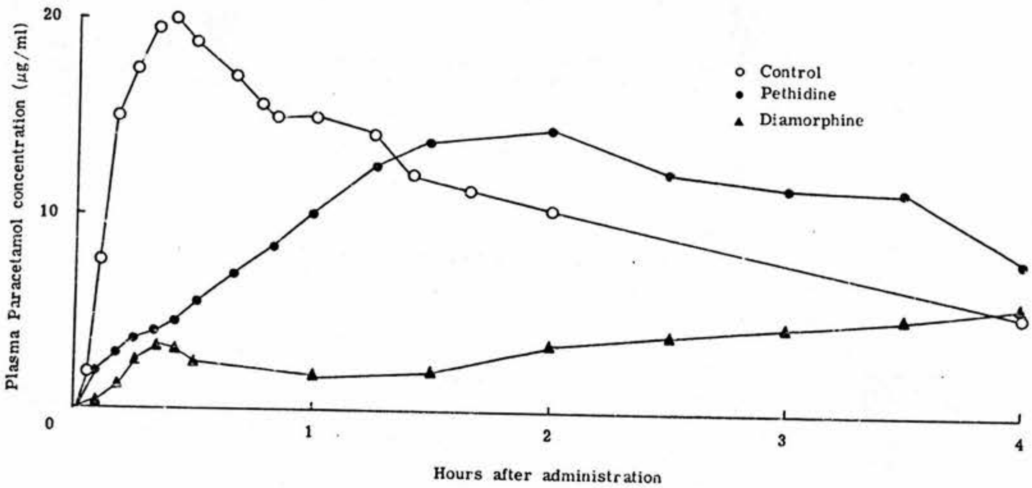

20
10
0
Plasma Paracetamol concentration (μg/ml)
Control
Diamorphine
50
100
150
Minutes

Figure 39

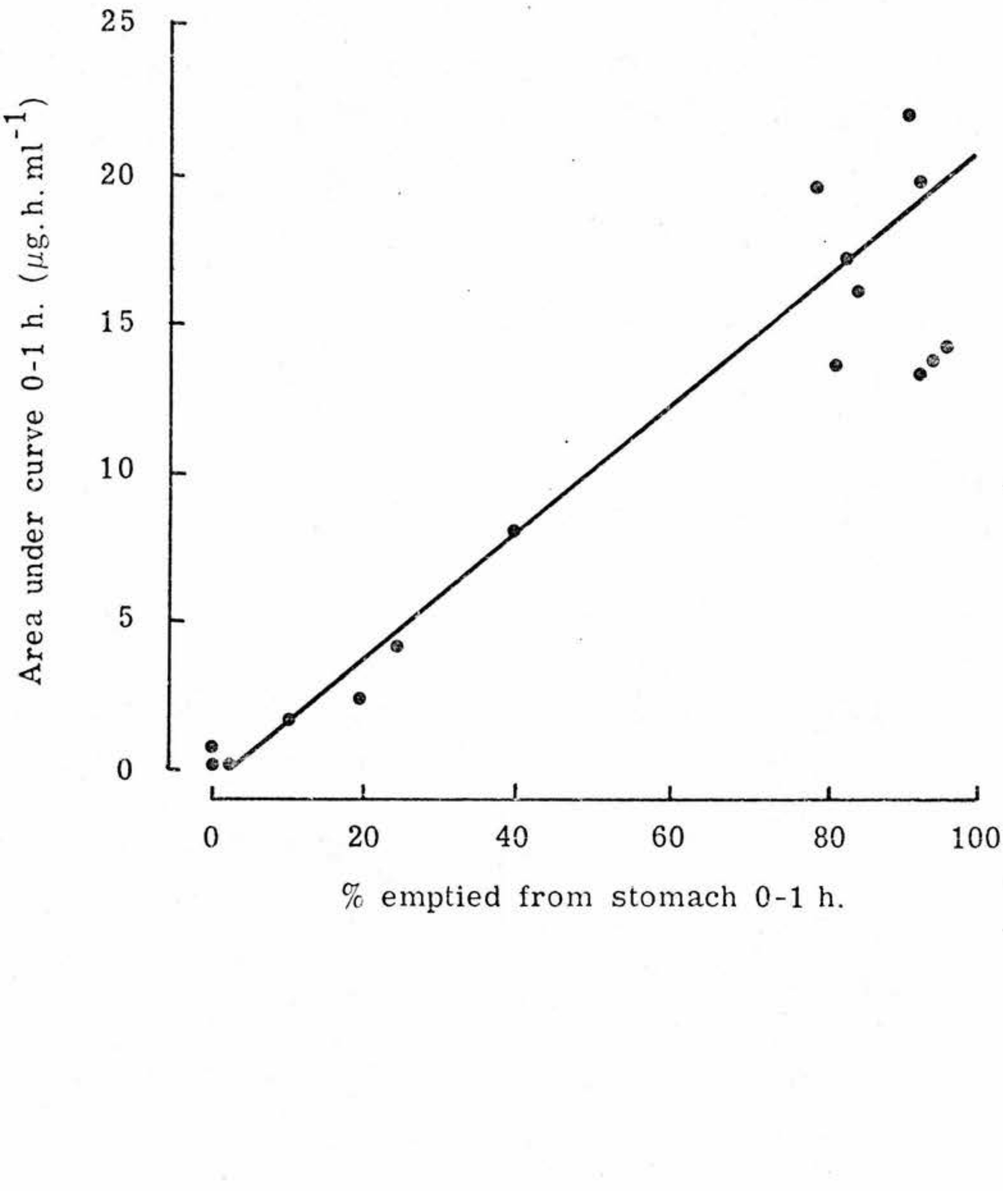
Mean plasma paracetamol concentrations in the control, pethidine and diamorphine studies. Error bars are omitted for clarity.



20
10
0
Plasma Paracetamol concentration (μg/ml)
Control
Pethidine
Diamorphine
1
2
3
4
Hours after administration

Figure 40

Correlation of the area under the plasma paracetamol-time curve (0 - 1 hour) with gastric emptying of the ingested solution at 1 hour in eight healthy subjects studied with and without prior administration of pethidine or diamorphine ($r = 0.94$).


Area under curve 0-1 h. (μg.h.ml-1)
25
20
15
10
5
0
0
20
40
60
80
100
% emptied from stomach 0-1 h.

they demonstrate directly that pethidine and diamorphine markedly inhibit gastric emptying and greatly retard paracetamol absorption. The effect of diamorphine was especially striking, with complete inhibition of gastric emptying in three of the four subjects for more than 1.5 hours. Both drugs had a much greater inhibitory effect than 30mg propantheline given intravenously (see Chapter 8).

These results give strong support to the suggestion by Nimmo et al (1975) that narcotic drugs are a major cause of delayed gastric emptying in women in labour. However, the action of narcotic analgesics on gastric emptying may have implications beyond obstetric practice. Since many drugs given by mouth are not absorbed to any significant extent in the stomach, it seems inevitable that their absorption, like that of paracetamol will be greatly retarded by concurrent administration of narcotics. Given the widespread use of narcotic drugs in all branches of medical practice and the magnitude of their effect on gastric emptying, it seems that this should be considered a major drug absorption interaction.

One further conclusion may be drawn from the present results - namely that Nimmo et al (1975) were successful in their use of paracetamol absorption as an index of gastric emptying in patients who were not easily studied by other methods. More recently, paracetamol absorption has been used by Harasawa, Tani, Suzuki, Miwa, Sakita, Nomiyama et al (1979) as an index of gastric emptying in a large study of peptic ulcer patients. The results presented in Chapter 8 and previously published (Heading et al, 1973) were cited as the principal justification of the method. However, studies in which paracetamol absorption is used in this way must be interpreted with great caution and whenever possible, direct measurements of emptying are much to be preferred.

Effect of naloxone on narcotic-induced delay in gastric emptying

Evidence that the effects of pethidine and diamorphine on gastric emptying were shared by pentazocine and could not be overcome by metoclopramide administration (Nimmo et al, 1975) prompted appraisal of the narcotic antagonist naloxone as a means of reversing the narcotic effect. Three studies of gastric emptying in paracetamol absorption were therefore carried out in each of four healthy volunteers, using the procedure already described for studies of pethidine and diamorphine. On each occasion the subjects were given an intramuscular injection of 60mg pentazocine or saline placebo 30 minutes before ingestion of the paracetamol solution and also an intravenous injection of naloxone (1.2mg) or placebo immediately before the paracetamol. Thus all four subjects were studied:-

(a) Under control conditions (IM and IV placebo)

(b) After pentazocine (IM pentazocine, IV placebo)

(c) After pentazocine and naloxone (IM pentazocine IV naloxone)

The order of the three studies was randomised and an interval of at least seven days was allowed between each.

The results are shown in Table 21. Statistical analysis was not attempted in view of the small number of subjects studied. However, in comparison with control studies, gastric emptying and paracetamol absorption were markedly delayed by pentazocine in all four subjects. These effects were largely prevented by the administration of naloxone. As in the previous studies, total absorption of paracetamol appeared to be independent of the rate at which the drug was absorbed. In the control, pentazocine and pentazocine plus naloxone studies, mean 24 hour urinary recoveries of paracetamol were respectively 75%, 79% and 74% of the ingested dose.

	Time to 50% emptying of ingested solution (min)	Peak plasma paracetamol concentration (µg/ml)	Time to peak (min after ingestion)
Control	13.0	23.8 ± 1.9	22.5 ± 1.3
Pentazocine	97.3	10.8 ± 0.6	160.0 ± 16.3
Pentazocine/ naloxone	27.8	15.0 ± 1.8	25.0 ± 1.8

Table 21 Effect of pentazocine and pentazocine plus naloxone on gastric emptying and paracetamol absorption in four healthy subjects. Data are means with SEM where appropriate.

SUMMARY

The effect of pethidine (150mg) and diamorphine (10mg) on gastric emptying and absorption of orally administered paracetamol was assessed in eight healthy volunteers. Both narcotic drugs produced a profound inhibition of gastric emptying and a marked delay in absorption of the paracetamol. In a subsequent study, pentazocine was shown to have similar actions, which could be prevented by concurrent administration of the narcotic antagonist, naloxone.

This effect of narcotic analgesics would appear to constitute a drug absorption interaction which has previously been unrecognised.

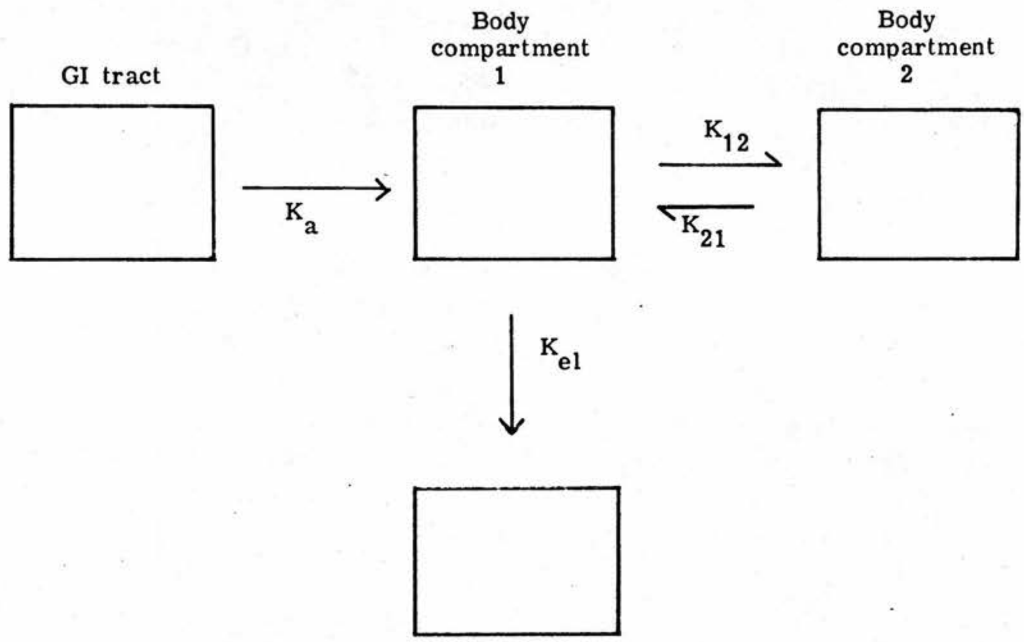
Pharmacokinetic analysis of paracetamol absorption data

Mathematical analysis of the kinetics of drug absorption and metabolism requires than an appropriate mathematical model be chosen to represent the system under study. One model widely used in the pharmacokinetic analysis of orally administered drugs is shown in Figure 41 (Gibaldi & Perrier, 1975). In this model, absorption of the drug from the gastrointestinal tract is represented as a first order process with a rate constant K_a. Clearly this is a major simplification of the biological reality, which causes K_a to be a hybrid constant, dependent on all the processes contributing to absorption of the drug. However, in practice, the value of K_a is determined principally by the slowest (i.e. rate limiting) step. The results presented so far indicate that for paracetamol, gastric emptying is the rate limiting step determining absorption and so for paracetamol, calculated values of K_a might be expected to approximate to gastric emptying rates.

Two considerations suggested that a more realistic mathematical model should be used to describe the kinetics of paracetamol absorption. Firstly, consideration of the gastric emptying patterns obtained in the studies with pethidine and pentazocine indicated that in many cases, emptying could not be represented satisfactorily by a first order function. Some of these emptying patterns are illustrated in Figure 42. However, there is an assumption inherent in the mathematical model shown in Figure 41 that the rate limiting step governing drug absorption can be considered a first order process. Another model was therefore devised (Fig. 43) in which the stomach and small intestine are represented as two separate compartments. Drug transfer from the small intestine to the central body compartment is represented by a first order rate constant K_a* and the presumption of first order kinetics for this/

Figure 41

The conventional mathematical model representing absorption, distribution and elimination of an orally administered drug. K_a = absorption rate constant, K_{12} and K_{21} = rate constants for exchange between body compartments. K_{el} = elimination rate constant.



GI tract
Body
compartment
1
Body
compartment
2
K12
K21
Ka
Kel

Figure 42

Gastric emptying results obtained from three subjects in whom the emptying patterns show considerable deviations from a monoexponential form.

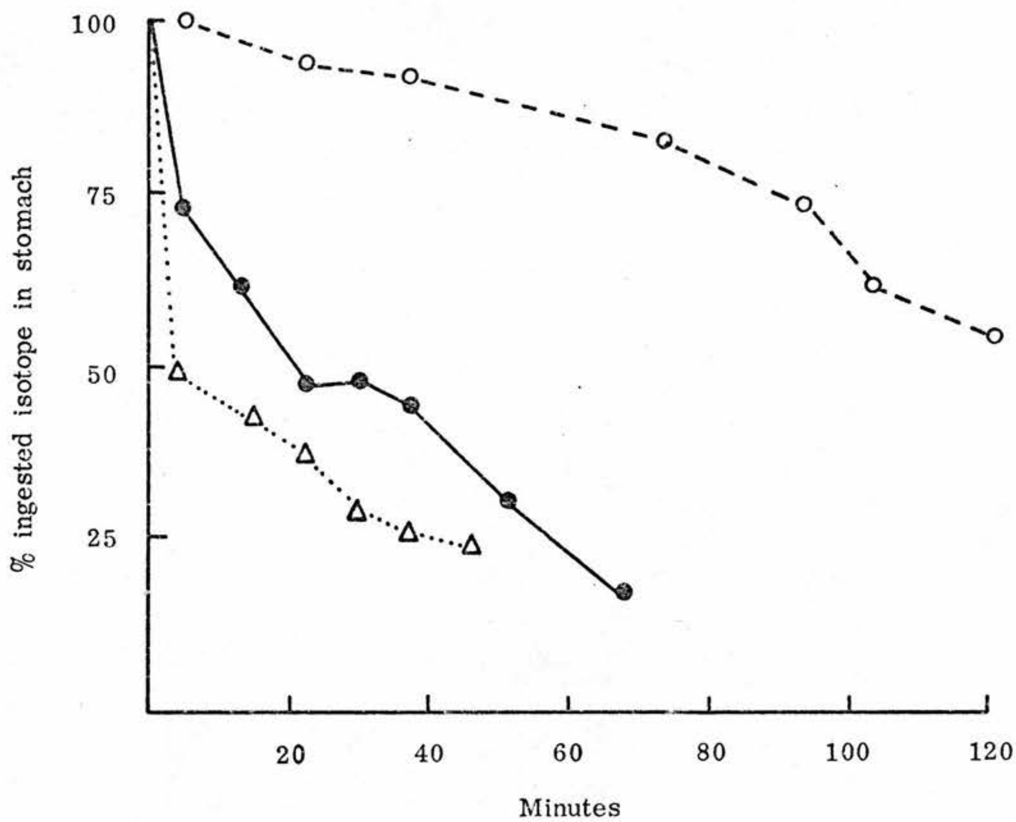
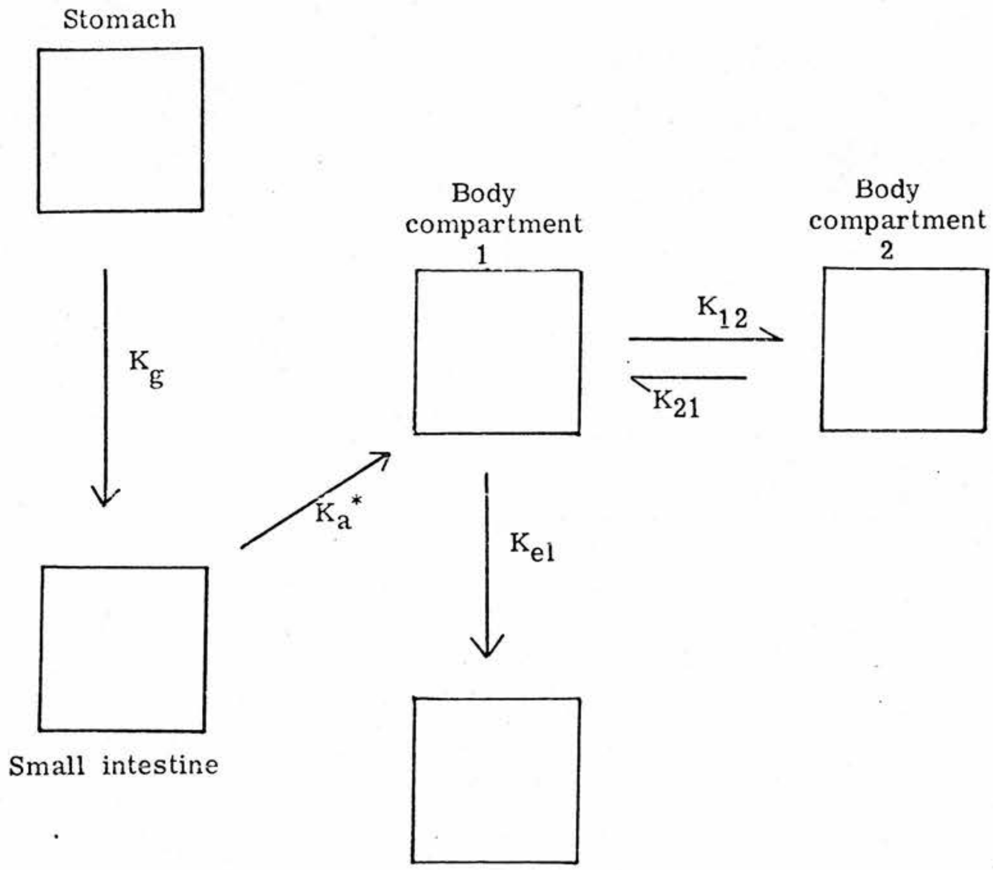

100
75
50
25
% ingested isotope in stomach
20
40
60
80
100
120
Minutes

Figure 43

A new mathematical model applicable to drug absorption studies. K_g = gastric emptying rate constant, K_a* = rate constant for absorption of the drug from the small intestine, other constants as in Figure 41.


Stomach
Body compartment 1
Body compartment 2
K_{12}
K_{21}
K_g
K_a^*
K_{el}
Small intestine

this process seems reasonable for passively absorbed drugs. This constant itself provides the second reason for adopting the new mathematical model, since K_a* can be calculated if gastric emptying data are known, and provides a new and potentially useful measurement of drug absorption from the small intestine.

Data processing procedures and the computer analysis necessary to calculate K_a* from experimental results were developed by Dr. John Clements of the Department of Pharmacy, Heriot-Watt University and were applied to the paracetamol absorption data obtained in the studies with pethidine and pentazocine. The methods and results have been reported in full (Clements, Heading, Nimmo & Prescott, 1978) and are not repeated here. However, they appear to justify the Figure 43 model and the analytical procedures were therefore used in further studies of paracetamol absorption which are described in the next chapter.

CHAPTER 10

EFFECTS OF GEL FIBRE ON GASTRIC EMPTYING

EFFECTS OF GEL FIBRE ON GASTRIC EMPTYING

The gel forming carbohydrates guar gum and pectin are types of dietary fibre resistant to digestion and absorption by the human alimentary tract. When these substances are added to glucose test meals, they reduce post-prandial blood glucose levels and in diabetic subjects, also reduce insulin requirements (Jenkins, Goff, Leeds, Alberti, Wolever, Gassull et al, 1976; Jenkins, Hockaday, Howarth, Apling, Wolever, Leeds et al, 1977; Jenkins, Leeds, Gassull, Cochet & Alberti, 1977). These observations have prompted the suggestion that dietary gel fibre might be helpful in the clinical control of diabetes (Jenkins, Hockaday, Wolever, Nineham, Goff, Haisman et al, 1979).

Despite convincing evidence that ingested gel fibre modifies post-prandial blood glucose levels, relatively little attention has been given to possible reasons for the effect. There are two obvious possibilities. Firstly incorporation of guar gum or pectin in a glucose solution may cause slowing of gastric emptying and so retard the absorption of glucose. One investigation has indicated that pectin produces delay in gastric emptying (Ralphs, Lawaetz, Brown & Leeds, 1978) but it is not known whether this delay is sufficient to explain the observed changes in blood glucose levels. An alternative, or perhaps additional, explanation of the effect is that gel fibres may interfere with the process of glucose absorption from the small intestinal lumen. Dietary pectin apparently enhances the absorption of paracetamol by rat small intestine (Brown, Kelleher, Walker & Losowsky, 1979).

In an attempt to resolve some of these uncertainties, further studies of the effect of gel fibre on absorption of glucose and paracetamol were carried out. Those with glucose were performed first/

first (Holt, Heading, Carter, Prescott & Tothill, 1979) and served to confirm and extend the observations previously reported by Jenkins et al. However, they did not provide a convincing answer to the main question concerning the role of altered gastric emptying as the basis for the changes in glucose tolerance induced by gel fibre. It appeared possible that this question might be answered by an investigation of paracetamol absorption.

Methods

Paracetamol absorption and gastric emptying were measured simultaneously in fourteen volunteers, six being healthy members of medical staff and eight being convalescent medical patients without known gastrointestinal disease. None of the subjects were taking any drug therapy.

After an overnight fast, each subject drank 400ml orange juice containing paracetamol (20mg/kg) and ^{113m}In DTPA as described in Chapter 9. On a subsequent occasion, eight of the subjects were given the same solution to which guar gum (16g) and pectin (10g) had been added. The gel fibres were dispersed in the solution by rapid sifting and the mixture was then allowed to stand for 15 minutes to form a homogeneous gel. On each occasion the subjects were allowed eight minutes for consumption of the test solution. Fluids were withheld for two hours thereafter and tobacco and food were withheld for four hours. Serial venous blood samples were taken up to eight hours, and urine was collected from 0-2 and 2-24 hours.

Gastric emptying rates were measured as previously described, except that the direct method was used for measurement of early emptying (see Chapter 3) and bilateral detection of intra-abdominal counts was used/

used throughout.

Unchanged and conjugated paracetamol concentrations in the plasma and urine samples were measured by high performance liquid chromatography (Adriaenssens & Prescott, 1978).

Statistical comparisons were performed using the Student t test for paired observations, except where otherwise indicated.

Results

Plasma paracetamol concentrations observed in the eight subjects studied with and without gel fibre are shown in Figure 44. The peak plasma paracetamol concentration attained was lower after guar gum and pectin than in the controls (12.6 compared with 17.9 µg/ml), $p < 0.0025$). The rate of gastric emptying was also significantly altered (Fig.45). The mean percentage of ingested ^{113m}In emptied from the stomach at 30 minutes was 31.9% after guar gum and pectin compared with 53.9% in controls ($p < 0.005$). The mean gastric emptying half-time was also longer after gel fibre (49.9 min.) than in controls (23.1 min, $p < 0.01$, signed ranks test).

To correlate the rate of gastric emptying with the rate of paracetamol absorption, the area under the plasma paracetamol concentration-time curve during the first 30 minutes was compared with the percentage of ingested test solution emptied from the stomach at 30 minutes. A significant positive correlation was obtained for the fourteen control studies ($r = 0.58$, $p < 0.05$; Fig. 46). To demonstrate that a similar relationship existed between paracetamol absorption and gastric emptying in the gel fibre studies, regression lines obtained from control ($r = 0.58$) and gel fibre studies ($r = 0.65$) were compared. Both/

Figure 44

Plasma paracetamol concentrations attained in fourteen control (solid line) and eight gel fibre (broken line) studies. Error bars indicate 1 SEM.

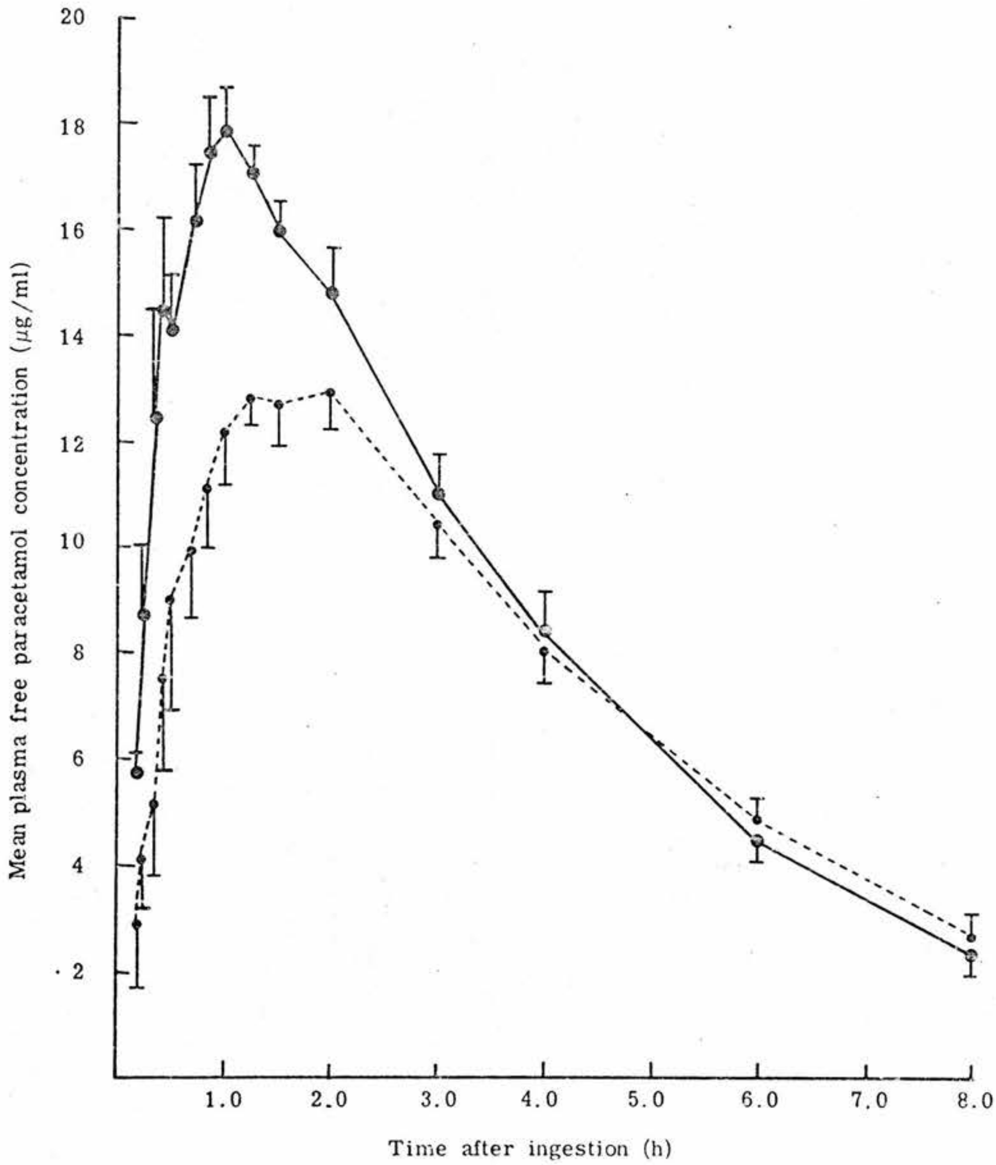

Mean plasma free paracetamol concentration (μg/ml)
20
18
16
14
12
10
8
6
4
2
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
Time after ingestion (h)

Figure 45

Effect of gel fibre on gastric emptying of the ingested solution in eight subjects.

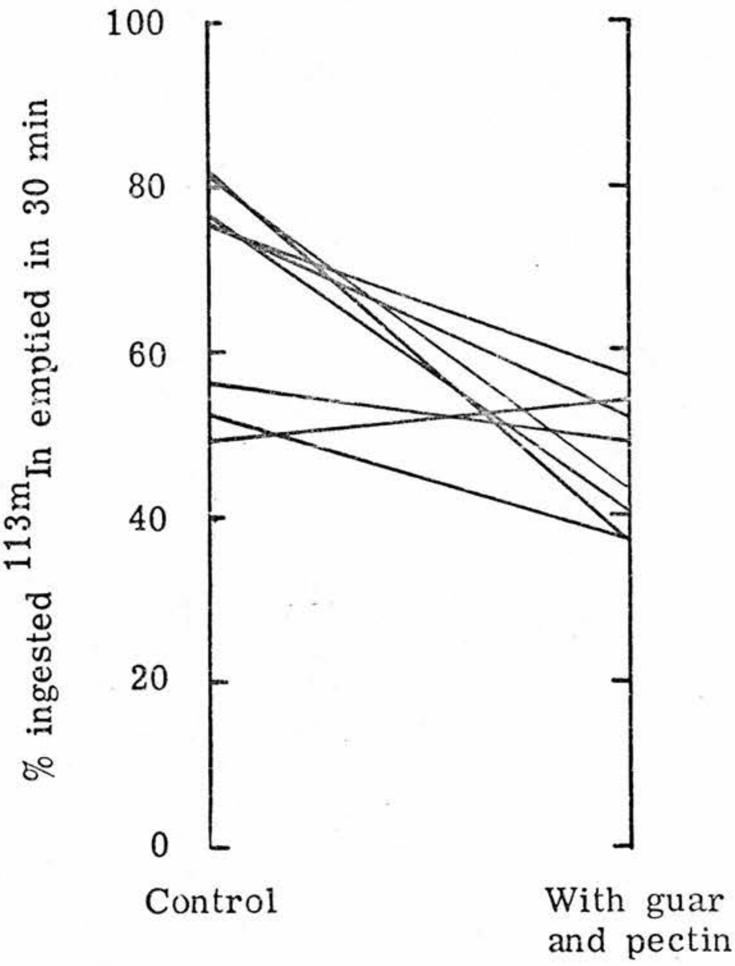
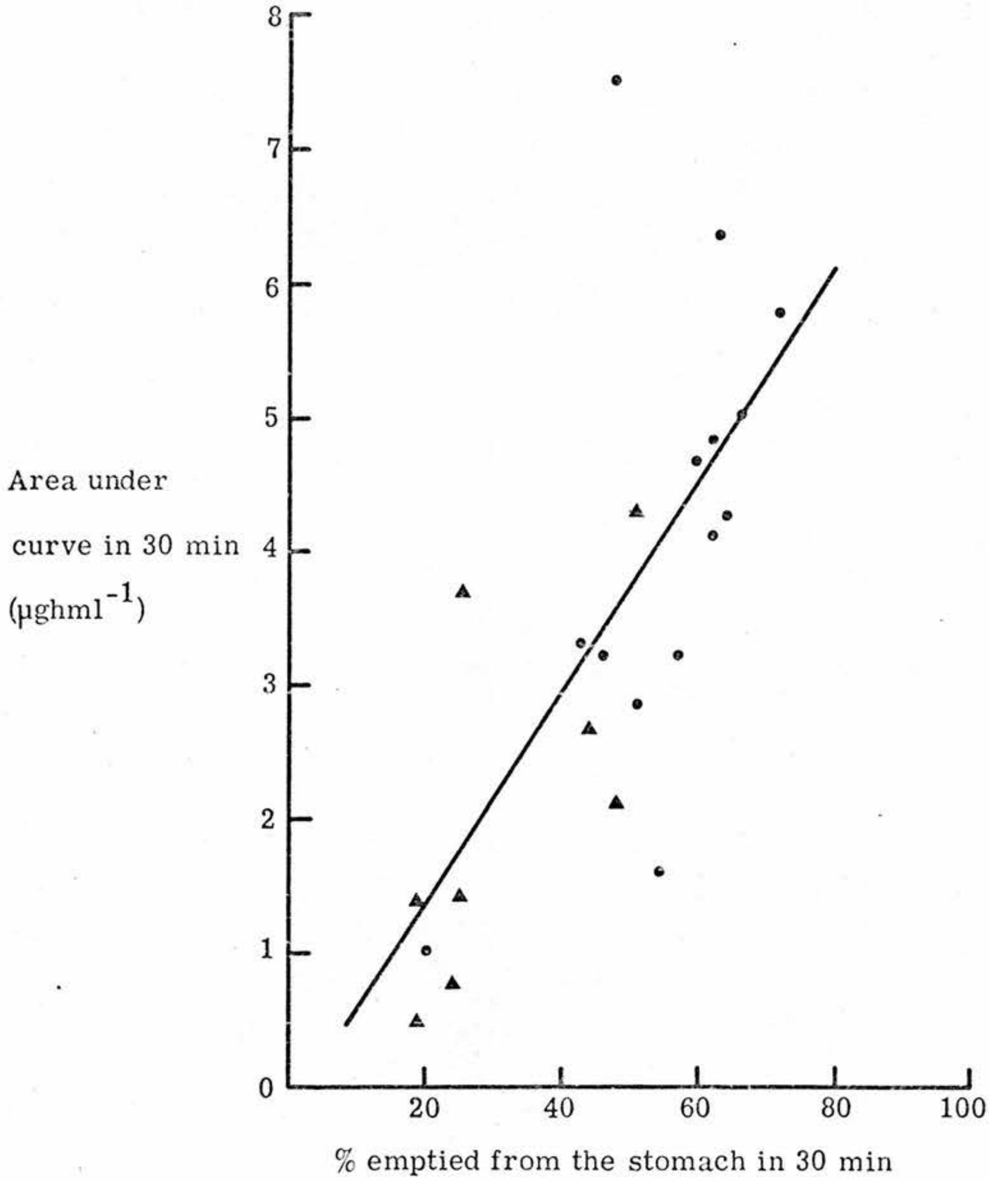

100
80
60
40
20
0
% ingested 113mIn emptied in 30 min
Control
With guar
and pectin

Figure 46

Relationship between the area under the plasma paracetamol concentration time curve (0-30 min) and gastric emptying of the ingested solution at 30 min in fourteen control (closed circles) and eight gel fibre studies (triangles). The regression line is derived from the control studies only.



Area under
curve in 30 min
(µghml^{-1})
0
1
2
3
4
5
6
7
8
20
40
60
80
100
% emptied from the stomach in 30 min

Both regression lines are based on observations in the same individuals (8 of the 14 subjects) and so standard statistical methods of comparison, which are based on independence of the observations do not apply. However, an extension of a method proposed by Yates (1939) is appropriate to the present situation. By applying this procedure, the regression lines derived from studies with and without the gel fibres show no significant differences in slope or intercept. This might appear to indicate that the relationship between gastric emptying and paracetamol absorption was similar in the control and gel fibre studies but since the regression is responsible for only 42% of the variance in the control studies ($r^2 = 0.42$), failure to distinguish the control and gel fibre regression lines is no more than weak evidence of their similarity.

Pharmacokinetic analysis of the paracetamol absorption data was therefore carried out as described on p 181. The observations made in one subject were excluded from the analysis, because emptying of the paracetamol solution with gel fibre was poorly represented by a monoexponential function and could not be satisfactorily incorporated in the analysis.

The results from the remaining seven subjects are given in Table 22. These results also show significant slowing of gastric emptying by the gel fibre ($p < 0.01$) but K_a*, the rate constant for paracetamol absorption from the small intestine was unaltered. This implies that the gel fibre had no material effect on paracetamol absorption from the small intestinal lumen.

The total absorption of paracetamol in studies with and without gel fibre was assessed by the 24 hour urinary recovery of paracetamol plus its metabolites (Table 23). A smaller proportion of the administered dose was recovered during the first 2 hours after gel fibre than/

Subject	Control		with guar and pectin	
	Gastric emptying half-time (min)	K_a* (min^{-1})	Gastric emptying half-time (min)	K_a* (min^{-1})
1	16	0.0962	52	0.0929
2	18	0.0958	41	0.0581
3	21	0.0942	43	0.0497
4	30	0.0637	38	0.0955
5	31	0.1009	50	0.0902
6	52	0.0426	50	0.0869
7	15	0.0762	24	0.1298
Mean	26.3	0.0814	48.6	0.0862
SEM		0.0031		0.0038

Table 22 Effect of gel fibre on gastric emptying and on the rate constant for paracetamol absorption from the small intestine, (K_a*) in seven subjects.

	% administered dose of paracetamol recovered in urine	
	0-2h	0-24h
Paracetamol solution alone	13.4 ± 6.0	86.3 ± 11.2
Paracetamol solution with guar and pectin	8.8 ± 3.4	75.6 ± 13.8

Table 23 Urinary recovery of paracetamol plus metabolites after ingestion of paracetamol solutions with and without gel fibre.

Data are means ± SD; n = 8.

than in controls (8.8 compared with 13.4%, $p < 0.05$) but the 24 hour urinary recovery was much the same. These findings support the plasma paracetamol results, indicating that absorption of the drug was delayed by gel fibre but that its total absorption was not significantly reduced.

Discussion

These studies clearly show that the addition of gel fibre to the ingested paracetamol solution caused a slowing of gastric emptying and a reduction in the peak plasma paracetamol concentration attained. The results further demonstrate that the alteration in emptying was largely, if not wholly, responsible for the reduced plasma concentrations of the drug. This conclusion is barely justified by the data shown in Figure 46, but is more firmly supported by the results of the pharmacokinetic analysis. This showed no evidence that the gel fibre inhibited small intestinal absorption of paracetamol - indeed the mean value for K_a* was marginally greater in the guar-pectin studies than in the controls.

The delay in gastric emptying produced by guar and pectin is presumably related to their physical form after hydration. Guar forms a viscous, colloidal suspension when hydrated, and it is probably the viscous nature of this suspension that is responsible for the effect on gastric emptying. The gel fibres produced no substantial changes in the osmotic pressures or pH of the solutions taken by the subjects. Although Hunt (1954) has suggested that viscosity has no effect on the gastric emptying of a test solution, his experiments employed solutions which were much less viscous than those used in the present study. Thus the experimental conditions are not comparable.

Studies/

Studies with glucose suggested that changes in gastric emptying could explain the effect of gel fibre on plasma glucose levels attained after ingestion of a glucose test meal (Holt et al, 1979). These observations with paracetamol demonstrate directly that gastric emptying is altered by incorporation of gel fibre in a test solution and imply that for paracetamol at least, changes in gastric emptying are solely responsible for changes in plasma levels of the drug. It seems highly likely that altered gastric emptying also accounts for the effect of gel fibre on absorption of glucose.

SUMMARY

To investigate the effect of gel fibre on the absorption of other orally administered substances, studies of gastric emptying and paracetamol absorption were undertaken with and without the addition of pectin and guar to the ingested paracetamol solution. Both gastric emptying and paracetamol absorption were slower in the studies with gel fibre than in controls, but the total absorption of paracetamol, reflected in the urinary recovery, was unaffected. Pharmacokinetic analysis of the observations permitted calculation of K_a*, the rate constant for paracetamol transfer from small intestine to blood. K_a* values were similar in the control and gel fibre studies, indicating that the effect of gel fibre on paracetamol absorption can be wholly explained by the changes in gastric emptying.

CHAPTER 11

FURTHER METHODOLOGICAL CONSIDERATIONS

FURTHER METHODOLOGICAL CONSIDERATIONS

Although the earliest scintigraphic measurements of gastric emptying in man were undertaken with a rectilinear scanner, gamma cameras have been used in almost all published work since 1970. It must therefore be admitted that the studies described in the preceding chapters, based as they are on use of a rectilinear scanner, have employed "unfashionable" equipment. The reasons for this choice merit further comment.

One major difference between the double-headed rectilinear scanner and a gamma camera is that simultaneous anterior and posterior counting is only possible with the former. The bilateral detection of intra-abdominal counts permits correction for changes in radiation attenuation due to differences in depth of activity within the abdomen, whereas no such allowances can be made if unilateral detection alone is used. Most gamma camera studies of gastric emptying in man have either disregarded completely the possible problem of changing attenuation of gamma emissions during emptying of the stomach, or have assumed that the resulting errors in measurement of emptying rate are insignificant. However, the limited comparison of unilateral and bilateral counting in determination of early emptying (described in Chapter 3) seemed to indicate that some concern was necessary. In due course, further attention was given to this problem in an attempt to determine more precisely the errors in gastric emptying measurements arising from use of unilateral count detection.

Retrospective Study

Methods

Gastric emptying measurements previously made in eighty subjects were/

were re-examined. These subjects included duodenal ulcer patients, patients who had undergone gastric surgery, diabetics with autonomic neuropathy and normal volunteers, so that there was a wide range of emptying rates. All subjects had been studied using the double isotope scanning procedure described in Chapter 3, with bilateral detection of intragastric radioactivity throughout the period of study. Anterior and posterior counts were recorded separately.

Studies in vitro

Scans of a bottle filled with ^{99m}Tc or ^{113m}In in solution were carried out at different depths in a phantom of unit density material. The variation in counts with depth approximated to a monoexponential with an attenuation coefficient, μ, of 0.12 cm^{-1} for the 140 keV emission of ^{99m}Tc and 0.09 cm^{-1} for the 390 keV emission of ^{113m}In. In accordance with theory, the geometric mean of counts recorded from opposed detectors was dependent only on overall thickness of the phantom and was independent of the source depth within the phantom.

Repeated measurements of a given source depth had a standard deviation of less than 1mm and measurements with the source at different depths showed that depth differences could be established with an accuracy of better than 5mm.

Calculations

Given an exponential attenuation, relative depths of activity may be inferred from the ratio, R, of count rates from the opposed detectors. If the total thickness is t and the distance of a source from the mid-plane of the body is d, the count rate recorded from one side is proportional to $e^{-\mu (t/2 - d)}$ and from the other side to $e^{-\mu (t/2 + d)}$. The/

The ratio R is thus $e^{2\mu d}$ so that $d = \ln R/2\mu$. Values of d were therefore calculated from the anterior and posterior counts in the stomach area on each of the scans, to determine the variations occurring during the emptying process. Values of d were normalised to zero on the first scan and a positive value on any subsequent scan represented a net anterior movement of intragastric radioactivity.

Results

Depth of Activity

Changes in depth of the intragastric ^{99m}Tc-labelled particles were determined in seventy-nine subjects. In fifty-nine cases, the radioactivity moved anteriorally by at least 5mm between the first and second scans. A corresponding posterior movement was recorded in four subjects and in sixteen cases any movement was less than 5mm. The mean movement was 13mm. Later scans exhibited a wider range of depths with no significant further movement of the mean.

The corresponding results for ^{113m}In showed that intragastric activity moved anteriorally by an average of 7mm between the first and second scans.

Effect on emptying rate measurements

The anterior movement of activity between the first and second scans leads to an increase in counting efficiency by the anterior detector amounting to a mean 17% increase for ^{99m}Tc and a mean 7% increase for ^{113m}In. These changes in detection efficiency inevitably affect the shape of an emptying-time curve and the mean results for all the ^{99m}Tc and ^{113m}In measurements are shown in Figures 47 and 48 respectively. These curves have been normalised to 1.0 at the time of/

Figure 47

Gastric emptying of ^{99m}Tc-labelled particles as determined from anterior counts (closed circles), posterior counts (open circles) and geometric mean counts (triangles). Intragastric activity at 10 min was arbitrarily defined as 1.0 in each case.

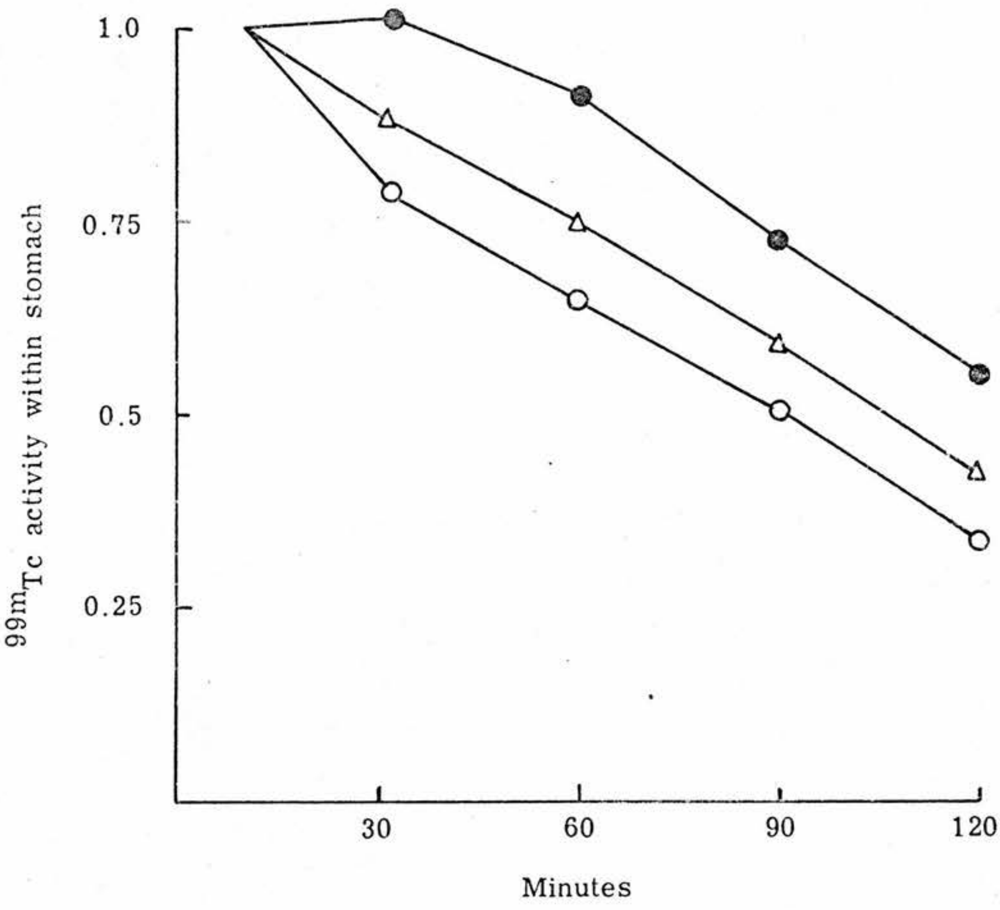
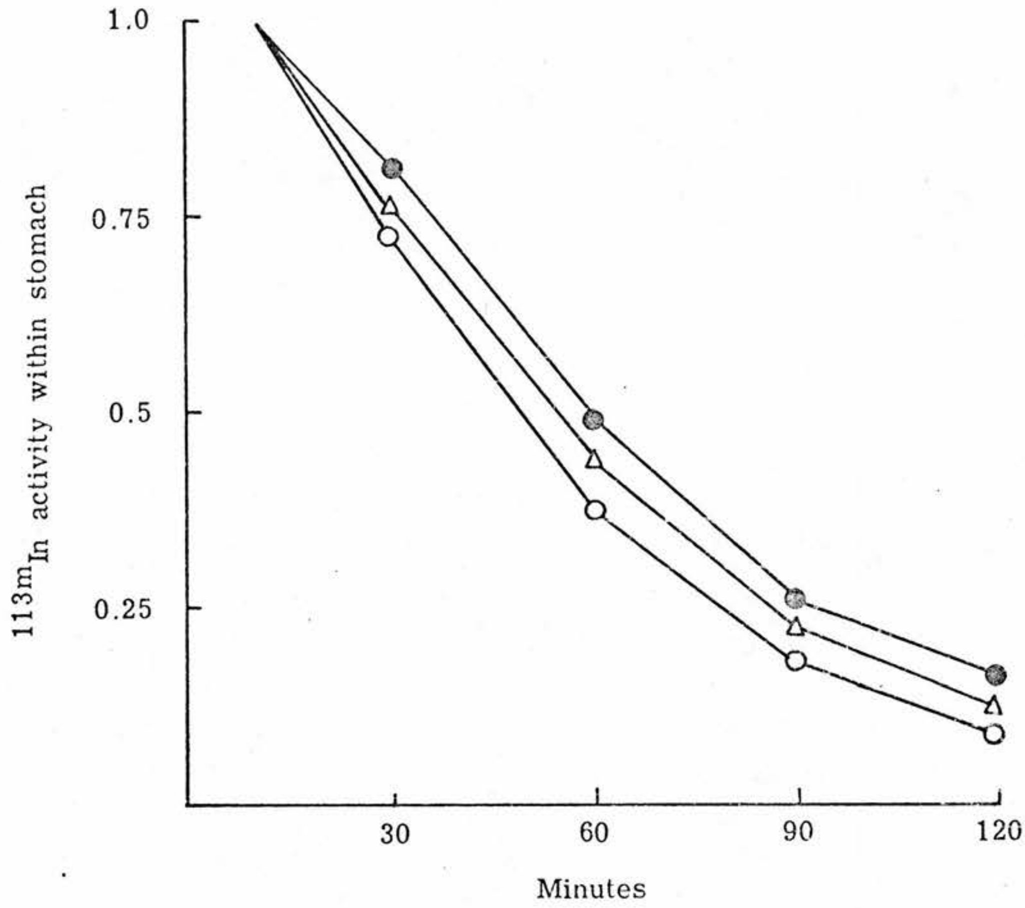

1.0
0.75
0.5
0.25
^{99m}Tc activity within stomach
30
60
90
120
Minutes

Figure 48

Gastric emptying of ^{113m}In DTPA as determined from anterior, posterior and geometric mean counts. Symbols as for Figure 47.


1.0
0.75
0.5
0.25
113m In activity within stomach
30
60
90
120
Minutes

of the first scan rather than expressed as 100% at zero time, so as to render them more readily comparable with the depth change results described above. It is clear from these curves that the use of an anterior detector alone produces a result somewhat different from that produced by the determination of geometric mean counts which, for the reasons already described, are assumed to be the accurate measurements. The ^{99m}Tc emptying rates, calculated by linear regression of the intragastric count-time plots were on average 26% lower when determined by the anterior detector alone than when calculated from geometric mean counts. However, the errors were proportionately greater in individuals with slow emptying rates. In some, intragastric radioactivity even appeared to increase between the first and second scans!

The emptying rate of ^{113m}In (expressed as a first order rate constant) was also underestimated by use of the anterior detector alone. The average error was 16%.

Early emptying measurements

Separate recording of whole abdomen counting from the opposed detectors was performed for ^{113m}In in eighteen subjects. On average, intragastric radioactivity was 3cm posterior to radioactivity in the rest of the abdomen at the time of the first scan, implying a relatively increased detection efficiency for the non-gastric intra-abdominal isotope. The average difference between early emptying measurements from anterior counts and geometric mean counts was 4% of ingested ^{113m}In or 18% of the mean value of 22% for the "true" (geometric mean) early emptying. This result is, of course, very similar to the discrepancy of 5% of ingested ^{113m}In previously observed and described in Chapter 3.

Discussion/

Discussion

This retrospective analysis of gastric emptying measurements shows that changes in depth of activity do occur during the gastric emptying process and that the resultant variations in counting efficiency lead to errors in emptying rate measurements. The magnitude of the average errors observed (26% for ^{99m}Tc and 16% for ^{113m}In emptying rates) suggests that the use of anterior detection alone is associated with inaccuracies greater than appreciated hitherto. Whether such errors are important will necessarily depend on the purpose for which the gastric emptying measurements are being made but it seems likely that errors of this size will sometimes constrain the interpretation of results.

The observation of an apparent plateau or even a rise in intragastric activity recorded by an anterior detector is not original and indeed a plateau may correctly represent a delay in the onset of emptying. However, it is possible that such a plateau may be due to activity within the duodenum or jejunum overlapping the selected gastric area, so causing a false impression of a delay in the onset of gastric emptying. This type of overlap undoubtedly occurs and may be especially marked in patients with gastric ulcer (Anselmi, Harding, Donovan & Alexander Williams, 1979). However, subjects in whom major overlap of gastric and small intestinal activity was recognised were excluded from the present study and it is clear that overlap artefact cannot explain the present observations, since it would inevitably register on the posterior as well as the anterior detector. Figures 47 and 48 clearly show that it does not and that the initial plateau of emptying shown by the anterior detector is caused by net forward movement of intragastric radioactivity. Presumably this forward movement/

movement is due to transfer of activity from the gastric body to the antrum, since with the subject supine, the vertebral column will cause the antrum to lie in a plane anterior to the gastric body.

The present observations are clear evidence that anterior detection of intragastric radioactivity may give rise to substantial errors in gastric emptying measurements. This gives cause for concern in relation to the use of gamma cameras but it would be wrong to declare that the present observations may be applied directly to emptying studies performed with a gamma camera. Most gamma camera studies are performed with the subject in a sitting position, not supine, and clearly this is a major difference. Further investigations were therefore undertaken to determine the importance of posture as an influence in measurement errors and to see whether these problems could be assessed directly using a gamma camera.

Methods

Posture study

Ten further subjects were studied, each on two occasions with an interval of 1-4 days. The procedure for the emptying measurement was identical to that described previously, except that (1) the standard meal contained the ^{99m}Tc particles but no ^{113m}In DTPA and (2) for one of the two studies on each subject, the frame of the scanner was rotated so that measurements were made with the subject standing.

Gamma camera study

Eight patients were examined. Emptying of the two isotope markers was studied sequentially, using first the cornflakes, sugar and milk meal containing ^{99m}Tc-labelled particles. The subject then sat in front/

front of a Nuclear Enterprises Mark V gamma camera fitted with a parallel hole medium energy collimator and images of the stomach area were accumulated at intervals, alternately from the anterior and posterior aspects of the upper abdomen. After 2 hours, a second meal of cornflakes, sugar and milk was given, this time containing the ^{113m}In DTPA. Images from the anterior and posterior aspects of the upper abdomen were again recorded. As there was an interval of 2-3 minutes between the anterior and posterior measurements, interpolations were performed on the calculated emptying curves to co-ordinate results and deduce the variations in depth of stomach activity.

Results

Posture study

Net antero-posterior movements of intragastric radioactivity are shown in Figure 49. The depth of activity on the first scan was again taken to define zero. In the supine subjects, there was a net anterior movement of radioactivity after the first scan, mean depth changes at the second, third, fourth and fifth scans being 4 mm, 13 mm, 12 mm and 21 mm respectively. With the exception of the first of these, the movements were significantly different from zero ($p < 0.02$).

These results are generally similar to those obtained previously. However, when the measurements were made with the patients upright, the changes in mean depth of activity were smaller (Fig. 49) and none were statistically different from zero.

The effects of depth changes on calculated emptying rates are shown for these ten subjects in Figure 50. For both the supine and upright measurements, there were positive correlations between the anterior movement of intragastric radioactivity and the amount by which/

Figure 49

Net movements of ^{99m}Tc-labelled particles recorded from ten subjects studied supine (solid line, open circles) and standing (broken line, closed circles) using the rectilinear scanner. Data are means ± SEM.

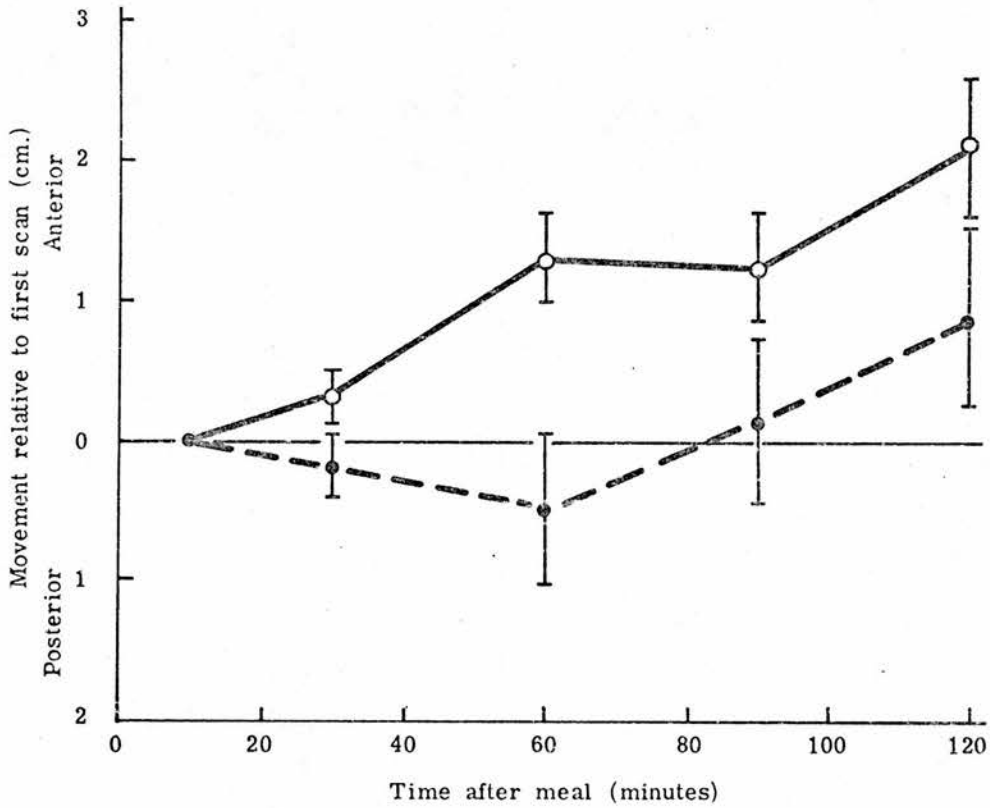
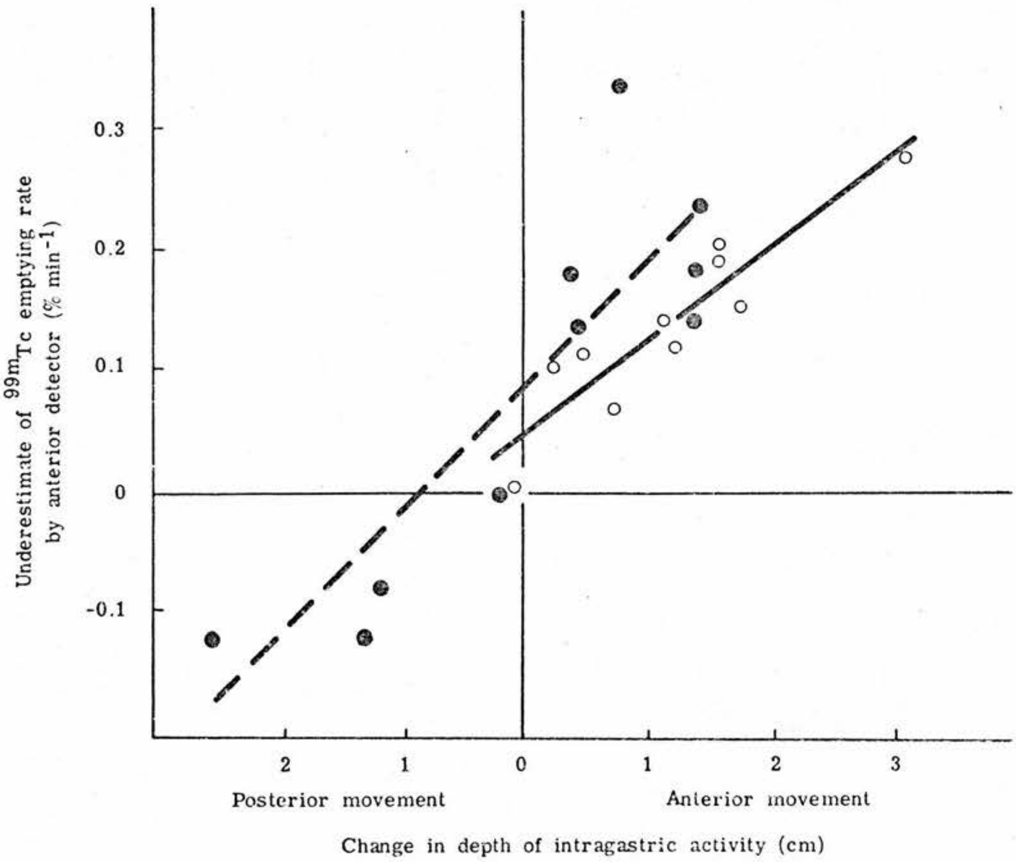

3
2
1
0
1
2
Anterior
Posterior
Movement relative to first scan (cm.)
0
20
40
60
80
100
120
Time after meal (minutes)

Figure 50

Correlations of change in depth of intragastric ^{99m}Tc-labelled particles with the error associated with unilateral determination of gastric emptying rate. Ten patients were studied supine (solid line, open circles) and standing (broken line, closed circles) using the rectilinear scanner.


0.3
0.2
0.1
0
-0.1
Underestimate of 99mTc emptying rate by anterior detector (% min-1)
2
1
0
1
2
3
Posterior movement
Anterior movement
Change in depth of intragastric activity (cm)

which the emptying rate determined from anterior counts underestimated the rate calculated from the geometric mean counts ($p < 0.001$). In both positions, anterior movement of 1 cm corresponded to an underestimate by about 0.1% min^{-1}. The major difference between the upright and supine measurements in these patients was that while anterior movement predominated with supine measurements, four of the ten exhibited a net posterior movement of radioactivity when upright. This led to "no net change in depth" in the group as a whole. However, this does not imply that depth changes (and measurement errors) did not occur in individual subjects.

Gamma camera study

The corresponding results of the gamma camera studies on eight further subjects are shown in Figures 51 and 52. In these patients, there was again a net forward movement of radioactivity, slightly more marked for the ^{99m}Tc particles than for ^{113m}In. Positive correlations between anterior movement and the underestimate of emptying rate by anterior detection alone were again found ($p < 0.05$ for ^{99m}Tc, $p < 0.02$ for ^{113m}In).

Discussion

These further results confirm the conclusions suggested by the earlier study. Variations in depth of radioactivity are still encountered when subjects are studied in the upright position and there are consequent errors in measured emptying rates if unilateral detection alone is used. Anterior movement of intragastric radioactivity occurs most frequently and leads to an underestimate of emptying rate by an anterior detector. However, it is notable that there is a major difference between the two isotopes in the average error/

Figure 51

Gastric emptying of (a) ^{99m}Tc-labelled particles and (b) ^{113m}In DTPA as determined by anterior and posterior counting with a gamma camera. Points are mean values from eight patients; intragastric activity at 10 min was arbitrarily taken to be 100.

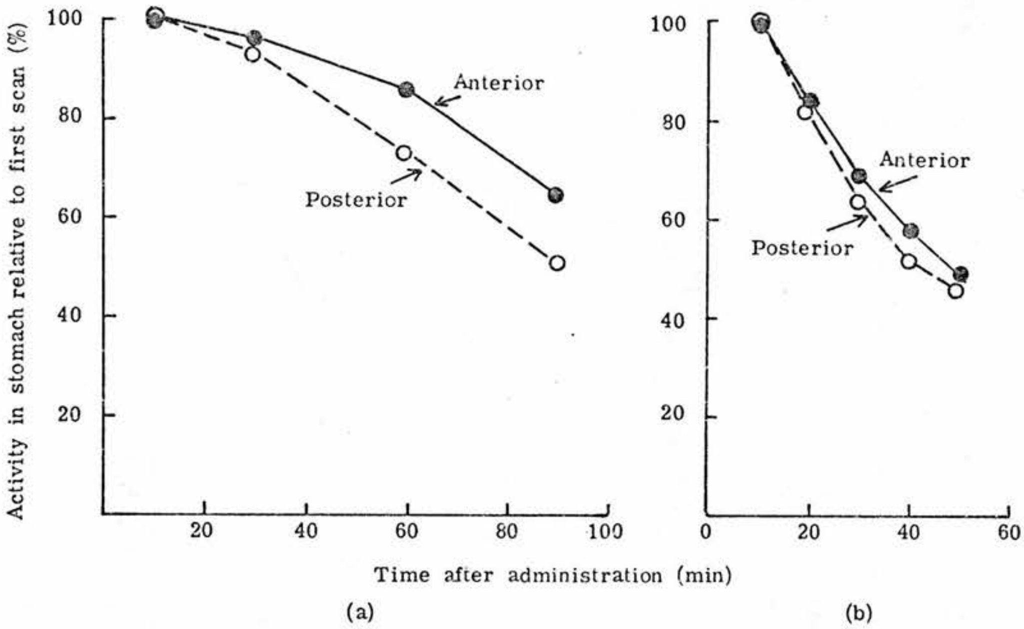
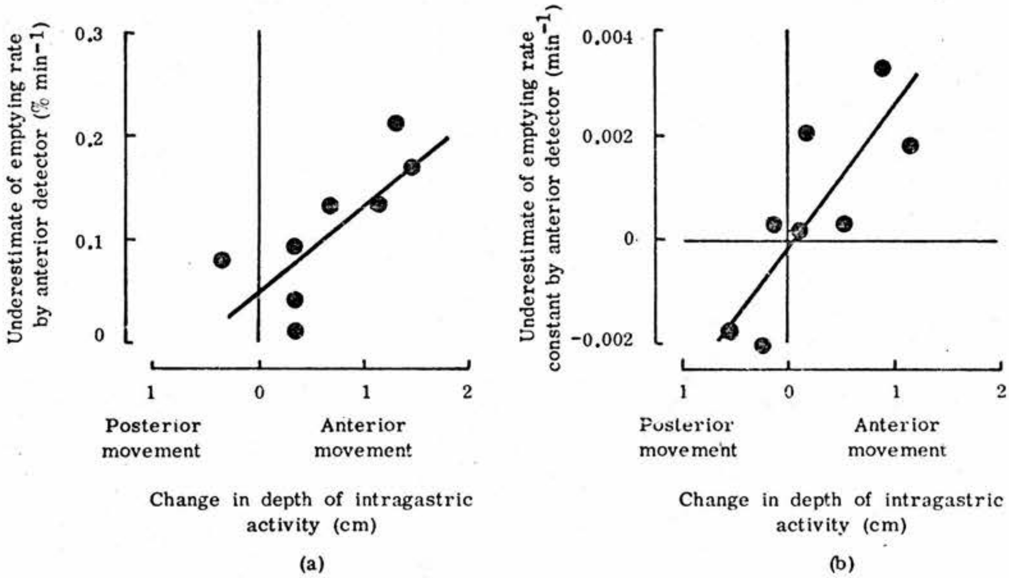

Activity in stomach relative to first scan (%)
100
80
60
40
20
Anterior
Posterior
20
40
60
80
100
Time after administration (min)
(a)
100
80
60
40
20
Anterior
Posterior
0
20
40
60
(b)

Figure 52

Correlations of change in depth of intragastric activity with the error associated with the use of anterior detection alone to measure gastric emptying rate. Eight patients were studied with ^{99m}Tc-labelled particles (a) and with ^{113m}In DTPA (b) using a gamma camera.



Underestimate of emptying rate by anterior detector (% min-1)
0.3
0.2
0.1
0
1
0
1
2
Posterior movement
Anterior movement
Change in depth of intragastric activity (cm)
(a)
Underestimate of emptying rate constant by anterior detector (min-1)
0.004
0.002
0
-0.002
1
0
1
2
Posterior movement
Anterior movement
Change in depth of intragastric activity (cm)
(b)

error due to this unilateral detection. The difference is due in part to the different energies of gamma emission of the two isotopes and in part to the smaller average anterior movement of the ^{113m}In. Thus in the gamma camera study, the average underestimate of emptying rate for the ^{99m}Tc-labelled particles was 0.076% min^{-1} (i.e. 15% of a typical normal emptying rate of 0.5% min^{-1}) whereas the comparable average error for ^{113m}In corresponds to an error of about one minute in a typical emptying half-time of 32 minutes (i.e. a 3% error). As before, it is not legitimate to assert from these results that the errors of measurement are either "significant" or "insignificant" since their importance will necessarily vary with the nature and purpose of the study for which gastric emptying measurements are being made. However, provided that patients are studied erect rather than supine, it is likely that for many purposes unilateral detection of ^{113m}In will be acceptable. For studies such as those presented in the preceding chapters, it would seem that ^{99m}Tc counting must be undertaken with opposed detectors, if acceptable accuracy is to be achieved.

The problem of area selection

Selection of the stomach area on an abdominal scan requires an arbitrary and subjective judgement which can be justified if the scintigraphic measurement of gastric emptying compares favourably with alternative methods of measurement. Chapter 2 includes results of one such comparison and more satisfactory comparisons have more recently been conducted by others (Delin, Axelsson Johansson & Poppen, 1978; Harding, Griffin & Donovan, 1979). However, it is also useful to assess errors in emptying rate measurements which result from errors in selection of the "optimal" gastric area. Different observers will sometimes disagree on the selection.

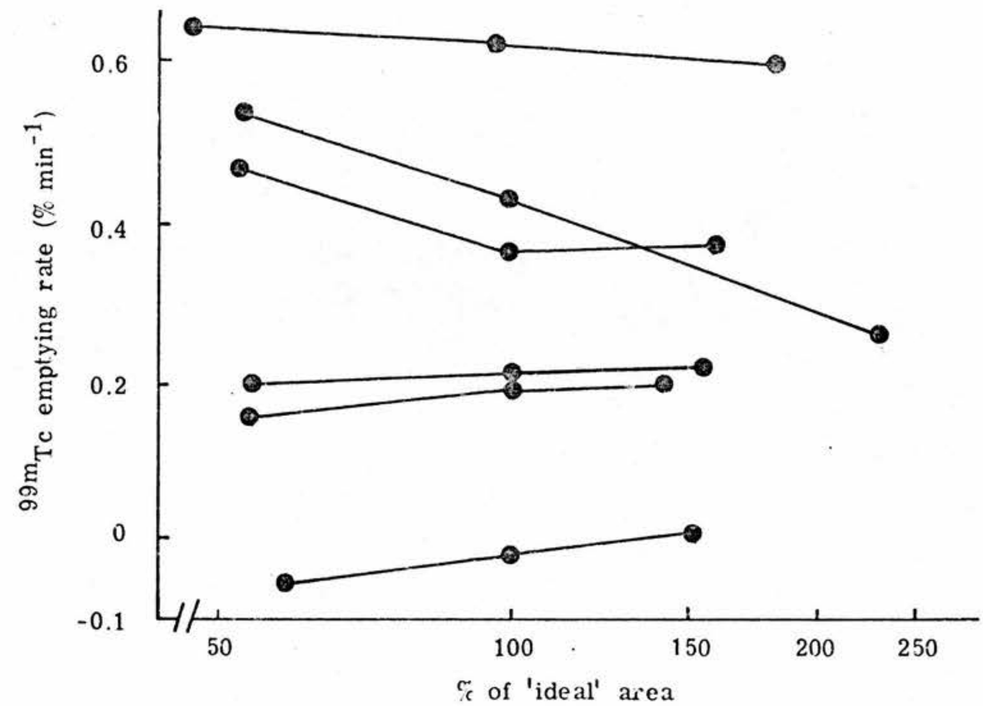
Emptying/

Emptying measurements were performed on six subjects using the double isotope scanning procedure with bilateral detection of counts throughout. Emptying rates for ^{113m}In and ^{99m}Tc were determined on the basis of a gastric area selected conventionally and assumed to be the optimal selection. Similar determinations were then made from two further area selections, deliberately chosen to be inappropriately large and inappropriately small.

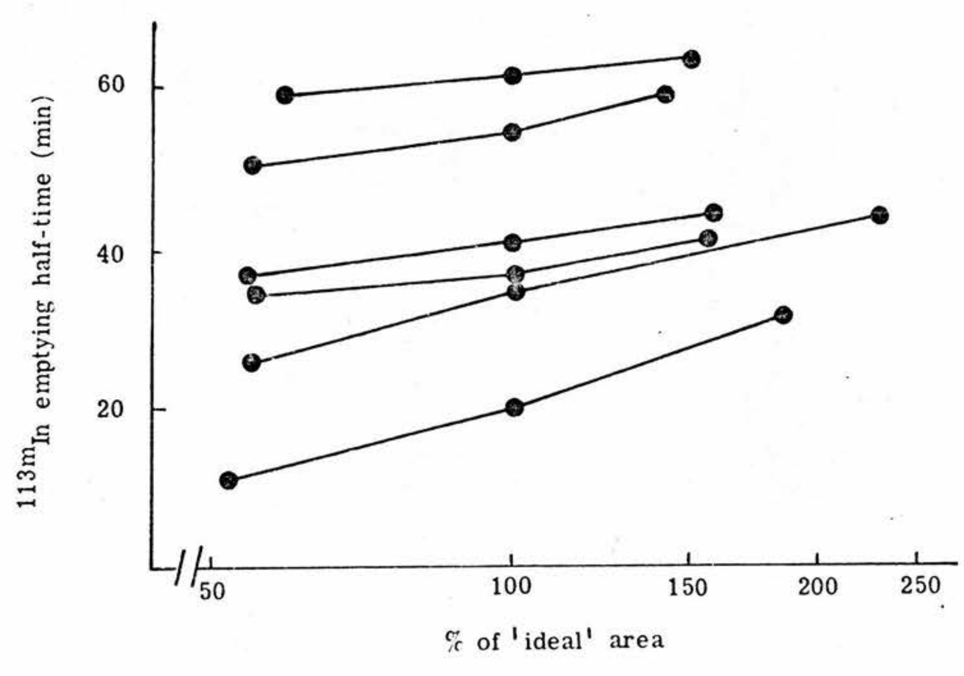
The effect of these area selections on calculated emptying rates is shown in Figure 53. It seems generally reassuring that the ^{113m}In emptying half-time and ^{99m}Tc emptying rate were in error by an average of only 5.5 min and 0.045% min^{-1} respectively when selection of the area was incorrect to this extent. It seems likely that inadvertent misjudgements of the optimal gastric area on a scan or gamma camera display can be expected to be smaller, with correspondingly reduced errors in the measured emptying rates. It is presumably because the emptying rate determinations are not critically dependent on area selection that fixed detector systems can be used to provide emptying rate measurements for which reasonable accuracy has been claimed (Ostick, Green, Howe, Dymock & Cowley, 1976; Blake & McKelvey, 1979).

Figure 53

Emptying rates of ^{99m}Tc-labelled particles and ^{113m}In DTPA determined from different area selections on the abdominal scans.



^{99m}Tc emptying rate (% min^{-1})
0.6
0.4
0.2
0
-0.1
50
100
150
200
250
% of 'ideal' area



^{113m}In emptying half-time (min)
60
40
20
50
100
150
200
250
% of 'ideal' area

SUMMARY

In studies with the rectilinear scanner and with a gamma camera, net anterior and posterior movements of intragastric radioactivity were measured during gastric emptying of the double isotope labelled test meal. When measurements were made with the subject supine, net anterior movement was usual and led to a misleadingly slow gastric emptying rate determination if only anterior detection of intragastric radioactivity was performed. When subjects were studied standing or sitting, the pattern was more variable but again anterior movement was seen in most cases. Greater movements occurred with ^{99m}Tc-labelled particles than with ^{113m}In DTPA and this, together with the greater tissue attenuation coefficient for the ^{99m}Tc gamma emission, resulted in much greater errors in ^{99m}Tc emptying rate measurements made by unilateral detection. The observations suggest that while unilateral detection is reasonably accurate for ^{113m}In, bilateral detection is necessary for comparable accuracy if ^{99m}Tc is chosen as the tracer.

POSTSCRIPT

WHY MEASURE GASTRIC EMPTYING?

WHY MEASURE GASTRIC EMPTYING?

Acceptably accurate measurements of gastric emptying by external counting methods are now seen to be feasible. However, it is clear that such measurements are only a worthy objective if they are performed in the context of some broader scientific or clinical purpose. It is therefore desirable to consider briefly possible reasons for performance of gastric emptying studies at the present time.

Gastric emptying measurements may be undertaken in the hope that a result obtained from an individual patient may be useful in relation to clinical diagnosis or management of that patient. At present, no systematic study has been published in which the value of such measurements has been appraised. Nevertheless, it seems possible that gastric emptying measurements may be of value in the assessment of patients with symptoms after gastric surgery or in patients with suspected gastric stasis. It is conceivable that measurements may also be useful in the assessment of individual responses to treatment of such disorders. However, this remains to be determined.

There are two broad categories of research activity in which gastric emptying studies may be appropriate. Firstly there are investigations which are intended to increase knowledge of physiology or pathophysiology of gastric motor function. In the foregoing chapters, most of the observations on early emptying and on solid-liquid discrimination can be considered relevant to gastric physiology. When abnormalities of gastric motor function are known to occur, emptying studies may be necessary in the assessment of attempts to correct those abnormalities. Such investigations are likely to be clinically orientated, but may be distinguished from studies undertaken in individuals/

individuals to gain information directly relevant to that individual.

A slightly different type of research study in which gastric emptying measurements may be appropriate is the one in which changes in gastric emptying may affect other events which are the prime focus of the investigation. For example, a recent study of paracetamol absorption in coeliac disease and Crohn's disease (Holt, Heading, McLoughlin & Prescott, 1979) would fall into this category, since gastric emptying measurements were highly relevant to the investigation but were not its primary objective.

It is probably unwise to attempt prediction of the nature of future studies of gastric emptying, although it seems likely that they will fall within these three broad categories. Meyer (1979) has reviewed some of the questions about gastric physiology that have been prompted by new knowledge gained with current intubation procedures and external detection methods and it is worth recording his conclusion:-

> "Progress in this rapidly developing field depends on identifying, quantitating and, hopefully, circumventing troublesome sources of error".

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