

**THE USE OF SCINTIGRAPHY TO STUDY GASTRIC
EMPTYING, MOTILITY AND SMALL INTESTINAL
TRANSIT IN PATIENTS WHO HAVE INGESTED A
SELECTION OF COMMON POISONS**

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DEDICATION

THIS WORK IS DEDICATED TO

MY WIFE BRONWYN

MY SON LUYOLA

MY DAUGHTERS CHENAZ AND CHARISSE

MY LATE FATHER NICHOLAS WILLIAM

MY MOTHER BLANCHE

MY MENTOR RICHARD DUDLEY

ABSTRACT

Poisoning is common and carries considerable morbidity and mortality. Two to three patients are admitted to the Emergency Unit at Groote Schuur Hospital every day with drug overdose. As absorption occurs in the small intestine the rates at which ingested poisons pass into and through the small bowel are important factors in determining the amount of poison potentially available for absorption. Although the effects of pharmacological doses of many drugs on gastric emptying and motility are known, information on the effects of higher doses is limited. I investigated patients who took overdoses of certain commonly used drugs to determine their effects on gastric emptying and motility and small intestinal transit.

The study was divided into two parts. One hundred and four patients were studied in Part 1. These patients took overdoses of tricyclic antidepressants (n = 31), carbamazepine (n = 15), phenytoin (n = 12), paracetamol (n = 29) and opioid-paracetamol mixtures (n = 17). They received standard hospital management of which sorbitol was not a part. Part 2 consisted of sixty-one patients who had sorbitol added to their treatment. These patients had taken overdoses of the tricyclic antidepressants (n = 15), carbamazepine (n = 7), phenytoin (n = 8), paracetamol (n = 13) and opioid - paracetamol mixtures (n = 18). The effects of sorbitol on gastric emptying and small intestinal transit were evaluated. A third study - the paracetamol control test was done on 5 healthy volunteers. Each subject was studied twice; the first time after taking 1G of paracetamol and the second time after no drug ingestion.

All the patients in Part 1 were imaged at presentation and again more than 7 half-lives of the ingested drug later. Drug levels in blood and urine were measured on each occasion. The clinical management which included gastric lavage, activated charcoal and antidotes where appropriate, was not altered. Patients recruited to the second phase of the study were imaged at presentation after receiving similar treatment to the patients in Part 1 except that the first dose of activated charcoal was mixed with sorbitol. Control studies were not done on this group of patients.

All the patients were given 20 MBq of Tc-99m tin colloid mixed with 10 ml of water to drink, followed by 10 ml of water to rinse the mouth. They were then scanned with a gamma camera fitted with a general purpose parallel-hole collimator. Images were taken at 15 minute intervals for the first hour and every 30 minutes for the next four hours. Regions of interest were drawn around the stomach and the rest of the gut and the proportion of activity in the stomach was calculated for each image. Two 10 minute dynamic studies were done at 20 and 50 minutes in the first hour. A visual evaluation of gastric motility was made on the dynamic display. The position of the radioactive meal in the stomach was recorded as a function of time. Oro-caecal and small intestinal (duodeno-caecal) transit times were calculated on the basis of a visual assessment of the passage of the leading edge of radioactivity into and through the small intestine.

Gastric emptying half-times were significantly prolonged after overdose for patients in Part 1 in all the groups of drugs tested when compared with half-times in the same patients at control. Median times (minutes) for gastric emptying half-times for patients in the various drug groups (overdose vs control) were: tricyclic antidepressants 103 vs 46; carbamazepine 164 vs 53; phenytoin 52 vs

27; paracetamol 98 vs 42 and opioids 115 vs 34.5. Twelve patients had gastric emptying half-times of over 300 minutes, 14 of over 200 minutes and 21 of over 120 minutes. Mean gastric motility scores of 3.2 for dynamic studies after overdose and 10.95 at control were significantly different ($p < 0.0008$).

Prolonged retention of the radioactive meal in the proximal half of the stomach correlated significantly with increased gastric emptying half-times. Oro-caecal and small intestinal transit times were significantly longer after overdose than at control for all of the drug groups.

Patients in Part 2 were also found to have prolonged gastric emptying half-times. Oro-caecal and small intestinal transit times were markedly prolonged for the tricyclic antidepressants and opioids. A comparison between Parts 1 and 2 revealed no significant difference between gastric emptying half-times. Small intestinal transit times were significantly longer in Part 1 than Part 2 for paracetamol, carbamazepine and phenytoin but not for tricyclic antidepressants or opioids. The sorbitol appeared to diminish intestinal transit times in patients ingesting the former 3 drugs.

One individual recruited to the paracetamol control test showed prolonged gastric emptying after paracetamol ingestion compared with his own control study. The rest of the subjects had slightly longer gastric emptying half-times after ingestion than at control.

It was clear that poisoning or related factors had caused gastric stasis and intestinal hypomotility in the majority of patients. However, drug level, the various drug types, age and gender together explained only 2.5% of the variance

for gastric emptying and 5.4% for small intestinal transit in Part 1. For Part 2 these figures were 28.3% and 5.4% respectively. This suggested other, untested for causes. The effect of stress was postulated as a significant contributory factor to and possible cause of delayed gastric emptying and inhibition of gastrointestinal motility in patients with poisoning. Gastrointestinal decontamination measures might also have played a role in diminishing gastrointestinal motility and the rate of gastric emptying.

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INTRODUCTION

Poisoning is common and carries considerable morbidity and mortality. The problem extends beyond the bounds of clinical medicine having major sociological, psychological and economic implications for society. A brief survey of reports from the United States of America, Europe and the United Kingdom verifies the great importance of the problem of poisoning. In adults by far the largest number of poisonings are the result of attempted suicides. Young persons, especially women, are particularly prone to this self-inflicted act. Tricyclic antidepressants are the commonest causative agents in all serious poisoning while the incidence of paracetamol overdose is increasing.

PREVALENCE OF POISONING

Yarbrough (1988) claims that approximately eight million persons are poisoned and thirty thousand persons commit suicide by ingesting drugs worldwide each year. In 1989 over 1.7 million poisonings (accidental and intentional) were reported to the American Association of Poison Control Centers (Litovitz et al 1990). However, it is estimated that the incidence of poisoning in the United States of America may be four to five million cases per year (Krenzelok and Dunmire 1992). The tricyclic antidepressants account for five hundred thousand overdose cases in the United States every year (Sparber and Mitchell, 1990). Fifteen percent of these die. Self-poisoning with this drug makes up one-third of poison admissions to intensive care units (Yarbrough 1988) and is the most common cause of death from prescription drugs in the USA (Haddad 1992). An extensive review of the English language literature on tricyclic antidepressant poisoning by Dzuikas and Vohra (1991) indicates a death rate of 2-3% of patients who reach the hospital.

In the United Kingdom the suicide rate is 11.1 per 100 000 of the population with self-poisoning accounting for over a quarter of male and over a half of female suicides (*The Health of the Nation* 1992 cited in El-Dosoky et al 1994). Ingestion of tricyclic antidepressants is the most frequent cause of fatal overdose in the United Kingdom (El-Dosoky et al 1994). Over 150 fatal cases of tricyclic antidepressant overdose were reported in Copenhagen between 1979 and 1985 (Worm and Steentoft 1990). Women in the 30 to 49 year age group predominated.

Between 1980-1990 five hundred and ninety six patients (approximately 5% of the total number of patients admitted with poisoning) required admission to intensive care units in Spanish hospitals. Seventy-nine percent of these were due to attempted suicides. Psychoactive drugs - diazepam and tricyclic antidepressants were the most common drugs taken (Nogue et al 1992).

Paracetamol poisoning is on the increase in both adults and children. Paracetamol is one of the most commonly reported, potentially toxic pharmaceuticals ingested in overdose. It resulted in over 100 000 calls to poison centres in the United States in 1991 (Litovitz et al 1992). The number of hospital admissions from paracetamol poisoning in England and Wales rose from 150 in 1968 to 7 000 in 1973 (Volans 1976). Reports indicate that as many as 40 000 people were treated for serious paracetamol overdoses in the United Kingdom in 1993 (Caelers 1993). These figures show an increasing trend of paracetamol abuse in self-poisoning. Makin et al (1994) citing the *Office of Population Censuses and Surveys, 1991*, state that paracetamol poisoning causes over 500 deaths each year in England and Wales. Six percent of all overdose deaths in the United Kingdom were attributed to paracetamol poisoning; the latter being

the commonest cause of fulminant hepatic failure accounting for 60-65% of all cases (Spooner and Harvey 1993). The peak incidence in paracetamol overdose is found in females aged twenty to thirty years (Prescott 1983).

Those social, economic and personal pressures that drive especially young adults to attempt suicide also prevail in South Africa where poisoning has become a significant problem. Attempted suicides, parasuicides and accidental overdose are the main causes of poisoning. Statistics from the Groote Schuur Hospital (GSH) show that drug overdose accounts for a significant number of patient admissions to the Emergency Department and Intensive Care Unit (GSH Emergency Unit Registers 1991, 1992, 1993 and personal communications with Dr Aboo, head of the Emergency Unit). In 1989 tricyclic antidepressants were implicated in 54% of Intensive Care Unit admissions for poisoning at the Groote Schuur Hospital (personal communications with Professor Potgieter, head of the Respiratory Intensive Care Unit, GSH 1992). Tricyclic antidepressants accounted for up to 18% of overdose admissions to the Emergency Unit at Groote Schuur Hospital (Emergency Unit Registers 1991, 1992, 1993). A total of 1029 patients were treated for self-poisoning at the Groote Schuur Hospital Emergency Unit during 1994 - an average of 86 patients each month (Emergency Unit Registers 1994). A retrospective study of admission records at Groote Schuur Hospital between 1981 and 1985 revealed a total of 91 patients with acute paracetamol poisoning (Monteagudo and Folb 1987). The median age of patients was 23 years and females were in the majority. A more recent survey of Emergency Unit records showed that paracetamol overdose accounted for up to 15% of all admissions for poisoning at the Emergency Unit at the Groote Schuur Hospital (Emergency Unit Registers 1991, 1992, 1993).

Poisoning is a world-wide problem of considerable significance. A common method of suicide it causes many deaths. The tricyclic antidepressants are implicated in a large proportion of life-threatening poisoning while the use of paracetamol for poisoning is on the increase.

PRINCIPAL QUESTIONS OF THIS STUDY

The study was done in two parts (Part 1 and Part 2). Each part was designed to answer different questions.

Part 1 seeks to answer two questions:

1.2.1 do overdoses of certain commonly used drugs alter the time it takes for the stomach to empty? If so, is this time shortened or prolonged - that is, to what extent is the rate of gastric emptying altered?

1.2.2 do overdoses of the aforementioned drugs alter oro-caecal and small intestinal transit times? If so, to what extent?

Part 2 attempts to answer the question:

1.2.3 does management with sorbitol, an osmotic laxative, have an effect on the changes (if any) caused by the selected drugs?

And, in terms of the imaging aspects of the study:

1.2.4 are there problems with the use of nuclear medicine techniques in gastric emptying, motility and small intestinal transit in patients with poisoning?

WHY THIS TOPIC?

The prevalence of poisoning in South Africa therefore dictates that proper strategies be developed for its management and possible prevention. Early intervention is important in the successful management of these patients. Health care providers at primary, secondary and tertiary level should, therefore, have the correct approach to the patient who presents with poisoning. This should be based on a thorough understanding of the pathophysiological changes brought about by the different poisons including their effects on gastric emptying and motility and small bowel transit. It should also take account of other factors that might influence the clinical state of the patient.

The goal of the study was to improve our understanding of the pathological changes in the stomach and small intestine induced by drug overdose. I studied gastric emptying rates and gastric motility as well as small intestinal transit times following overdosage. These are important factors that determine the rate at which poison passes into and through the small intestine and, therefore, the amount of poison potentially available for absorption by the intestinal mucosa.

The clinical condition of the patient is determined in large part by the amount of poison absorbed. Although the effects of pharmacological doses of many drugs on gastric emptying and motility are known, information on the effects of higher doses is limited. I felt that the information derived would be useful in assisting with clinical management which is an area of ongoing debate and controversy.

THE TOPIC WAS CHOSEN FOR THE FOLLOWING REASONS:

1. Poisoning is a common clinical problem as pointed out earlier. Approximately 3 patients are admitted to the Emergency Unit at the Groote Schuur Hospital every day with drug overdose.
2. Most research has dealt with the toxicological and therapeutic aspects of poisoning but the functioning of the gastrointestinal tract under the influence of orally ingested poisons has been the subject of few investigations. In particular, those organs that provide a reservoir for and a route into the circulation for orally ingested poisons - the stomach and small intestine have received little attention.
3. Alterations in gastric emptying rates and small intestinal transit in patients with poisoning may hold profound implications for our understanding of the pathophysiological changes induced by poisoning and may be important for clinical management of these patients. The use of radionuclide imaging is particularly suited to providing information on the gastrointestinal tract in these patients. It is simple, non-invasive, safe and does not interfere with the routine management of the patients.
4. Therapeutic doses of tricyclic antidepressants and opioids are thought to diminish gastrointestinal motility, although nothing is known about the effects of high doses of these and other drugs in common use such as paracetamol and the anticonvulsants on the gastrointestinal tract.

THE INTENDED CONTRIBUTION OF THE STUDY

The application of a diagnostic tool like nuclear medicine scintigraphy to the common clinical problem of drug overdose held out the promise of being of benefit to the patient, clinician, pharmacologist and the nuclear medicine physician. Furthermore, the study process would encourage collaboration between the disciplines of nuclear medicine, internal medicine and pharmacology. It was necessary to investigate whether gastrointestinal imaging could be incorporated in the clinical workup of selected patients. A report that poisoning caused a marked alteration, for example, a delay in gastric emptying would enable the clinician to use gastric decontamination measures even if the patient presented to hospital several hours after drug ingestion. But if the bulk of poison has already passed into the small intestine the use of oral charcoal in a patient with gastroparesis would be of limited value.

Evidence of changes in gastrointestinal motility would improve our understanding of the pathological processes at work and promote an insight into the different clinical patterns that occur with different drug overdosage. The study had the potential of providing information that could assist the clinician with important management decisions. Optimal times for gastric lavage and the administration of activated charcoal are two examples. The study could prompt a review of current patient management and contribute to resolving certain of the more controversial areas of treatment.

Information regarding gastric emptying and motility following drug overdose would also be of value to pharmacology and gastroenterology.

In providing answers to some of the questions the study could create new areas of and opportunities for investigation. The study, therefore, had the potential to benefit future patients as well as providing a multidisciplinary approach to the problem of poisoning.

HOW WAS THE STUDY CONDUCTED?

The study was first mooted in October 1991. The idea of applying nuclear medicine scintigraphy to gastrointestinal motility studies in patients with poisoning was suggested by Professor Mann, who heads both the Nuclear Medicine Department and the Poisons Unit at the Red Cross Hospital.

After preliminary discussions with the head of the Emergency Unit, Dr Aboo, a preparatory survey was set up. Patient registers were reviewed over a 3 month period and the most frequently ingested poisons were identified. In consultation with Dr Aboo and Professor Folb, head of the Pharmacology Department, it was decided to study patients who had taken one of 4 groups of drugs, singly or in combination:

1. tricyclic antidepressants
2. anticonvulsants - carbamazepine, phenytoin, phenobarbitone
3. paracetamol (acetaminophen)
4. opioids including opioid-paracetamol mixtures.

Patients who took overdoses of these commonly used drugs were selected for the study. Two of the drugs chosen for this study, namely, the tricyclic antidepressants and the opioids are known to delay gut motility in pharmacological doses, but the effects of higher doses are unknown. On the other hand, drugs like paracetamol and certain anticonvulsants are thought to have little effect on gastrointestinal motility at therapeutic levels. The effects of toxic levels of the latter drugs are also not known.

The study took the form of a natural experiment as there were a number of variables over which I could exert little, if any, control. Ethical, clinical and physical constraints made it impossible for me to alter standard management or to determine accurately the amounts, combinations of drugs taken and the time between ingestion and imaging. Patient management was the prerogative and responsibility of the attending clinician. The use of each patient as his/her own control enabled me to eliminate the problem of selecting matched controls and dealing with the varying gastric emptying rates that occur in different individuals. Although certain aspects of management like gastric lavage might alter gastric motility I could not subject those patients who returned for their control studies to, in the words of Vale and Proudfoot (p469; 1993) "the trauma, indignity, and inefficiency of...gastric lavage."

THE STRUCTURE OF THE STUDY

The study was carried out as two separate parts. One hundred and four patients (108 minus 4 exclusions) were investigated in the first part (Part 1) of the study. These patients had standard hospital management which at the time did not include sorbitol as part of their treatment.

The second part (Part 2) of the study involved testing 61 patients who had received sorbitol as part of their management. Sorbitol was introduced because of the results obtained in the Part 1. In addition, results from Part 1 prompted me to perform another small study (the paracetamol control study - Part 3) on five volunteers who had their gastric emptying rates measured after taking therapeutic doses of paracetamol.



NORMAL GASTROINTESTINAL MOTILITY AND GASTRIC EMPTYING

Before the effect of drugs and other relevant factors on gastric emptying and motility are considered, a brief review of the physiological aspects is necessary. The stomach governs access to the drug-absorbing small intestine. It is, therefore, important to know how the stomach delivers its contents to the small intestine. The ability of the stomach to contract spontaneously and in response to certain stimuli plays an important role in gastric emptying. This contractility is referred to as gastric motility.

NORMAL GASTRIC CONTRACTILITY

The stomach can be divided into 2 main functional compartments. The proximal stomach consists of the fundus and upper body which acts as a reservoir for food. And the distal stomach is made up of the lower body and antrum, which is responsible for mixing of stomach contents and the breakdown of solids (Minami and McCallum 1984).

Meyer (1991) holds that the proximal stomach does not exhibit phasic contractions but alters its tone over many minutes or, that it contracts slowly with moderate force over one to six minutes. In another review, Minami and McCallum (1984) state that the proximal stomach exhibits slow, sustained contractions with more rapid, phasic contractions superimposed on the former. The distal stomach is said to undergo vigorous phasic contractions of great force over ten seconds (Meyer 1991). The contractions of the stomach result in closure and distortion of the gastric walls that can be discerned by gamma scintigraphy when the stomach is filled with radionuclide.

NORMAL PATTERNS OF GASTROINTESTINAL MOTILITY

INTERDIGESTIVE MOTILITY - THE FASTING PATTERN

In the fasting state gastric and small bowel aboral contractile activity alternates with periods of quiescence. The entire cycle takes 80 to 120 minutes and is called the interdigestive motility complex (IDMC) (Kellow 1986; Schurizek 1989a). The contractions empty residual and fasting contents from the stomach and small intestine. The interdigestive motility complex is divided into 3 phases:

Phase 1

This is a quiet phase lasting 30 to 40 minutes during which a few sporadic or no contractions occur (Kelly 1981).

Phase 2

Intermittent contractions occur over a period lasting 30 to 90 minutes. On average 0 to 12 contractions occur every 5 minutes in the gastric antrum and 2 to 38 every 5 minutes in the duodenum (Schurizek 1989a; 1991). The contractions become more frequent as phase 2 ends heralding the onset of phase 3.

Phase 3

Regular contractions with an average frequency of 3 every minute in the gastric antrum are a feature of this phase which lasts for 5 to 15 minutes (Kellow 1986). These are forceful contractions that obliterate the antral lumen. The phase 3 activity is commonly called the migrating myoelectric or motor complex (MMC) (Meyer 1991). Meyer (1991) describes a fourth phase in which a period of diminishing contractility separates phase 3 from the ensuing phase 1.

This temporal pattern of fasting motility passes sequentially from the stomach down the entire length of the small intestine over the 80 to 120 minute period until the start of a new cycle in the distal oesophagus. But great variability exists and the lack of a well-defined interdigestive motility complex following a 3 hour fast is not necessarily abnormal (Schurizek et al 1989a; 1989b). Schurizek et al (1989a; 1989b) demonstrated nine phase 2 periods lasting longer than 2 hours in healthy volunteers.

The interdigestive motility complex has shown circadian variations in that they occur more frequently at night during sleep (Thompson et al 1980) with the duration of phase 2 being diminished or absent at night (Kumar et al 1986). This suggests that phase 2 activity during the day may be due to the effects of the aroused central nervous system on gastrointestinal motility (Kumar et al 1986).

RESPONSE TO FEEDING - THE FED PATTERN

In contrast to the fasting state the fed pattern is not cyclical but persists for as long as food remains in the stomach. The conversion from the fasting to the fed pattern depends on the physical state of the meal (liquid or solid) and its nutrient content. Water and nutrient-poor liquids do not alter fasting motility (Schurizek et al 1989a; 1989b; 1989c). The ingestion of as much as 200 ml of water does not disrupt the fasting pattern (Oberle et al 1988).

A nutrient liquid meal inhibits the interdigestive motility complex, diminishes the size of antral contractions and gives rise to irregular small intestinal contractions (Rees et al 1978). A solid meal causes vigorous phasic antral contractions (Rees et al 1979) while the small bowel pattern is similar to that following a liquid meal. The duration for which the interdigestive motility complex is interrupted by the meal varies with the quantity and type of food eaten. Even small meals have been shown to interrupt the fasting pattern for between 90 and 240 minutes (Kellow et al 1986).

THE CONTROL OF GASTROINTESTINAL MOTILITY

The control of the gastrointestinal motility is complex with a number of neurohumoral agents acting at both central and gut levels.

The central nervous system regulates gastrointestinal motility via both the autonomic nervous system and hormonal pathways. Anxiety, fear and pain have been demonstrated to inhibit gastric emptying (Thompson et al 1982; Simpson and Stakes 1986; Valori et al 1986). McIntyre et al (1988) found that during sympathetic activation both alpha and beta receptors act via their respective adrenergic pathways to delay gastric emptying and oro-caecal transit, and to inhibit antral motility. A vagal link has been proposed between the central and the enteric nervous systems in which the vagus acts in a mainly sensory capacity (Wingate 1985; Valori et al 1986). The activity of the enteric nervous system is thought to be modulated by the central nervous system in response to vagal sensory inputs (Wingate 1985; Schurizek 1991). In addition, peaks in vagal efferent nerve activity coincide with the start of phase 3 interdigestive motility complex activity and stressful stimuli induce migrating motor complexes in the duodenum suggesting autonomic neural control via the vagus (Meyer 1991; Stanghellini 1983). Furthermore, the vagus is thought to mediate, at least in part, the change from the fasting to the fed pattern. Truncal vagotomy inhibits conversion of fasting to fed patterns in dogs and rats, and reduces the time that the fed pattern persists after a meal (Marik and Code 1975; Wilen et al 1983). Receptive and adaptive relaxation of the proximal stomach is controlled by the vagus and vagal transection abolishes these reflexes. Vagotomy has been shown to speed up the gastric emptying of liquids in dogs (Wilbur and Kelly 1973).

The hormone, motilin seems to play an important role in stimulating phase 3 activity. Blood concentrations of this peptide have been shown to peak at the onset of phase 3 (Bormans et al 1987; Sarr et al 1983). In vitro studies have provided evidence that a number of peptides released from the gastrointestinal mucosa into the bloodstream act on isolated gastrointestinal smooth muscle. These peptides are released from nerve endings near muscle cells in the gut (Meyer 1991). The peptides act in combination to play a regulatory role in gastric motility and emptying. Gut contraction is stimulated by cholecystokinin (CCK) and gastrin through the same receptor while acetylcholine causes contraction via a different receptor. Although vasoactive peptide (VIP), secretin and glucagon relax already contracted smooth muscle in vitro, in physiologic doses in human subjects CCK and secretin have been shown to inhibit gastric emptying (Kleibeuker et al 1988; Liddle et al 1986). Gastric emptying is retarded by CCK relaxation of the fundus and contraction of the pylorus which outweigh the increased antral contractility that it causes (Yamagashi and Debas 1978).

Enterogastric and gastroenteric reflexes also play an important role in gastrointestinal motility. Fundal tone and antral peristalsis are reduced by duodeno-jejunal distension thereby inhibiting gastric emptying (De Ponti et al 1987; Grundy and Scratcherd 1982). Feedback inhibition of antral peristalsis and gastric emptying by nutrients or acid in the small intestine are also the result of enterogastric reflexes (Aspiroz and Malagelada 1986; Stanghellini et al 1983). Nutrient exposure of the ileocaecal region retards gastric emptying and small intestinal transit and decreases small intestinal motility (Layer and Groger 1992). In addition ileal nutrients may, under certain conditions, convert intestinal motility from digestive to interdigestive patterns and inhibit the secretory activity of the proximal gastrointestinal tract (Layer and Groger 1992). Gastric distension

impedes the flow of liquids through the small intestine as a result of a gastroenteric reflex (Miller et al 1981).

MEASURING GASTROINTESTINAL MOTILITY

A number of different methods have been used to measure gastrointestinal motility.

ELECTROMYOGRAPHY

Electromyography has been used to measure gastrointestinal contractions in man (Fleckenstein 1978a; 1978b; Fleckenstein and Oigaard 1978; Hellstrom et al 1989). This method measures changes in electric potential in gastrointestinal smooth muscle using various types of intraluminal electrodes. The "spike potentials" correspond to gastrointestinal contractions (Szurszewski 1987). Migrating myoelectric complexes have been demonstrated in the small intestine in fasting human subjects (Fleckenstein and Oigaard 1978; Fleckenstein 1978). These complexes migrate through the entire small intestine at hourly intervals (Fleckenstein and Oigaard 1978) at a mean velocity of 12 cm/min and a duration of approximately 5 minutes (Fleckenstein 1978). In addition, a "peristaltic rush" was observed which propagated distally at a mean velocity of 2 cm/sec and a duration of 5 seconds. Vantrappen et al (1986) have improved the sensitivity of the method by developing a myoelectric probe capable of detecting electrical patterns in man that were previously identified only in animals.

Disadvantages of electromyography include poor electrode contact with the intestinal muscle wall, poor recording of slow waves and signal loss resulting in interrupted recordings (Hellstrom et al 1989). In addition, patients have to be intubated.

RADIOTELEMETRY

Thompson et al (1980) recorded migrating activity in the gastrointestinal tract using an ingested pressure-sensitive radiotelemetry capsule tethered at the duodenojejunal flexure. Valori et al (1986) used twin pressure-sensitive radiotelemetry capsules tethered in the small bowel to detect a reduction in fasting migrating motor complexes during periods of stress. Some signal loss has been reported with this method. Patient intubation is another disadvantage.

ULTRASONOGRAPHY

King et al (1984) monitored events at the gastric outlet with real-time ultrasonography on 10 healthy volunteers following a test meal. They detected both antero- and retrograde transpyloric fluid movement that showed no relationship to the antral peristaltic contraction. This method does not appear to have yielded any valuable information regarding gastrointestinal motility. Antroduodenal motility has also been studied using duplex sonography (Hausken et al 1992) but too few studies have been done to make a proper assessment of this technique.

The method is time-consuming and requires considerable skill.

MANOMETRY

Intraluminal hydraulic and pneumohydraulic systems are used to measure pressure changes that occur with gastrointestinal contractions (Oberle et al

1990; Camilleri et al 1985 and 1986). This method has been used by a number of investigators in recent years to evaluate gastric and intestinal motility (Oberle et al 1990; Camilleri et al 1985 and 1986; Valori et al 1986; Keane et al 1981). Manometry is found to correlate well with electromyographic measurements in humans (Henneresse et al 1988). Camilleri et al (1985) demonstrated a positive correlation between postcibal antral contractility measured manometrically (an antral motility index is calculated), and the rate of gastric emptying of a radiolabelled meal measured radioscintigraphically in healthy individuals. They demonstrated an inverse relationship between antral motility and the lag period (a period of slow gastric emptying soon after ingestion of solids) for solids, and a positive correlation during the solid-emptying phase (Camilleri et al 1985). In contrast, no significant correlation was found between antral motility and the overall liquid emptying phase. But antral motility was related to liquid emptying after allowing for an initial lag period (as for solids) indicating that antral contractions have a role in the propulsion of liquids from the stomach (Camilleri et al 1985).

Camilleri et al (1986) using manometry and scintigraphy showed a relationship between impaired gastric emptying and abnormal gastrointestinal motility in patients with gastrointestinal dysmotility conditions. Antral hypomotility was associated with prolonged gastric emptying of both liquids and solids in certain patients while intestinal dysmotility was found to be the cause of the gastric emptying delay in others. Camilleri et al (1986) postulate, therefore, that the gastric stasis is due to impaired antral peristalsis (hypomotility) or increased resistance to flow into the small intestine due to intestinal dysmotility.

Manometry has certain disadvantages. Quantifying fundal pressures and therefore detecting proximal gastric motility disorders appears technically difficult with manometry (Camilleri et al 1986). The siting of the sensors may be altered by the stomach or intestine "sleeving" over the tube (Schurizek 1991). Perfused catheters may be insensitive to changes in intragastric pressures thus failing to record some gastric contractions, and antral contractions may be missed if fewer than three antral recording sites are used (Schurizek 1991). In addition, the procedure is invasive and not universally available.

Camilleri and Prather (1994) describe the use of an axial traction force catheter to measure longitudinally directed gastric forces during gastric emptying in man. The emptying of liquid was characterised by axial force peaks that coincided mainly with proximal antral pressure measured manometrically. The major proportion of axial force peaks during the emptying of solids coincided with distal antral pressure activity. These findings confirm that the antrum plays a role in the emptying of both solids and liquids. Although the early report is promising the method cannot account for 20% of "isolated" axial forces and detects mainly antral occluding contractions. This suggests that smaller contractions and those involving the non-antral part of the stomach are not detected. Furthermore, it is invasive and requires considerable patient co-operation.

MAGNETIC RESONANCE IMAGING (MRI)

Recent studies indicate that gastric motility can be measured by MRI (Fraser et al 1994; Schwizer et al 1994). This method has the advantage of a visual assessment of gastric wall motion and contractility. Both studies demonstrate

the role of antral contractility in the emptying of nutrient liquid meals (Fraser et al 1994; Schwizer et al 1994). The simultaneous evaluation of gastric emptying and secretion are added advantages. The lack of exposure of patients to ionising radiation is a further boon. However, the studies involve small numbers of subjects and the method requires further validation. The lack of general availability and the expense are drawbacks to the use of MRI. This technique requires patient co-operation and cannot be performed on the unco-operative and the comatose.

RADIONUCLIDE SCINTIGRAPHY

Akkermans et al (1984) described a new scintigraphic technique to measure fundal and antral contractions. They measured the redistribution of gastric contents between the fundus and antrum and gastric emptying simultaneously. This method was modified by Stacher et al (1987) using a dual-headed gamma-camera to evaluate antral motor activity. This technique permits the reliable quantitation of the amplitude, frequency and propagation velocity of antral contractions. Three second frames are viewed in a closed-loop cinematic display that reveal gastric contractions which commence at the fundal-corporal border along the greater curvature of the stomach and sweep aborally. Antral motility is quantitated by recording variations in activity in three antral regions of interest drawn at right angles to its long axis (Stacher et al 1987; Stacher and Bergmann 1992).

Camilleri et al (1985; 1986) used simultaneous manometry and radioscinigraphy to compare gastrointestinal motility and both liquid and solid emptying phases.

Gastric emptying of solids was divided into lag and emptying phases and a power exponential was used to calculate liquid emptying (Camilleri et al 1985).

Stacher and Bergmann (1992) described a technique using factor analysis of a series of images acquired at three second frame times to assess antral motility. Factor curves represent variation of activity intensities with time and thus underlying antral contractility. Refined Fourier analysis of dynamic scintigraphic data has also been used to evaluate antral contractions and gastric motility parameters (Urbain et al 1993; Hausmann et al 1993; Van den Maegdenbergh et al 1993). Hausmann et al (1993) also made a visual assessment of a cine display of dynamic studies at 3 seconds per frame and noted rhythmic peristaltic contractions with a forward progression of portions of the test meal in the duodenum.

A recent innovation has been the use of a dynamic single photon emission computer tomography (SPECT) for the assessment of antral contractile activity (Bergmann and Stacher 1994). Rotating gamma cameras are used to acquire tomographic images in short periods of time. Counts in the antral slices are proportional to the area of the cross-section through the antrum. Antral contractility is demonstrated by increases and reductions in this area as reflected in corresponding changes in antral slice counts. This method eliminates overlying small bowel activity and has the added advantage of directly imaging the moving structures following a semi-solid meal labelled with a mere 37 MBq ^{99m}Tc -sulphur colloid. New methods using a triple-headed rotating gamma camera to create a 3-dimensional visualisation of gastric motor activity and gastric emptying simultaneously and to measure gastric emptying "stroke

volumes" and "ejection fractions" are being developed (Akkermans and Van Isselt 1994).

These methods require a high level of patient cooperation and expertise. Patients with poisoning are often severely ill and confused. They do not lie still for the times required by the methods described above. Less complex and more robust methods that are not prejudiced by the unconscious patient are required when investigating the effects of poisoning on gastric emptying and motility.

NORMAL GASTRIC EMPTYING

Gastric emptying is defined as the delivery of food (in fragmented and liquefied forms) from the stomach into the duodenum in an orderly fashion (Chaudhuri and Chaudhuri 1984). The gastric emptying rate is the rate at which gastric contents pass from the stomach into the duodenum. The gastric emptying half-time is that time taken for half the gastric contents to empty from the stomach into the duodenum. Gastric emptying rates and half-times are different for liquid and solid meals.

GASTRIC EMPTYING DURING FASTING

The rate of gastric emptying of chyme is determined by the pressure difference between the stomach and the duodenum and the resistance to flow across the pyloric canal (Schurizek 1991). The stomach empties when the pressure gradient between the gastric and duodenal lumens is sufficiently high. Gastric emptying is facilitated by a series of contractions in the antrum and proximal duodenum (Weisbrodt et al 1969). Schindlbeck et al (1989) found that gastric emptying of endogenous secretions was greater during phases 2 and 3 of the interdigestive myoelectric complex than during phase 1.

Oberle et al (1990) measured gastric emptying by sampling gastric contents following 50 and 200 ml drinks marked with phenol red and found that neither volume was large enough to alter the fasting pattern or convert it to the fed pattern. Following an initial lag period during which there was little gastric emptying, emptying became linear when a logarithmic transformation was

performed on the measurements. They demonstrated an inverse relationship between gastric emptying rate and the period between ingestion and the next phase 3, and a direct relationship between the speed of gastric emptying and antral motility. The 200 ml drinks emptied faster than the 50 ml drinks in each corresponding phase of the interdigestive myoelectric complex. Solids like tablets are expelled with powerful contractions during phase 3 (Meyer 1991).

GASTRIC EMPTYING AFTER FEEDING

As has been observed the stomach can be divided into two functional parts: the fundus and upper corpus which together serve as a reservoir and exert mainly tonic activity or "sustained contractions" (Minami and McCallum 1984), and the distal part in which antral motility plays a major role. The proximal stomach has the dominant role in gastric emptying of liquids while the distal stomach has the major role in gastric emptying of solids (Kelly 1980). Deglutition results in "receptive" relaxation of the proximal stomach which is thought to be due to a vagal reflex (Meyer 1991). This is followed by the prolonged "adaptive" relaxation due to the gastric distension caused by the ingested bolus. During the adaptive phase the tonic activity of the proximal stomach continues to push the ingesta aborally towards the antrum (Stacher and Bergmann 1992). Antral contractions cause gastric emptying as well as mixing and breaking down of particles.

GASTRIC EMPTYING OF LIQUIDS IN NORMALS

The emptying of liquids is thought to be due to the pressure gradient between the stomach and the duodenum which is largely dependent on tonic activity of the proximal stomach (Wilbur and Kelly 1973; Kelly 1980). Antral contractions are thought to assist with the propulsion of liquids into the duodenum (Weisbrodt et al 1969). Gravity is also thought to facilitate liquid emptying (Gulsrud et al 1980; McKelvey 1970).

Water (Dubois et al 1977), 0.15 mol/L saline (McHugh and Moran 1978) or very dilute glucose (Costill and Saltin 1979) are liquids that empty from the stomach as a simple exponential, that is, they exhibit constant fractional emptying (Meyer 1991). The monoexponential pattern of liquid emptying was confirmed by scintigraphic methods (Collins et al 1983). More concentrated glucose and nutrient solutions inhibit gastric emptying by triggering feedback from intestinal sensors via neurohumoral mechanisms (Lin et al 1989a, 1989b; White et al 1983). This feedback is dependent on the length of small intestine exposed to the nutrient (Lin et al 1989a, 1989b). Other solutes like mannitol that impart high osmolality to luminal contents also inhibit gastric emptying via intestinal feedback inhibition (Meyer 1991).

The rate of gastric emptying of liquid has been determined using different methods including intubation and aspiration tests (Hunt and Spurrell 1951), radiological techniques (Sheiner 1975), ultrasound (Dapoigny et al 1991, Bolondi et al 1985, Bateman and Whittingham 1982), paracetamol absorption (Schurizek 1991) and radiosciintigraphy (Caner et al 1991; Datz et al 1991, 1987; Dapoigny et al 1991; Christian et al 1990; Brophy et al 1986; Collins et al 1983; Malmud et

al 1982). The different methods are discussed later in this section: "Quantitation of Gastric Emptying Rates".

Radioscintigraphic measurements of gastric emptying half-times for liquids have ranged between 10 and 55 minutes. Factors that could account for the big range include the imaging technique (which is discussed later in this chapter in the section: "Quantitation of Gastric Emptying Rates"), age, gender, hormonal status, intra- and inter-subject variation. These are discussed in the section: "Factors That Alter Gastrointestinal Motility and Gastric Emptying In Poisoning."

GASTRIC EMPTYING OF SOLIDS

Digestible solid foods empty more slowly than liquids. Solids are emptied from the stomach only after they have been fragmented by the antrum to particles approximately 1 mm in size (Meyer et al 1981). Both trituration of solids and gastric emptying are the result of peristaltic gastric contractions that occur as a result of gastric pacemaker activity in the proximal stomach along the greater curvature which spreads aborally to the distal stomach. Powerful antral contractions play a major role in fragmentation of solids and their emptying. The normal rate of contractions in humans is 3 to 4 per minute (Minami and McCallum 1984; Hausmann et al 1993). Large particles which defy fragmentation are retained in the stomach until they are emptied by the phase 3 migrating motor complex. A slow lag phase representing slow emptying occurs soon after ingestion of solids. This is followed by almost linear emptying once the food is sufficiently ground. Finally, antral contractions diminish in strength and gastric emptying slows down again.

Radioscintigraphic studies have reported a wide range of gastric emptying half-times for solids. These vary between approximately 40 and 120 minutes (Urbain et al 1993; Dapoigny et al 1991; Datz et al 1991; Chaudhuri and Hudgins 1982; Malmud et al 1982; Malagelada et al 1976, 1977; Chaudhuri 1976; Coates et al 1973; Harvey 1970; Griffith 1966;). The same factors that influence the rate of liquid emptying result in the wide range of half-times for solids. These include differences in imaging technique, demographic features of the subjects and intra- and inter-subject variations. Semi-solids empty more slowly than liquids but quicker than solids (Stacher et al 1991; Kiss et al 1990; Harding 1990).

DELAYED GASTRIC EMPTYING

This could be caused by several factors:

1. decreased tonic activity in the proximal stomach;
2. diminished force of antral contractions;
3. increased pyloric and increased duodenal motor activity (1-3 Stacher and Bergmann 1992).
4. abnormal sequence of contractions (Horowitz et al 1994).
5. abnormal sensory feedback from the small intestine (Lin 1994).

DISTRIBUTION OF RADIOACTIVE MEAL IN THE STOMACH

In healthy subjects no abnormal retention of a test meal was noted (Van den Maegdenbergh et al 1993). However, retention of significant portions of the radiolabeled meal was observed in the proximal stomach in patients with delayed gastric emptying (Van den Maegdenbergh et al 1993; Hausmann et al 1993). In both of these studies the delayed gastric emptying and retention of the meal were accompanied by reduced gastric motor activity in the distal corpus (Hausmann et al 1993) and antrum (Hausmann et al 1993; Van den Maegdenbergh et al 1993).

QUANTITATION OF GASTRIC EMPTYING RATES

INTUBATION AND ASPIRATION TESTS

Gastric aspiration after ingestion of test meals or dyes yields useful information on gastric emptying rates and volumes of gastric secretions (Hunt and Spurrell 1951; George 1968; Meeroff et al 1973). The limitations of the technique are that it requires intubation, there is uncertainty as to whether the entire meal has been aspirated or emptied, and gastric secretions interfere with the analysis.

RADIOLOGICAL TECHNIQUES

Radiographic tests have been performed using barium sulphate liquid, barium enteric coated granules, the barium burger and radiopaque meals (Perkel et al 1981, 1979; Buckler 1967). Urograffin has also been used. Despite the good resolution of the radiological techniques the sensitivity is poor because temporal resolution is lacking. Moreover, the contrast material cannot be accurately quantified. Small amounts of barium sulphate cannot be seen and there is no way of knowing how much there is when the barium is observed. Intermittent radiological screening especially in patients with delayed gastric emptying results in a high radiation burden. Scintigraphy, on the other hand, is very sensitive in detecting small amounts of radioactivity and the number of counts present is easily determined. In addition, the radiation dose administered to the patient is totally independent of the imaging times or number of images taken.

Moreover, barium sulphate is totally unphysiologic with a specific gravity of 2 and may irritate the gastric mucosa thereby altering gastric emptying rates (Sheiner 1975). The flavourants with which the barium sulphate is mixed might also affect gastric emptying. For radionuclide imaging the use of radiocolloid mixed with water (containing no flavourants) overcomes this problem.

REAL-TIME ULTRASOUND

Dapoigny et al (1991) found comparable gastric emptying times for liquids and solids with ultrasound and scintigraphy. This technique permits direct observation of gastric volumes and antral motility (Bolondi et al 1985; Bateman and Whittingham 1982). It is non-invasive and does not use ionising radiation thus making it possible to investigate pregnant women. Limitations of the method include difficulties with positioning of the probe and interpretation. Furthermore, only liquids and freely dispersible solids can be measured.

A close correlation has been shown between gastric emptying half-times from the body of the stomach measured by simple ultrasound and scintigraphy, but not for the gastric antrum (Takaoka et al 1993).

APPLIED POTENTIAL TOMOGRAPHY

This technique uses multiple surface electrodes on the abdomen to measure changes in tissue resistance. Sequential measurements of resistivity of gastric contents create a gastric emptying profile. However, acid secretion has to be

inhibited by cimetidine for gastric emptying rates of liquids and semi-solids to approximate those measured by scintigraphy (Avill et al 1987; Mangnall et al 1987).

MEASURING GASTRIC EMPTYING RATES USING DRUG LEVELS IN PLASMA FOLLOWING ABSORPTION - PARACETAMOL ABSORPTION TEST

Paracetamol levels in plasma are used to measure gastric emptying on the assumption that paracetamol absorption and, therefore, blood levels directly reflect the rate of gastric emptying. Nimmo and his colleagues (1975) demonstrated a significant correlation between the amount of paracetamol emptied from the stomach at one hour and the amount absorbed at one hour. As virtually all paracetamol absorption occurs from the small intestine and virtually none from the stomach (Heading et al 1973), the amount of paracetamol absorbed as measured by plasma levels is directly related to the amount that has passed from the stomach into the small intestine. A close correlation exists between gastric emptying and small intestinal absorption of paracetamol.

When the gastric emptying rate is accelerated by metoclopramide or inhibited by propantheline, the rate of paracetamol absorption is increased or reduced respectively (Nimmo et al 1973). As paracetamol absorption rates are directly determined by gastric emptying rates this has led to the extensive use of the acetaminophen absorption test as a quantitative indirect measurement of gastric emptying (Van Wyk et al 1993; 1992; 1990; Inoue et al 1993; Hu et al 1993; Whitehead et al 1993; Gainsborough et al 1993; Kuroda et al 1992; Mushambi et

al 1992; Vance et al 1992; Wright et al 1992; Macfie et al 1992; Kasano et al 1991; Waller et al 1991; Schurizek 1991; Petring and Flachs 1990; Kluger et al; McNeill et al 1990).

But Schurizek (1991) calls our attention to the disadvantages of using paracetamol absorption as an index of gastric emptying: the inability to assess the magnitude of gut metabolism of paracetamol or the hepatic first pass effect; blood samples taken at fixed times resulting in uncertainties regarding maximum plasma concentrations and the time taken to reach these levels. Schurizek (1991) also found big variations in serum paracetamol concentrations with some patients showing a second peak indicating redistribution of paracetamol. Bhargava and Hirate (1989) found an extensive first pass effect in mice that was thought to be due to intestinal enzymes following the administration of large doses of paracetamol (200 mg/kg). They postulate that this phenomenon may be dose-dependent. Petring and Flachs (1990) did not demonstrate a statistically significant relationship between gastric emptying measured scintigraphically and the paracetamol absorption parameters.

The conflicting results obtained using this method make it difficult to assess whether accurate quantitation of gastric emptying rates is possible.

MAGNETIC RESONANCE IMAGING (MRI)

An initial study has shown MRI to be a technique that can accurately measure gastric emptying (Schwizer et al 1992). Subsequent studies showed a very good statistical correlation between gastric emptying half-times of a 10% dextrose

meal derived by MRI and those calculated by scintigraphy (Schwizer et al 1994). Fraser et al (1994) showed significant differences in gastric emptying half-times between 10% and 25% dextrose meals using this method. Although these early studies appear promising a greater number of studies on many more patients will be required to validate the reliability and reproducibility of MRI. Moreover, it will be difficult to perform MRI on unco-operative or unconscious patients.

SCINTIGRAPHIC MEASURES OF GASTRIC EMPTYING

Radionuclide techniques have proven to be the most physiological and accurate of the methods for determining the rate of gastric emptying. Scintigraphy is quantitative, does not require intubation, can be used with liquid and solid meals and gives a low radiation burden to the patient making repetitive studies possible (Malmud et al 1982). By comparison the other methods are either invasive, making them unacceptable to the patient, or non-quantitative, rendering them less suitable as a measure of gastric emptying rates.

In 1966 Griffith et al introduced a radionuclide test for gastric emptying. They labelled a porridge and egg meal with chromium-51 (^{51}Cr) sodium chromate and used external probes for quantitation. Subsequent developments in technology and radiopharmacy, and refinement of technique have made scintigraphy the most reliable, reproducible and safe method for the quantitation of gastric emptying (Chaudhuri 1974; Malmud et al 1982). Equipment has ranged from the simple probes and rectilinear scanners of yesteryear to the modern gamma camera with the facility to perform dual radionuclide scintigraphy, and dual headed and SPECT cameras. The patient receives a relatively low radiation

dose with the radiopharmaceuticals in current use (Madsen and Krogsgaard 1989; Siegel et al 1983).

RADIOACTIVE MARKERS

Liquid, semi-solid and solid meals have been labelled with a number of radioactive markers. The first radionuclide employed was ^{51}Cr which is detected by a probe. This was followed by Iodine-131 (^{131}I) which had the advantage of being able to be imaged as well as counted, but ^{131}I human serum albumin had the drawback of dissociating in the duodenum. This led to the absorption of the ^{131}I in the small intestine and its resecretion in the gastric juice making it impossible to determine whether the radioactivity in the stomach was due to ^{131}I human serum albumin that had not emptied or the ^{131}I label that had been secreted by the gastric mucosa. The beta emissions from this radionuclide increases the radiation burden to the patient and keeps the administered dose low (Malmud et al 1982). In time ^{131}I was replaced by more suitable gamma emitting radionuclides - ^{111}In , $^{113\text{m}}\text{In}$ and $^{99\text{m}}\text{Tc}$. These radiolabels are more nearly optimal (especially $^{99\text{m}}\text{Tc}$) due to their short half-lives, suitable imaging characteristics, high count rates and relatively low radiation burdens to the patient making them suitable for repetitive studies.

Stacher and Bergmann (1992) describe the characteristics of the ideal marker as:

1. inexpensive;
2. non-absorbable by the gastrointestinal mucosa;

3. having a high labelling efficiency;
4. being homogeneously distributed within the meal;
5. remaining stable throughout the procedure;
6. having suitable imaging characteristics for the gamma camera.

MEALS

The meal in gastric emptying studies requires the following criteria (Mather et al 1991):

1. it must be reproducible, having set ingredients and method of preparation;
2. it must provide a normal physiological stimulus in terms of bulk, calorie content, energy density and composition and must not interfere with gastric emptying;
3. it must have stable radiotracers which accurately reflect the distribution of the liquid or solid or both phases.

The most commonly used radionuclide labels are ^{99m}Tc and ^{111}In which may be used for simultaneous imaging of both liquid and solid phase emptying, each marker labeling a different phase. The liquid, usually water or orange juice, is labelled with either ^{99m}Tc - or ^{111}In - diethylenetriaminepentaacetic acid (DTPA) or sulphur or tin colloid. These radiopharmaceuticals are neither absorbed nor digested by the gastrointestinal tract. Numerous solid and semi-solid meals have been labeled with ^{99m}Tc colloid and ^{111}In (Frier and Perkins 1994; Mather et al 1991; Stacher et al 1987; Christian et al 1984; Theodorakis et al 1982; Christian et al 1981; Kroop et al 1979; Meyer et al 1976).

For the purposes of my study a radiolabeled meal was required that could be used in poisoned patients, a number of whom were unconscious or had depressed levels of consciousness. A liquid marker was required that would reflect what was happening to the activated charcoal-poison complex and yet not interfere with patient management. ^{99m}Tc colloid in water was chosen because it was easy to administer through the tube following gastric lavage or via a nasogastric tube in patients who were obtunded. I worked on the assumption that the ^{99m}Tc colloid would be adsorbed onto the vast surface area of the activated charcoal and closely mirror the passage of the activated charcoal-poison complex through the gastrointestinal tract.

RADIATION DOSE ESTIMATES

Siegel et al (1983) and Madsen and Krogsgaard (1989) calculated radiation dosimetry for a number of radionuclides used for the study of upper gastrointestinal tract function. Based on the figures of these investigators a 20 MBq dose of ^{99m}Tc -sulphur colloid (SC) (Siegel et al 1983) and the same dose of ^{99m}Tc -labelled cellulose fibres (CELL) (Madsen and Krogsgaard 1989) demonstrated the radiation burdens shown in Table 1.

TABLE : 1 RADIATION DOSIMETRY

	20MBq ^{99m} Tc-SC (mGy)	20MBq ^{99m} Tc-CELL (mGy)
Stomach	0.50	1.07-1.16
S Int	1.50	1.63-1.80
L Int (upper)	2.88	0.55-3.55
L Int (lower)	1.75	0.22-4.70
Ovaries	0.52	0.50-0.65
Testes	0.036	0.01-0.05
Total Body	0.09	0.12

S Int = small intestine
L Int (upper) = proximal large intestine
L Int (lower) = distal large intestine

The radiation doses to the stomach and small intestine are lower with the ^{99m}Tc colloid in water than the ^{99m}Tc cellulose fibres because the colloid liquid meal has a shorter residence time in the upper gastrointestinal tract than the cellulose fibres.

These absorbed target dose values are well within the values laid down for the general public in the International Commission on Radiological Protection Publication 60 (1991). Patients in my study received a 20 MBq dose of ^{99m}Tc-tin colloid, the equivalent of the dose of sulphur colloid used by Siegel et al (1983).

IMAGING TECHNIQUES

Studies may be done simultaneously by dual radionuclide scintigraphy using both phases or, individually using either the solid or liquid phase depending upon the particular clinical circumstances. Patients are imaged on a large-field-of-view (lfov) gamma camera with either a single or dual detector following ingestion of the radiolabelled meal. There are a number of different ways of performing radionuclide scintigraphy but they all have the following characteristics:

1. The study is performed after a period of several hours of fasting.
2. Skin markers are used to facilitate repositioning of the patient for subsequent views.
3. The test meal is quickly consumed.
4. The patient is placed in a supine or sitting position.
5. Anterior or anterior and posterior images are acquired either simultaneously on a dual-headed camera or sequentially on a single headed camera. When a single phase is studied and a ^{99m}Tc -label is used the camera is fitted with a low energy, general purpose parallel-hole collimator (lepc). For dual radioisotope scintigraphy a medium energy collimator is used to accommodate both the ^{99m}Tc (140 keV) and the ^{111}In (247 keV) photopeaks.

6. Images are acquired at regular intervals. Datz et al (1991a) acquire images for 40 seconds each at 15 minute intervals for the first hour, then at 30 minute intervals until less than half of the food remains in the stomach. Stacher and Bergmann (1992) acquire serial images of 1 minute per frame for at least 50 minutes.
7. Data is processed by using the computer to identify the stomach region of interest and to obtain the counts for the radionuclide (or separately for both tracers if the dual photopeak method has been used) as a proportion of the total counts in the field of view at each imaging time. The geometric mean of the counts (Cgm) is calculated by the formula:

$$(Cgm = [\text{anterior} \times \text{posterior count}]^{1/2}).$$

8. A time-activity curve is generated from the counts at each time interval.
9. Half-emptying times are derived for the liquid, or solid or both phases.

Gastric scintigraphy has also been used to investigate intragastric distribution of food and gastric emptying patterns. Collins et al (1988) used a ^{99m}Tc -labelled digestible solid meal to determine the intragastric distribution of the food in 13 healthy subjects. They identified different gastric emptying patterns in the proximal and distal stomachs. Emptying from the total stomach could be divided into two phases - an initial lag period due to redistribution of food from the proximal to the distal stomach, and a phase of linear emptying with food leaving the stomach.

SPECIAL PRECAUTIONS AND CORRECTIONS

THE MEAL

Meal size and composition are standardised so as to make meaningful comparisons between patients and healthy controls. Moore et al (1984) found a significant delay in gastric emptying rates when the mean caloric intake was increased in 9 volunteers who were fed both liquid and solid meals of different caloric content. Interestingly, liquid emptying rates were not influenced as markedly by the caloric content (Moore et al 1984). Lin et al (1989) demonstrated that of 3 varying concentrations of glucose (750ml) the rate of gastric emptying was fastest for the smallest load of glucose and slowest for the meal with the greatest load. Gastric emptying is slowed for both liquids and solids in direct proportion to meal mass (Moore et al 1981).

THE MARKER

The choice of a radiotracer is also important. Mather et al (1991) tested liquid and solid phase radiolabelled meals in vitro. They found that virtually all the non-colloidal liquid markers showed some degree of adsorption onto the solid phase. Colloidal markers demonstrated the most accurate delineation of the liquid phase. If the radioactive tag is not sufficiently stable it will elute, mix with both phases and give a partly solid and partly liquid emptying time (Datz 1991b).

FASTING

Studies are done on fasting subjects to obviate interference by unlabelled gastric contents and to prevent any radiolabel that may elute from the test meal from adsorbing onto previously ingested food and giving false emptying rates.

IMAGING TECHNIQUE

POSITION AND EXERCISE

Patients are imaged in the same position, as posture influences gastric emptying rates (Moore 1989). A study on eight healthy subjects in four different positions - lying, sitting, standing and combined sitting-standing - showed that the recumbent position significantly slowed gastric emptying of a solid meal. A decrease in emptying times of 51% and 35% occurred in the combined sitting-standing position compared to the lying and sitting position respectively (Moore et al 1989). Exercise, even walking, enhances gastric emptying of solids and it is therefore necessary for patients to remain quiet between imaging sessions (Moore et al 1990). See Table 2.

TABLE 2 THE EFFECTS OF POSITION AND WALKING ON GASTRIC EMPTYING HALF-TIMES (MOORE ET AL 1990).

Position	Gastric Emptying Half-Times (Minutes)
Standing	72.6
Walking (3.2 Km/H)	44.5
Walking (6.4 Km/H)	32.9

Oro-caecal transit times were reduced from 98 minutes at rest to 75 minutes (Keeling et al 1990) and from 66 +/-10 minutes at rest to 44 +/- 6 minutes (Keeling and Martin 1987) during mild exercise when measured by the lactulose hydrogen breath test.

PATIENT MOVEMENT

Patient movement during acquisition or inaccurate repositioning will falsely shorten gastric emptying times if stomach activity has moved outside of the stomach region of interest (Glowniak and Wahl 1985). Skin markers facilitate accurate repositioning of the patient and allow motion artifacts to be corrected by drawing a new region of interest (Datz 1991b).

CORRECTIONS

DECAY AND DOWNSCATTER

Decay correction is required for short half-life radionuclides like ^{99m}Tc (6 hours) or the emptying time will be underestimated particularly in patients with marked delays in gastric emptying (Christian et al 1983). In dual solid-liquid phase imaging Compton downscatter from the higher energy radionuclide into the lower energy window should be corrected for.

DEPTH CORRECTION

Correction for depth is important as the gastric fundus is more posterior than the antrum. Therefore, with anterior imaging the counts increase as the radiotracer moves from the proximal to the distal stomach as a result of decreased tissue attenuation and scatter. Studies show that gastric emptying half-times of solids are overestimated by an average of 38% (emptying rates are underestimated) when anterior counts are used to calculate them (Christian et al 1980). Moore et al (1985) confirmed this finding for solid phase gastric emptying but they demonstrated only slight differences between anterior, and anterior and posterior geometric mean corrected emptying rates for liquids.

Depth correction can be achieved in a number of different ways:

1. Firstly, geometric means are calculated from counts derived from anterior and posterior images done in rapid sequence on a single-headed camera or simultaneously on a dual-headed camera. Studies using phantoms indicate that

calculated geometric means give count rates that vary less than 2% for depths ranging between 2.5 to 20 cm (Christian et al 1980).

2. Collins et al (1983) correct for attenuation by using a lateral image taken at the end of the study after the subject ingested 3.7 MBq of ^{99m}Tc -DTPA in 150 ml of water. The lateral image is used to calculate the distance from the midpoint of the stomach to the collimator surface at all levels from the fundus to the pylorus. Line correction factors for solid and liquid phases of the study were generated. The fact that tissue attenuation effects were found to be less marked for liquids in this study was thought to be due to the higher energy of ^{113m}In - the liquid marker. Collins et al (1983) demonstrated gastric emptying rates that were overestimated by 22% for solids and 17% for liquids before correction. The overestimation, in contrast to other studies that used anterior data (Tothill et al 1978; Moore et al 1985; Christian et al 1980), was due to the greater attenuation from the posterior projection which Collins et al (1983) used.

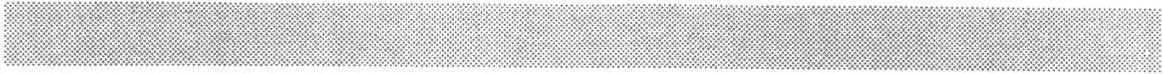
3. Ford et al (1992) imaged 42 patients in the anterior, posterior and left anterior oblique (LAO) views after each ingested a standard solid meal. They obtained linear regressions using the anterior, LAO and geometric means data. A very close correlation was obtained for gastric emptying half-times as calculated by geometric means and LAO counts ($R = 0.95$) for 35 patients. No significant difference was shown between the half-times calculated using the geometric mean and the LAO view ($P > 0.05$). Whereas a significant difference was shown between the anterior and geometric means calculated half-times ($R = 0.84$; $P < 0.05$). The authors suggest that the LAO method for determining gastric emptying times could be used instead of the geometric means. This confirms the findings of Fahey et al (1989) that emptying rates for solids from the left

anterior oblique projections correlate very well with those derived from geometric means.

4. A peak-to-scatter ratio has been used to derive a correction factor that gives results similar to the geometric mean (VanDeventer et al 1982). But the peak-to-scatter ratio can be changed by sources from outside of the field of view of the camera and is more complicated than the geometric mean correction technique (Datz 1991b), and it fails to compensate adequately for attenuation (Fahey et al 1989).

SUMMARY

In summary, gastric emptying and motility patterns in normal subjects have been described. Mean gastric emptying half-times of liquids ranged between 20 and 55 minutes in the studies quoted above. As I studied liquid emptying in my patients, these figures are particularly pertinent. Scintigraphic methods, markers and meals are discussed for the quantitation of gastric emptying rates and gastric motility. Special precautions, corrections and radiation dosimetry are considered in some detail as they are regarded as essential prerequisites to my study.



ORO-CAECAL AND SMALL INTESTINAL TRANSIT

Whereas gastric emptying influences the rate of drug absorption by governing access to the chief absorptive surface, the small intestine is regarded as the main site of drug absorption in man. The extent of drug absorption in the gastrointestinal tract is related to contact time with the small intestinal mucosa (Hirtz 1985). Therefore, the small intestinal transit time is an important determining factor in the absorption of many drugs.

The small intestinal transit time is the time that it takes for a meal to pass from the proximal duodenum to the caecum (colonic entry time minus duodenal entry time) (Pressman et al 1987). Both small intestinal transit and oro-caecal transit times are frequently measured by a number of different methods. The principal methods are the lactulose hydrogen breath test and gamma scintigraphy.

QUANTITATION OF ORO-CAECAI AND SMALL INTESTINAL TRANSIT TIMES

THE LACTULOSE HYDROGEN BREATH TEST

A non-absorbable disaccharide, lactulose (10-20g) is given orally (La Brooy 1983; Riley 1992). Lactulose passes unchanged through the stomach and small intestine and on reaching the caecum it is metabolised by colonic flora with the production of hydrogen. A rise in the concentration of hydrogen in the breath indicates that the head of the lactulose has reached the caecum. The lactulose hydrogen breath test is, therefore, an effective measure of oro-caecal transit time (Bond et al 1975). The test is simple, non-invasive and does not require the use of radioactivity. Comparative studies show a good correlation between the

lactulose hydrogen breath test and scintigraphic methods used for determining small intestinal transit times (Sciarretta et al 1994; Lartigue et al 1991; Prokop et al 1988; Caride et al 1984) and external counting of a radioactive marker (Read et al 1980). The radioactive tests were done simultaneously with the breath test by adding the radioactive marker to the lactulose prior to ingestion.

There are, however, several limitations to the lactulose hydrogen test.

The lactulose hydrogen breath test cannot determine the effect of gastric emptying on small bowel transit. The influence of variations and abnormalities in gastric emptying on oro-caecal transit times cannot be examined by using this method on its own. Another test has to be performed simultaneously to determine the contribution of gastric emptying to the overall result. Gastric emptying time is a particularly important consideration when investigating the effect of pharmacologic agents on small bowel transit (McCallum 1984). Scintigraphy (Sciarretta et al 1994; Riley et al 1992; Wegener et al 1992) and the acetaminophen (paracetamol) absorption test (Thoren et al 1989) are used in conjunction with the lactulose hydrogen breath test to evaluate gastric emptying.

Up to 25% of people cannot metabolise the lactulose because they lack the proper bacterial strains in the colon (Gilat et al 1978; Ravich et al 1983). Moreover, hydrogen production may be reduced by a low colonic pH (Perman et al 1981). Systemic antibiotics and laxatives interfere with the results by altering colonic flora (Gilat et al 1978). Before the study the subject's mouth has to be washed thoroughly to reduce contamination by oropharyngeal microflora which

could make the test difficult to interpret (Riley et al 1992). Prolonged fasting is required to minimise the effects on hydrogen excretion by carbohydrates eaten the night before.

Studies in healthy volunteers show significant intersubject variability in oro-caecal transit times (La Brooy et al 1983; Riley et al 1992).

The criterion for determining the end point of oro-caecal transit time on the hydrogen time curve is controversial and differs with investigators (La Brooy 1983; Read et al 1980; Bond and Levitt 1975). The accuracy of the test depends on the level of the increment of hydrogen concentration in the breath. A rise in breath hydrogen concentration of 5 parts per million (ppm) above threshold levels enhances the sensitivity of the test (Sciarretta et al 1994; Hirakawa et al 1988) as opposed to using the time for the breath hydrogen to reach a concentration of over 10 ppm above fasting levels (Hirakawa et al 1988). The absence of a sustained and sharp increase in breath hydrogen in some subjects and early increases in breath hydrogen in others can be misleading (McCallum 1984).

Bacterial overgrowth in the small intestine will result in an early rise in the breath hydrogen concentration creating a false impression that the lactulose has reached the caecum. Bacterial colonisation of the small intestine has been reported in diabetics (Spengler et al 1989) and patients with cystic fibrosis (Bali et al 1983).

A study on 102 healthy adults - 69 in India and 33 in the United States has shown that fasting hydrogen breath levels differ according to dietary habits and

that shorter oro-caecal transit times are associated with higher fasting breath hydrogen levels (Patel et al 1986). Oro-caecal transit times decrease, the greater the dose of lactulose that is used (Read et al 1980; La Brooy et al 1983).

The lactulose hydrogen breath test would be extremely difficult to perform in poisoned patients who were unconscious and/or on respirators.

MEASUREMENTS OF ORO-CAECAL TRANSIT TIMES

Several studies have been done on healthy volunteers.

Oro-caecal transit times from the various lactulose hydrogen breath studies on healthy subjects vary from study to study emphasising the limitations discussed above. The following are examples of the times in minutes measured by the different investigators in healthy subjects following a lactulose liquid meal (mean +/- SD):

103 +/- 8 (Harris and Martin 1994)

104 +/- 14.5 (Chiaroni et al 1993)

104.4 +/- 4.8 (Soffer and Launspach 1993)

88 +/- 37.2 and 90 +/- 51 (Vazquez-Olivencia et al 1992)

90 +/- 13 (Harris et al 1990)

81 +/- 33 (Hirakawa et al 1990)

100 +/- 11 and 93 +/- 20 (Piccione et al 1990)

75 (40-170) median (range) (Basilisco et al 1989)

66 +/- 10 (Keeling and Martin 1987)

85.5 +/- 35.7 (Basilisco et al 1987)

75.1 +/- 8.3 (Caride et al 1984).

GAMMA SCINTIGRAPHY

Images are taken at regular intervals following the ingestion of a radiolabeled liquid or solid meal. The time it takes for the leading edge of the radioactivity to arrive in the caecal region is a measure of the oro-caecal transit time. The passage of radioactivity is followed visually permitting precise localisation of the caecum in most patients. Moreover, the method allows the investigator to see the head of activity entering the duodenum making it easy to calculate the small intestinal transit time. Being able to measure the gastric emptying time accurately as part of the same test is an additional advantage. The test is simple, non-invasive and can be carried out using a small dose of radioactivity. The test can be used in obtunded patients by administering a liquid meal like radiolabeled water through an intragastric tube and taking images of the abdomen at regular intervals.

A number of different liquid and solid test meals and markers are used. These are discussed in the previous chapter under the sections "Radioactive markers" and "Meals".

Gamma scintigraphy has certain disadvantages.

Accurately identifying the ileo-caecal region is difficult in certain patients (Caride et al 1984). Small intestinal radioactivity may obscure the caecal area delaying

detection of caecal radioactivity. Methods have been developed in attempts to overcome this problem. McCallum (1984) and Caride et al (1984) propose using an area that corresponds to a known intestinal segment, usually the hepatic flexure or midascending colon. The time of appearance of activity in these regions is used as a reference for analysis of curves obtained proximal to this point. This method presupposes that the activity will pass into the colon within the imaging period. But this may not occur in patients in whom there is a considerable delay in oro-caecal transit time. Jian et al (1984) use a dual isotope method - a ^{51}Cr chloride colonic marker administered orally 8 hours prior to ingestion of a $^{99\text{m}}\text{Tc}$ sulphur colloid meal. The right colon was localised using the ^{51}Cr chloride image and a region of interest drawn on this image was transposed onto the image in the $^{99\text{m}}\text{Tc}$ window. This permitted direct and accurate localisation of the caecum (Jian et al 1984). However, this method cannot be used in an acute situation to evaluate the effects of a recently taken poison on the intestinal transit.

Inter- and intra-subject variations have been shown (Caride et al 1984; McCallum 1984). Sciarretta et al (1994) found a coefficient of variation of 16% for scintigraphy in 10 subjects of whom each had 2 scintigraphic tests. Intestinal transit times could be influenced by simultaneous lactulose ingestion.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT TIMES USING SCINTIGRAPHY

Studies have been done using gamma camera scintigraphy to determine small intestinal and oro-caecal transit times. The following transit times (mean +/- SD in minutes and n = number of subjects) were reported in normal subjects:

SMALL INTESTINAL TRANSIT FOR LIQUID MEALS:

81 +/- 11 (n = 10) ^{99m}Tc-DTPA in lactulose (Prokop et al 1988)

73 +/- 6.5 (n = 19) ^{99m}Tc-DTPA in lactulose (Caride et al 1984)

ORO-CAECAL TRANSIT TIMES FOR LIQUID MEALS:

45 (range: 10-75) (n = 10 X 2 tests each) ^{99m}Tc-DTPA in lactulose (Sciarretta et al 1994).

The differences noted between the mean intestinal transit times for the first 2 studies and the third could be accounted for by the different amounts of lactulose given. Prokop et al (1988) and Caride et al (1984) gave subjects 10 G lactulose while Sciarretta's patients received 20 G. Furthermore, different methods were used for detecting the arrival of radioactivity at the caecum.

SMALL INTESTINAL TRANSIT FOR SOLID MEALS

169 (median) (range: 47-427) ^{99m}Tc-cellulose fibre (Madsen 1990)

158 (median) (range: 71-422) ¹¹¹In-plastic particles (Madsen 1990)

234 +/- 90 (mean +/- SD) ^{99m}Tc-sulphur colloid-bran (Kerlin et al 1989)

231 +/- 37 (mean +/- SD) ^{99m}Tc-cellulose fibre (Madsen and Jensen 1989)

242 +/- 20 (mean +/- SD) ¹¹¹In-plastic particles (Madsen and Jensen 1989)

SUMMARY

In assessing the strengths and weaknesses of the 2 different tests what becomes apparent is that the lactulose hydrogen breath test, although used more frequently, has a greater number of shortcomings. Scintigraphy has a greater number of advantages and fewer associated drawbacks. Scintigraphy permits continuous measurement of the progression of the head of the test meal without influencing the physiologic mechanisms that control small intestinal transit. It is easily modifiable to accommodate specific needs. Scintigraphy is therefore the method best suited to investigating obtunded or confused patients. As both gastric emptying and small intestinal transit times are measured using the same radiotracer and dose of radioactivity, the radiation burden to the patient is identical whether one or both studies are carried out. The radiation burden is discussed in the previous chapter under "Radiation dose estimates". Oro-caecal and small intestinal transit times measured by a number of investigators have been detailed as these (especially transit times for liquids) are important to my study. The range for the means using either of the methods is 45 to 90 minutes for scintigraphy and approximately 60 to 105 minutes for the lactulose hydrogen breath test.

EXTERNAL GAMMA COUNTERS

Patients are fed a radiolabeled (usually a ^{99m}Tc tin or sulphur colloid or DTPA marker is used) liquid or solid meal. A scintillation counter (a crystal scintillation detector connected to a counter ratemeter) is placed over the abdomen. An increase in counts over the caecal region (2 cm medial to the anterior superior iliac spine) heralds the arrival of the head of the radiolabeled meal (Read et al

1980). Oro-caecal and small intestinal transit times (Read et al 1980) as well as gastric emptying times (Riley et al 1992) can be determined using this method. The method is limited by the fact that radioactive meal is not visualised. This makes it difficult to localise the radioactivity precisely and tell when it has arrived at the caecum.

RADIOLOGICAL METHODS

BARIUM MEAL AND RADIOPAQUE CAPSULES

Radiographs are taken at regular intervals following the oral ingestion of a barium sulphate meal (Hirakawa et al 1988) or radiopaque capsules (Reele et al 1982) to determine the arrival time in the caecum. Simultaneous ingestion of a barium meal is required to identify the caecum in subjects who have received radiopaque capsules. The capsules are more difficult to detect against the barium background. The shortcomings of the use of barium in gastrointestinal studies have been outlined in the previous chapter under "Radiological Techniques". These are aptly summarised by McCallum (1984) in the following points. Barium is an artificial meal and the results cannot be extrapolated to other meals. In addition, different barium formulations may alter intestinal transit times. Furthermore, multiple exposures are required to accurately follow the movement of barium through the intestine delivering a significant radiation burden to the subject.

The oro-caecal transit time for a barium meal was 63 +/- 9 minutes which correlated well with the time of 74 +/- 9 minutes measured by lactulose hydrogen breath test (Hirakawa et al 1988).

SULPHASALAZINE/SULPHAPYRIDINE TEST

Mouth-to-caecum transit times have been measured by exploiting a special property of sulphasalazine (salicylazosulphapyridine) (Kennedy et al 1979). This drug is not absorbed in the upper gastrointestinal tract but is metabolised by microbial flora in the large bowel to generate sulphapyridine which is rapidly absorbed. The time lapse before detection of sulphapyridine in plasma gives an estimate of the oro-caecal transit time. This method, however, yields considerably longer oro-caecal transit times (4 to 5 hours) than the other methods (Gramatte and Terhaag 1991).

CARBON-14 LACTULOSE BREATH TEST

This method involves estimating the colonic entry time of C-14 labeled lactulose by measuring the $^{14}\text{C}\text{O}_2$ excretion in breath. When compared to hydrogen excretion on the one hand and gamma scintigraphy on the other (Pressman et al 1987), $^{14}\text{C}\text{O}_2$ output was delayed. The correlations were low to moderate. Radioactivity appeared in the caecum as assessed by scintigraphy 2 hours before $^{14}\text{C}\text{O}_2$ appeared in the breath. There was marked variability between subjects (coefficient of variation = 56%). This method lacks the necessary sensitivity to be useful.

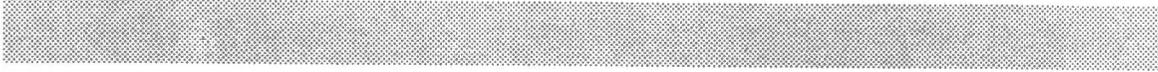
MAGNETIC METHOD

An externally applied magnetic transducer is used to detect the presence of an ingested ferromagnetic material dispersed in a test meal upon its arrival in the caecal area (Benmair et al 1977). The mouth-to-caecum transit time is thus

determined. The test is non-invasive and does not require radiation but precise localisation of the caecum is difficult.

Metal particles detected by a portable metal detector have been used to measure intestinal transit (Ewe et al 1989). This method is limited by the lack of direct visualisation of the caecal region.

Non-absorbable markers such as polyethylene glycol require an intraluminal tube to retrieve samples from different locations in the small intestine. This produces stimuli that could influence intestinal transit and cause discomfort (Sarr and Kelly 1980).



FACTORS THAT ALTER GASTROINTESTINAL MOTILITY AND GASTRIC EMPTYING IN POISONING

Factors that may influence gastrointestinal motility and gastric emptying in patients with poisoning include: the type and quantity of drug taken, gender, age, mental state, diurnal variation and certain iatrogenic measures. In a study of the nature that I undertook these factors had to be understood and controlled where possible so that any perceived changes could be related directly to the causative agent - the drug in question.

DRUGS IN THERAPEUTIC DOSES

TRICYCLIC ANTIDEPRESSANTS

The tricyclic antidepressants have powerful muscarinic receptor blocking properties (Richelson 1983). These are reported to cause adverse gastrointestinal effects at therapeutic doses of tricyclic antidepressants including dry mouth, constipation and, rarely, paralytic ileus (Katzung 1984; Pradhan 1986). The anticholinergic activity of the tricyclic antidepressants are thought to inhibit gastrointestinal motility and delay gastric emptying by reducing gastric tone and motility (Nimmo 1975). Drug interactions resulting in the delayed absorption of drugs such as phenylbutazone (Consolo et al, 1970) and levodopa (Morgan et al, 1975) when given simultaneously with therapeutic doses of tricyclic antidepressants were attributed to a delay in gastric emptying. There is, however, little direct evidence that therapeutic doses of the tricyclic antidepressants retard gastric emptying.

ANTICONVULSANTS

CARBAMAZEPINE

Carbamazepine has a chemical structure that is similar to the tricyclic antidepressants (Raines 1986) but there is no evidence to suggest that it shares the anti-muscarinic properties to which the gastrointestinal disturbances of the tricyclic antidepressants are attributed.

PHENYTOIN

There is little evidence to suggest that phenytoin inhibits intestinal motility or delays gastric emptying. Nimmo (1976) bases his contention that phenytoin delays gastric emptying on work by Woodbury (1969) showing that the drug reduced spontaneous gastrointestinal smooth muscle activity in animals, and a report by Ahmad (1974) who suggested that the delayed response to oral frusemide in patients on chronic anticonvulsant therapy might be due to delayed gastric emptying. The latter hypothesis has since been disproved by a study by Riley et al (1992) which showed that the rate and extent of frusemide absorption were unrelated to the rate of gastric emptying.

PHENOBARBITONE

Although barbiturate anaesthesia was found to delay the velocity of propagation of the interdigestive myoelectric complex (Schurizek et al 1989c), there appears to be little if any information on whether phenobarbitone influences gastrointestinal motility or emptying rates.

ACETAMINOPHEN - PARACETAMOL

Paracetamol is not considered a drug that per se alters gastric motility and emptying. This is one of the reasons for its choice as a measure of the gastric emptying rate. Schurizek et al (1989a) performed a study on 11 healthy subjects and demonstrated three different absorption and motility responses to paracetamol (20mg/Kg):

- a. The first group of 5 subjects were rapid absorbers with a short time to maximum plasma levels (t_{max}) of one hour, antral activity, a high motility index (the frequency x amplitude of the contraction measured manometrically), and short duration of phase 2 of the interdigestive myoelectric complex (33-60 minutes). All, except for one, completed Phase 3 of the interdigestive myoelectric complex.
- b. The second group consisting of 4 individuals had a t_{max} of 1.5 hours and a longer phase 2 period (80-133 minutes). The phase 3s were all incomplete.
- c. The last group made up of only 2 subjects comprised slow absorbers, t_{max} was not reached during the investigation period of three hours, no antral contractions were seen and the motility index was very low.

The incidence and the duration of phase 3 activity were diminished after therapeutic doses of paracetamol when comparing the total phase 3 activity in the basal state with that following paracetamol ingestion. These responses to paracetamol were thought to be due to diurnal variations and positioning of the gastroduodenal manometry tube prior to paracetamol administration (Schurizek et al 1989a).

However, the small numbers of subjects in each group makes it difficult to draw any valid conclusions from these results. Whether therapeutic doses of paracetamol can cause a delay in gastric emptying and thereby diminish absorption of paracetamol remains unanswered. This obviously has implications for both my study and the paracetamol absorption test as a measure of gastric emptying. It became one of the motivations, along with the results in the first part of my study, for setting up a small pilot study in which I measured gastric emptying in 5 healthy volunteers after each received 1 000mg of paracetamol.

Posture has been shown to affect paracetamol absorption. Nimmo et al (1978) demonstrated a significant delay in absorption in subjects lying on their left sides, presumably due to slower gastric emptying in that position. Another study confirmed that paracetamol absorption was lowest in the left lateral decubitus position in 12 healthy subjects who were given 80mg/kg of paracetamol to simulate an acute overdose. Although absorption in this position did not differ significantly from the supine, both of the aforementioned differed significantly from the prone, right lateral decubitus and sitting positions which had higher absorption (Vance et al 1992).

All of the patients in my study were imaged in the supine position.

OPIOIDS - CODEINE (METHYLMORPHINE)

The effects of opioid drugs on gastrointestinal motility depend on a variety of opiate receptors in the brain, spinal cord and the gut itself (Burks et al 1987). The fact that endogenous opioids play a role in regulating gastrointestinal motor and secretory functions is supported by the presence of opioid peptides and

receptors distributed along the gastrointestinal tract (Rees et al 1983; Bueno and Fioramonti 1988; Telford et al 1989).

Animal studies indicate that different receptor subclasses might be important and that these vary from species to species. For example, opiates with a predominantly mu agonist activity inhibit gastric motility and delay gastric emptying in rats via both peripheral and central receptors (Bueno and Fioramonti 1988; Shook et al 1987; Tavani et al 1990; Manara et al 1986), while both kappa and mu agonists play a role in the guinea pig (Culpepper-Morgan et al 1988). It is thought that the actions of the opioid drugs are similar to those of endogenous opioid peptides. In vitro experiments have shown that opioids inhibit acetylcholine release from the myenteric plexus which is thought to be the basis for opioid-induced inhibition of gastrointestinal motility (Paton 1957; Schaumann 1957). Radioassay has shown concentrations of morphine in the longitudinal muscle of the small intestine with attached myenteric plexus after parenteral administration of the drug (Manara et al 1986). The investigators conclude that the inhibition of gastrointestinal transit was the result of direct action of morphine on gut opioid sites (Manara et al 1986).

Some report that therapeutic doses of opioids delay gastric emptying by reducing gastric motility and increasing antral tone which together delay the passage of gastric contents to the small intestine (Pradhan and Dutta 1986; Way and Way 1984). The opioids are thought to delay gastric emptying by increasing the tone in the duodenal antrum thus reducing the pressure gradient between the stomach and the duodenum (Camilleri et al 1986). Morphine is reported to prolong the mean gastric emptying and small intestinal transit times in healthy volunteers (Yee et al 1991; Prokop et al 1988). The absorption of oral

paracetamol (McNeill et al 1990; Kluger et al 1991) and glucose and insulin (Sullivan et al 1986) are markedly delayed after the administration of morphine suggesting a delay in gastric emptying.

In contrast, other studies have shown that opioids have little effect on gastric emptying rates. Riley et al (1992) found that codeine phosphate had no influence on gastric emptying but oro-caecal transit was delayed two-fold. After ingesting a 30-mg tablet of oral morphine, 10 healthy volunteers showed no difference in gastric emptying times when compared with a group that had taken placebos (Clyburn and Rosen 1989).

Reports indicate that opioids slow the passage of material through the intestine (Riley et al 1992; Sommers et al 1992). The opioids are known to increase considerably the tone of the small (and large) intestine including the ileo-caecal valve, and to reduce propulsive peristaltic movements (Pradhan and Dutta 1986). Clyburn and Rosen (1989) demonstrated a markedly delayed mean small intestinal transit time of 300 minutes in 8 subjects, six of whom had transit times of over 480 minutes after each had ingested a 300mg morphine tablet. Barrow et al (1993) showed that codeine delays transit of a radioactive bolus from the mouth to the terminal ileum in healthy subjects in whom diarrhoea was induced by lactulose. The mean small intestinal transit time in 10 subjects doubled from 81 +/- 11 minutes (baseline) to 161 +/- 15 minutes after they received 8mg of morphine intravenously (Prokop et al 1988). Opioids are reported to cause a dose dependent increase in frequency of the interdigestive myoelectric complex but a decrease in the velocity of propagation (Schurizek 1991). Intestinal perfusion studies indicate that codeine retards jejunal transit (Schiller et al 1982). Rees et al (1983) demonstrated decreased antroduodenal

contractility in man following the administration of naloxone, an opioid antagonist, in the absence of exogenous opioids. This supports a functional role for endogenous opioids in vivo.

Kromer (1989) suggests that the apparently conflicting data on the effects of opioids on gastrointestinal motility might be due to functionally contrasting opioid systems regulating the same physiological functions. And that these may cause opposite effects depending on the balance between the systems at the time of drug administration. Inhibitory neuromodulation at multiple sites causing either inhibition or disinhibition by opioids may result in their contrasting effects (Kromer 1989).

DRUG OVERDOSE

In an extensive review on the subject Rosenberg et al (1981) conclude that the pharmacokinetics of drugs taken in overdose differ from those following therapeutic doses. Drug absorption, distribution and elimination are often altered after drug overdose. They highlight problems that make interpretation of the data difficult when it comes to analysing data on pharmacokinetics following drug overdose. These include:

1. uncertainty regarding the dose and time of drug ingestion;
2. a prolonged drug absorption period and a brief blood sampling time making it difficult to distinguish between absorption and elimination phases of the drug;

3. the types, amounts and concentrations of concomitantly ingested drugs are often not known;
4. pre-existing disease states and their patho-physiological effects on drug pharmacokinetics are often not taken into consideration;
5. the effects of specific organ toxicities on drug metabolism are often not evaluated;
6. the individual responses of patients to different concentrations of drug in the blood and tissues;
7. the identification and quantification of active metabolites and measurements of protein binding are often overlooked; and
8. patient management including emesis, lavage, administration of activated charcoal or cathartics may alter the amount of drug available for absorption.

These factors could account for the poor correlation between the clinical findings in overdose patients and the blood concentrations of ingested drugs.

EFFECTS OF OVERDOSE ON PHARMACOKINETIC PROCESSES

ABSORPTION AND BIOAVAILABILITY

As the small intestine is the chief site of drug absorption the rate of absorption depends principally on the rate of gastric emptying which determines the time for passage into the small intestine (Rowland 1978), and the rate of drug dissolution. Rosenberg et al (1981) maintain that the delay in absorption due to drug overdose delays the onset or peak intensity of the drug's action. This delay may be due to the greater proportion of drug reaching the systemic circulation following an overdose than after a therapeutic dose. Saturation of presystemic or first-pass metabolism are possible mechanisms (Rosenberg et al 1981). Drugs with significant first-pass metabolism include: narcotic analgesics, tricyclic antidepressants, and phenothiazines. Nimmo (1976) suggests that delayed absorption is due to the formation of a poorly soluble mass of the drug, and diminished gastrointestinal motility.

Gastrointestinal motility is affected by specific drug actions on the one hand - it is depressed by anticholinergic drugs, and by the general nervous system depression caused by a number of drugs on the other. Drugs that directly affect gastrointestinal smooth muscle and those that depress the autonomic nervous system all reduce gastrointestinal motility.

Retarding gastrointestinal motility may lead to a decrease in the rate but an increase in the amount of drug absorbed. It could also result in prolonged, erratic and delayed absorption (Rosenberg et al 1981). Reduced

gastrointestinal motility may occur with poorly water-soluble drugs and result in an increase in the eventual amount of the drug absorbed because of the prolonged period for absorption. Patients may, therefore, present with toxicity several days after a single ingestion possibly due to persistence of the drug in the small intestine with continuing absorption (Rosenberg et al 1981). Gastric decontamination may be indicated for several hours after an overdose in these patients.

DRUG DISTRIBUTION

The distribution of the drug depends on a number of different factors including the route of administration, plasma and tissue protein-binding, tissue perfusion and the extent of partitioning to the tissues (Rowland 1978). Drug distribution may alter after an overdose with important clinical implications. Certain drugs like the salicylates may saturate plasma binding protein sites even at therapeutic levels. As the concentration continues to increase the unbound fraction of the drug increases while the amount bound remains constant. Taken together with the fact that protein binding varies from individual to individual, it is difficult to relate total blood concentrations of drugs to clinical effects. The concentration of free drug might more closely reflect clinical effects (Rosenberg et al 1981).

The rate of diffusion of the drug into the tissues is usually more rapid than its rate of absorption and elimination. Therefore, the rate at which clinical effects manifest depends on the rate at which the drug enters the systemic circulation.

ELIMINATION

The rate of metabolism and elimination are dependent on the capacity of enzyme or carrier-mediated systems which may become saturated at overdose levels. Phenytoin is a case in point (Arnold and Gerber 1970). Possible mechanisms of saturation include: simple saturation of the enzyme or carrier, inhibition of enzyme activity by the drug, decrease in enzyme affinity or activity due to a metabolic product of the drug, exhaustion of cofactors and inactivation or destruction of the enzyme or carrier (Rosenberg et al 1981). Certain barbiturates destroy cytochrome P-450 haem thus inhibiting hepatic metabolism of the drug (Levin et al 1972).

In the overdosed patient certain drugs like the barbiturates (Forrest et al 1974; Prescott et al 1973) and paracetamol (Slattery and Levy 1979) exhibit concentration dependent pharmacokinetics and elimination rates. In these instances endogenous drug clearance decreases as drug concentration increases (Rosenberg et al 1981). Methods for the removal of the drug from the body are, therefore, of greater relative importance at high plasma levels. Furthermore, in these conditions the drug "half-life" is prolonged and the area under the plasma concentration-time curve at sufficiently high dosage levels may approximate the square rather than the dose itself (Gibaldi and Perrier 1975).

ALTERED PHARMACOKINETICS OF DRUGS IN OVERDOSE

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants taken in large quantities have altered pharmacokinetics. The tricyclic antidepressants depress gastrointestinal motility by their strong anticholinergic activity. This could alter their rate of absorption (Rosenberg 1981). In a small number of patients (n=3) the half-life after overdose was shown to be considerably increased (60-81 hours) compared with the normal half-life range of 16-24 hours (Spiker and Biggs 1976; Hollister 1978). The final elimination of a big portion of the absorbed tricyclic antidepressant is delayed by significant enterohepatic recirculation. Saturation of the enzymes for tricyclic antidepressant benzyl-hydroxylation reduces its elimination to zero-order kinetics. The unbound fraction of tricyclic antidepressants may increase due to an acidosis resulting from respiratory depression (Jarvis 1991).

Tricyclic antidepressant pharmacokinetics may be greatly modified by other drugs ingested in the suicide attempt. Ethanol metabolites inhibit tricyclic antidepressant oxidative metabolism while neuroleptics directly inhibit its hydroxylation. Paracetamol poisoning generates hepatic metabolites which delay tricyclic antidepressant elimination (Jarvis 1991). The rate of drug elimination is slower in the elderly who are therefore particularly susceptible to tricyclic antidepressant overdosage. Delayed gastric emptying has been reported in elderly patients on therapeutic doses of tricyclic antidepressants at therapeutic blood levels (Woodhouse and Bateman 1985).

Confirmation that high doses of tricyclic antidepressants suppress gastrointestinal motility and prolong gastric emptying might help explain delayed absorption and provide the rationale for gastrointestinal decontamination in patients presenting several hours after ingestion of these drugs.

ANTICONVULSANTS

BARBITURATES

Absorption of most barbiturates occurs within an hour after a therapeutic dose. But prolonged absorption associated with overdose is thought to be due to delayed gastric emptying (Rosenberg et al 1981). Holzer et al (1987) demonstrated profound suppression of gastric emptying following a dose of 150 mg/kg to rats. Phenobarbitone blocked the peristaltic reflex in isolated guinea-pig small intestine suggesting a direct inhibitory effect on the digestive tract (Holzer et al 1987). These investigators also found considerable amounts of phenobarbitone in the stomach of an intoxicated patient 3 days after drug intake.

This suggests that gastric decontamination may prove effective in patients who have ingested the drug several hours earlier and that these measures should be considered in the treatment of protracted barbiturate poisoning. Neuvonen et al (1980) showed that the administration of multiple dose activated charcoal (MDAC) reduced the half-life of phenobarbitone from 110 to 20 hours suggesting interruption of an enterohepatic or enteroenteric circulation. The half-life of barbiturates following overdose is shorter than following therapeutic doses

possibly due to microsomal enzyme induction leading to an increased rate of elimination (Martin et al 1979; Prescott et al 1973; Forrest et al 1974).

As animal studies provide some evidence for gastric retention of phenobarbitone when taken in high doses it is necessary to determine whether gastrointestinal motility is altered in humans.

PHENYTOIN

Although Rosenberg et al (1981) state that phenytoin, a poorly water-soluble drug, decreases gastrointestinal motility thus prolonging absorption after ingestion of a toxic dose, they provide little evidence for this. A number of reports indicate peak plasma concentrations of phenytoin 24-48 hours after an overdose (Holcomb et al 1972; Pruitt et al 1975; Wilder et al 1973; Wilson et al 1979). Plasma concentration half-times are prolonged following overdosage from more than 60 hours (Holcomb et al 1972; Wilder 1973; Richens 1979) to 9.6 days (Gill et al 1978) and even 22 days (Wilson et al 1979). Elimination of phenytoin is dose dependent and therefore delayed following an overdose and patients may remain intoxicated for lengthy periods (Rosenberg et al 1981). Multiple doses of activated charcoal were shown to significantly reduce phenytoin absorption and increase the phenytoin elimination in 8 healthy volunteers (Rowden et al 1990).

There is little evidence to show that phenytoin overdose diminishes gastrointestinal motility and prolongs gastric emptying times. Confirmation of

delayed gastric emptying might support the use of activated charcoal in patients with both acute and chronic overdoses of the drug.

CARBAMAZEPINE

Four patients with acute carbamazepine overdose had delayed gastric emptying as part of a broad spectrum of clinical signs. The elimination half-lives of carbamazepine varied from 10-29 hours (normal = 15 - 20 hours) (Sullivan 1981). High doses of carbamazepine have been shown to depress gastric emptying in rats (Nakatsuji et al 1987).

There is therefore no quantitative evidence to suggest that carbamazepine overdose diminishes gastrointestinal motility and prolongs gastric emptying times in humans.

PARACETAMOL

The principal complication of paracetamol overdosage is hepatic necrosis and failure (Smilkstein et al 1988; Prescott 1983). Acute renal failure, pancreatic and cardiac complications also occur but these are less common (Prescott and Wright 1973; Proudfoot and Wright 1970; Rumack and Matthew 1975; Williams and Davis 1977).

After therapeutic doses paracetamol is absorbed rapidly with plasma concentrations reaching a maximum at 0.5 to 1 hour with doses of 500 and

1000mg. When the dose is increased to 2000mg the plasma concentration continues to rise for 2 hours suggesting a slower absorption at higher doses (Rawlins et al 1977). Spontaneous and induced vomiting following overdosage is common making it difficult to measure the percentage of the dose absorbed, but in patients with liver damage absorption appears to be greater (Prescott and Wright 1973).

The elimination time of paracetamol from the body is prolonged in overdosed patients especially when there is liver damage. Prescott et al (1971) demonstrated a plasma paracetamol half-life of 7.6 +/- 0.8 hours in 17 patients who developed liver damage. This was twice as long as in 13 patients who did not develop liver damage (2.9 +/- 0.3 hours) and more than 3 times as long as the half-life in 17 normal subjects given therapeutic doses of paracetamol (2.0 +/- 0.1 hours). The prolonged half-life of paracetamol might be the result of liver injury, with the group that did not develop clinical signs of liver damage being less affected than the first group. But other mechanisms such as enzyme saturation or lack of glucuronic acid or sulphates (important for paracetamol elimination) might also account for the prolonged paracetamol half-life at high plasma concentrations (Rosenberg et al 1981).

As paracetamol is metabolised by the hepatic microsomal mono-oxygenase system, concomitant ingestion of the microsomal enzyme inducers, phenobarbarbitone and phenytoin, enhances paracetamol metabolism thus increasing its toxic metabolite (N-hydroxyparacetamol) and hence the tendency to hepatic necrosis (Mitchell et al 1973). Nimmo et al (1979) showed that the absorption of paracetamol was slowed when ingested concurrently with propoxyphene. This was thought to be the result of a propoxyphene induced

delay in gastric emptying. Paracetamol absorption and, by inference, gastric emptying are also retarded by narcotic analgesics and antimuscarinic agents in both healthy volunteers (Nimmo et al 1975) and patients who have taken overdoses of paracetamol (Müller et al 1983).

Following a single high dose of paracetamol to rats via various routes - oral, intra-arterial, intravenous and portal vein - the relative contribution of the gastrointestinal tract, liver and lung to the oral extraction ratio (first-pass effect after oral absorption) was determined. The mean relative extraction ratio of the gastrointestinal tract, liver and lung were 0.52, 0.07 and 0 respectively, indicating a major contribution by the gastrointestinal tract (Bhargava and Hirate 1989). This is in contrast to other studies which indicated a negligible gastrointestinal contribution to the oral first-pass effect when lower doses were used. Bhargava and Hirate's (1989) findings therefore suggest a possible dose-dependent mechanism.

There is no data on the effects of high doses of paracetamol on gastric emptying and gastrointestinal motility in humans. A delay in gastric emptying may explain the slow absorption whereas an unaltered or enhanced gastric motility may suggest an intestinal mechanism for slow absorption.

CODEINE (METHYLMORPHINE)

Studies have shown that opioids delay gastric emptying, diminish gastrointestinal motility and prolong small intestinal transit times in therapeutic doses but the effects of high doses are less well documented. The elimination half-life of

codeine after therapeutic doses is 2.4-2.9 hours (Findlay et al 1978). Huffman and Ferguson (1975) reported a patient in whom the blood concentrations of codeine fell only slightly over the first 48 hours after an overdose. This may be due to depressed gastrointestinal motility associated with opioid action.

Data is lacking on the effects of overdoses of opioids on gastrointestinal motility and gastric emptying. It is necessary to determine whether and to what extent opioid overdose alters gastric emptying and motility.

GENDER DIFFERENCES IN GASTRIC EMPTYING

A study comparing 15 healthy males between the ages 20-53 years (mean 30 years) and 15 healthy females between the ages 20-45 years (mean 32 years) demonstrated significantly different gastric emptying rates for both liquids and solids in the 2 groups. The half-emptying time of the stomach for men was: solids 59.8 +/- 3.7 minutes, liquids 30.3 +/- 2.3 minutes; and for women: solids 92.4 +/- 7.5 minutes and liquids 53.8 +/- 4.9 minutes (Datz et al 1987a). In 15 postmenopausal women (46-68 years) studied at the same centre the half-emptying times were: solids 69.5 +/- 5.5 minutes; liquids 41.9 +/- 3.6 minutes (Datz et al 1987b). The gastric emptying half-times were significantly shorter in postmenopausal than premenopausal women.

The markedly slower gastric emptying for both liquids and solids in premenopausal women is thought to be due to the smooth muscle relaxant effect of the sex hormones progesterone and oestradiol. This theory is supported by animal studies (Wald et al 1981; Bruce and Behsudi 1979; Scott and DeFlora 1983) and the fact that the mouth-to-caecum transit time is prolonged in pregnancy particularly during the third trimester when progesterone and oestradiol are at their highest levels (Wald et al 1982). In a study on 5 healthy women serving as their own controls Petring and Flachs (1990) demonstrated that the gastric emptying rate of a semi-solid meal decreased linearly during the menstrual cycle towards the luteal phase. But emptying of the liquid phase was unaltered. In addition, gastric emptying times in elderly women who have low sex hormone levels are no different from men of similar age (Horowitz et al 1984).

In contrast, Monés et al (1993) and Horowitz et al (1985) demonstrated no difference at the various phases of the menstrual cycle. Monés and his co-workers also failed to show any significant differences between gastric emptying times in pre- and postmenopausal women. Possible reasons for these conflicting results include: the different volume, composition and caloric content of the meals; different imaging positions (supine vs upright); imaging techniques (anterior and posterior views vs anterior view only); and the paucity of subjects in the different studies. In addition, controlled studies using the indirect paracetamol absorption technique failed to show significant differences in gastric emptying times of women in the three trimesters of pregnancy and non-pregnant women (Whitehead et al 1993, Macfie et al 1992).

A study comparing gastric emptying and small intestinal transit times using ^{99m}Tc-labeled cellulose fibre in 17 healthy young subjects (21-27 years; 9 men and 8 women) and 16 healthy older individuals (55-74 years; 8 men and 8 women) showed gender made no significant difference (Madsen 1992).

As a result of a preparatory survey of Emergency Unit patient records and in discussions with the staff it became clear that my study sample would consist of both males and females with a preponderance of the latter. I could expect premenopausal women to make up the greatest proportion of patients in my study. Pregnant women were excluded from the study. I intended to minimise the effects of gender by using each patient as his/her own control.

AGE

Gastric emptying rates were compared in 19 healthy elderly and 19 fit young volunteers using paracetamol absorption kinetics. The results showed no significant difference between the two groups suggesting that ageing does not impair gastric emptying (Gainsborough et al 1993). Madsen (1992) reported no difference in gastric emptying or small intestinal transit times when comparing 17 young with 16 older subjects. Piccione et al (1990) also failed to show a significant difference in oro-caecal transit times when comparing an older group with a group of younger adult controls (oro-caecal transit time of 100 +/- 11 minutes vs 93 +/- 20 minutes).

But Moore et al (1983) using a dual radiotope method showed a delay in gastric emptying of liquid in an aged group of men when compared with a younger group. There was no difference in gastric emptying of solids.

The studies comparing aged with younger men are conflicting but any possible age effect was minimised by using each subject as his/her own control.

CIRCADIAN RHYTHM IN GASTRIC EMPTYING

Goo et al (1987) performed a study on 16 healthy male subjects to determine whether gastric emptying rates showed circadian changes. Each volunteer had 2 gastric emptying studies done, at 08h00 and 20h00 separated by an interval of 7 to 21 days. Solid and liquid phase emptying rates were measured simultaneously. Gastric emptying half-times of solids was significantly more

rapid in the morning (64.8 +/- 6.4 minutes) compared with the evening times (97.1 +/- 11.5 minutes). No significant difference was found between the morning and evening liquid emptying rates. The liquid phase emptying rates were consistently higher than the solids (Goo et al 1987).

A possible explanation for the circadian variation of gastric emptying may lie in the decreased nocturnal propagating velocity of the migrating motor complex (Kumar et al 1986). Differences in gastric emptying may account, to some extent, for the circadian variability in the absorption of several orally administered drugs with morning drug administration resulting in higher peak plasma concentrations, shorter time to peak plasma concentrations and quicker drug elimination (Reinberg et al 1982).

In comparing gastric motility the time of the day appears important especially when using the solid phase. Ideally the control studies should be conducted at the same time of day as the initial study. I selected a liquid meal as it can be given by intragastric tube, if necessary, and because it does not interfere with patient management. The available data suggests that circadian rhythm has no significant effect on the gastric emptying of liquids.

THE EFFECT OF STRESS ON GASTRIC EMPTYING

A number of studies have shown that acute stress, anxiety, fear and pain retard gastric emptying and alter gastrointestinal motility (Thompson 1982; Valori et al 1986; Simpson and Stakes 1987). A variety of methods have been used to induce physical and psychological stress in both man and animals under experimental conditions to assess their influence on gastrointestinal motility (Camilleri and Neri 1989). Camilleri and Neri (1989) suggest that different stressful stimuli may be mediated by different afferent pathways and may reach different centres in the brain. These may induce gastrointestinal effects in a number of different ways.

Valori et al (1986) used radiotelemetry to detect stress-induced inhibition of fasting migrating motor complexes in 37 healthy volunteers. In another study twelve healthy male volunteers underwent combined solid and liquid phase gastric emptying scintigraphic studies on 3 separate occasions: firstly a control study; secondly after mental stress; and thirdly following physical stress (Datz et al 1990). Gastric emptying half-times of both liquids and solids were slower in patients subjected to stress (liquids : 33.9 +/- 3.6 minutes for controls as against 60.0 +/- 4.9 minutes for physical stress and 44.2 +/- 5.3 minutes for mental stress; and solids: 60.2 +/- 3.4 minutes for controls versus 90.3 +/- 3.6 for physical and 70.3 +/- 7.8 minutes for mental stress). Physical stress significantly delayed gastric emptying while psychological stress prolonged emptying times to a lesser extent.

A third study using a painful stimulus (intermittent immersion of subjects' feet in ice-cold water) failed to show any delay in gastric emptying, oro-caecal transit

time or intestinal transit after the cold pain stress (Thoren et al 1989). Transcutaneous electrical nerve stimulation applied to the hand or abdominal skin reduced postprandial antral motility (Camilleri et al 1984). Simpson and Stakes (1987) demonstrated gastric stasis by reduced and delayed paracetamol absorption in preoperative patients with a low predisposition to anxiety. Labyrinthine stimulation induced by cold water irrigation of the tympanic membrane retarded gastric emptying and the postprandial duodenal motility was changed to one resembling the fasted state (Thompson et al 1982). However, Harris and Martin (1994) failed to show a significant difference in oro-caecal transit times in subjects during final examinations and on a control day. Oro-caecal transit times were 103 +/- 8 minutes under control and 106 +/- 8 minutes under examination conditions.

In fasted dogs acoustic stress resulted in a lengthening of the gastric migrating motor complex and gastric hypomotility but intestinal motility was unaffected (Gue et al 1988). Wrap restraint stress in rats inhibited small intestinal transit but had no effect on gastric emptying (Williams et al 1988).

Camilleri et al (1986) noting that beta-endorphin levels rise during acute stress, found that physiological quantities of intravenously administered beta-endorphin increased pyloric pressure and reduced phasic pressure in the antrum in healthy humans. The gastrointestinal effects of this opiate agonist were reversed by naloxone, an opiate antagonist. Corticotropin-releasing factor administered into the lateral cerebral ventricle in rats significantly inhibited gastric emptying and small intestinal transit (Lenz et al 1988). This is thought to occur by modulation of the autonomic nervous system and, partly, by opioid pathways.

On the balance of reviewed data it can be concluded that certain forms of acute stress inhibit gastrointestinal motility and gastric emptying. It is difficult to predict whether a stress threshold exists for individuals above which there might occur a dramatic change in gastric emptying and small intestinal transit. Patients in my study would endure significant psychological trauma and stress at the time of the first study. It was necessary, therefore, for me to be aware of possible differences in gastric motility that might occur between the initial and control studies at which time the stress will have abated in many patients.

COMA AND GENERAL ANAESTHESIA

In discussions with the Emergency Unit and Respiratory intensive care unit staff it became clear that a number of the more toxic patients would be obtunded. It is thus important to establish whether coma or general anaesthesia could alter gastric motility.

Inoue et al (1993) conducted a study using the acetaminophen absorption method on elderly patients with cerebral vascular diseases and other causes of coma. The investigators showed delayed gastric emptying in the comatose groups when compared with a group with cerebral vascular disease who could walk (Inoue et al 1993). This suggests that delayed gastric emptying is due to the comatose state and/or possibly the posture of the comatose groups. Patients with severe head injury who developed a delayed gastric emptying pattern subsequent to rapid emptying on an initial study (biphasic pattern) were found to have more severe brain damage, oedema and/or brain stem injury on computer tomography than patients with a normal gastric emptying pattern (Ryo

et al 1990; Ott et al 1991). These findings indicate that the head injury played some role in altering gastric emptying (emptying times were not reported) and that the changes were not due solely to patient posture. Comatose patients in my study were imaged in the supine position by a mobile gamma camera in the intensive care unit.

Groups of patients who had general anaesthesia induced by 3 different agents all had significantly delayed gastric emptying rates when compared with the control group (Mushambi et al 1992). The 3 groups who underwent general anaesthesia had similar gastric emptying rates as determined by the paracetamol absorption test. A review of a number of studies indicates that general anaesthesia depresses antral motility and gastric emptying and reduces the duration of the IDMC (Schurizek 1991; Schurizek et al 1989b; 1989c).

PRIMARY ANOREXIA NERVOSA AND BULIMIA NERVOSA

A number of reports have shown that impaired gastric emptying occurs in both of these psychiatric conditions. Marked delays in gastric emptying have been demonstrated in patients with primary anorexia nervosa (Dubois et al 1979; Holt et al 1981; McCallum et al 1985; Stacher et al 1986,1987,1991). Using a standard radiolabeled semi-solid meal, Stacher et al (1991) found a gastric emptying half-time range of 41.4 to 277.1 minutes (median of 98.3 minutes) in patients with primary anorexia nervosa. This was significantly slower than that of a group of 48 healthy subjects in whom the 75th percentile of the half-times was 64 minutes and median 53.4 minutes. In subsequent studies Stacher and his co-workers (1993a; 1993b) demonstrated an acceleration of gastric emptying in

patients with primary anorexia nervosa following the administration of cisapride and erythromycin. Hirakawa et al (1990) demonstrated prolonged gastrocaecal transit times in 10 patients suffering from anorexia nervosa (117 +/- 31 minutes) when compared with a control group (81 +/- 33 minutes).

Kiss et al (1990) studied 24 patients with bulimia nervosa and found significantly slower gastric emptying rates than in healthy controls. In 9 patients there was a gross delay in emptying. Gastric emptying half-times after the standard semi-solid meal ranged between 99 and 272 minutes with a median of 74 minutes compared with 47 minutes for the control group. Shih et al (1987) studied 20 patients with bulimia and found delayed gastric emptying in 12 and rapid emptying in 8 patients.

Delayed gastric emptying, diminished antral contraction amplitude and impaired antral contractility to meals are features of both primary anorexia nervosa and bulimia (Stacher et al 1987; Kiss et al 1990). The underlying mechanisms for the impaired gastric motor function in patients with these conditions are not known.

I anticipated that the majority of my patients would be young women. This meant that they fitted the age and gender profiles of patients who develop primary anorexia nervosa and bulimia. This made a consideration of the effects of these conditions on gastrointestinal motility important.

IATROGENIC MEASURES

INDUCED EMESIS

Saetta et al (1991) gave patients with self-poisoning barium impregnated pellets with ipecacuanha in water and took an abdominal radiograph directly after they stopped vomiting. Forty percent of the pellets were seen in the small intestine as a result, the authors felt, of intragastric forces generated during the vomiting.

Although patients in my study did not receive emetics certain of them vomited because of the drug-induced nausea.

GASTRIC LAVAGE AND INTRAGASTRIC TUBES

Gastric lavage forms a part of the management of many patients admitted to the Emergency Unit at Groote Schuur Hospital. As such it was important for me to establish whether this procedure could affect gastric motility.

Müller-Lissner and his colleagues (1982) measured gastric emptying rates after placing a naso-gastric tube (Levin tube, inner diameter of 3.0mm) with its tip in the antrum. Gastric emptying rates of a milk-cream liquid meal were no different when the tube was in situ as compared with other occasions in the same 8 healthy subjects in the absence of the tube. Gastric emptying was similar whether the meal was instilled via the tube or was swallowed. The fractional gastric emptying rate was also not affected by a transpyloric duodenal tube (outer diameter of 5.0mm).

Blake and McKelvey (1981) measured gastric emptying times by aspiration of gastric contents following a liquid meal (a milk, sugar, water emulsion) with a double sampling technique in 14 normal subjects. The latter method required that a nasogastric tube be placed in the most dependent part of the stomach so that serial calculations of gastric volume could be made. The mean gastric emptying half-time in this group was approximately 74 minutes (range 22-145 minutes). Another study on 5 healthy men demonstrated no effect on gastric emptying of a solid meal (measured by volume aspirated) in the presence of a transpyloric duodenal tube (outer diameter of 4.0mm) (Longstreth et al 1975).

Read et al (1983), found that gastrointestinal intubation significantly delayed gastric emptying in 12 healthy subjects when comparing them with 10 counterparts who were not intubated. A 4 metre long tube consisting of 4 polyvinyl catheters bonded together (diameter not specified) was swallowed the day before the study and allowed to pass to the terminal ileum. Gastric emptying times after a solid test meal were 90 +/- 6 minutes for the intubated group and 72 +/- 6 minutes for the controls. They postulate that the delay may be due to stimulation of mucosal mechanoreceptors in the oesophagus, stomach and small intestine which inhibit contractions in the gastric body and antrum. In addition, the gastric fundus is relaxed by pharyngeal stimulation in the cat (Abrahamsson and Jansson 1969). Read et al (1983) concede, however, that stress may have played a role in delaying gastric emptying.

Although the findings of Read et al (1983) are different from those of the other studies factors like stress, the longer tube and the considerably longer period for which the tube was in situ before the study was done might have influenced the results. The other investigators used shorter tubes for a shorter duration thus

more closely mimicking the situation in which gastric lavage is done on poisoned patients.

But caution has to be exercised when comparing these results with my study. Gastric lavage in a poisoned patient requires a wide calibre tube (outer diameter of 35mm) and a rapid procedure. When this is carried out on an uncooperative, at times frightened patient, the risk of traumatising the oesophageal and gastric mucosa must be greater than when the procedure is performed under controlled conditions with a narrow bore tube. Saetta and Quinton (1991) discovered bruising of the cardia as a result of gastric lavage in four out of seventeen patients on whom they performed endoscopy after lavage. It is not known whether, or to what extent gastric emptying could be affected in these circumstances. As I could not control for this variable I had to determine its significance statistically by comparing gastric emptying times in those who had gastric lavages with those who did not.

ACTIVATED CHARCOAL

I have not been able to find any evidence to suggest that activated charcoal influences gastric emptying rates. However, Russel and Bass (1985) have shown that a slurry of 90 g of a synthetic polymer, polycarbophil, empties slowly from the stomach (gastric emptying half-time of 4 hours) in dogs. Gastric emptying was measured by aspirating the stomach. The delay in gastric emptying was thought to be due to the viscosity of the slurry. The particle size ranged from 1-3mm. Another study showed that non-digestible, solid particles of varying sizes (0.5-6.4mm) and densities were discharged from the stomachs of

fasted dogs as a result of one migrating motor complex in phase 3 (Gruber et al 1987).

The activated charcoal water suspension used as part of patient management and in the controls in my study had a particle size of 0.04mm. This was considerably smaller than the particles used in the trials quoted above. I attempted to minimise its influence on my study by administering a similar dose to the patient when he/she returned for the control test in part one.

ANTIDOTES - N-ACETYLCYSTEINE AND S-CARBOXYMETHYLCYSTEINE

The cysteine derivative, N-acetylcysteine is commonly administered to protect against paracetamol-induced liver necrosis resulting from an overdose of paracetamol (Smilkstein et al 1988). A second derivative, S-carboxymethylcysteine has also proved to be an effective antidote (Beneke et al 1983).

Beneke and Müller (1983) have shown that S-carboxymethylcysteine causes marked inhibition of gastric emptying in rats. N-acetylcysteine has also been shown to delay gastric emptying in mice (Whitehouse 1981). The exact mechanism for this action remains unclear but the authors postulate that the inhibition in gastric emptying causes a reduction in paracetamol small intestinal absorption. Whitehouse et al (1981) suggest that the delay in gastric emptying could be a major mechanism for the protective action of N-acetylcysteine in mice.

Several patients who present with paracetamol overdose are treated with intravenous N-acetylcysteine at the Emergency Unit at Groote Schuur Hospital. Certain of them are given the drug on the basis of the history and clinical picture gained by the physician while other patients receive N-acetylcysteine once their paracetamol levels have been shown to be within the toxic range. N-acetylcysteine causes nausea, vomiting and diarrhoea (Flanagan and Meredith 1991; Holdiness 1991), whether it inhibits gastric emptying in humans is a question which remains unanswered.

OTHER DRUGS

DIAZEPAM

Diazepam has been shown to increase gastric emptying rates by enhancing antral contractility (Schurizek 1988; 1991). The influence of diazepam on gastric emptying is an important consideration as the majority of patients who are admitted to the intensive care unit on respirators are given the drug routinely. Intravenous diazepam is given at regular intervals or when necessary to prevent restless, disorientated patients from removing endotracheal tubes.

NICOTINE - CIGARETTE SMOKING

Mouth to caecum transit times were prolonged in a study on 20 habitual smokers (10 males and 10 females). The oro-caecal times were significantly delayed when subjects smoked cigarettes or took nicotine tablets immediately after a

standard liquid meal, when compared with the times after they took placebos. Median oro-caecal times for smoking and nicotine tablets were 120 vs 100 minutes for sham cigarettes and placebos (Scott et al 1992). The investigators conclude that the delay caused by cigarettes is probably due to nicotine. What is important is that the smoking appears to have an acute effect on gastrointestinal function. The oro-caecal times were not prolonged in those on placebos even though they, too, were habitual smokers (Scott et al 1992).

Patients are prohibited from smoking in the hospital and smoking is disallowed before and during nuclear medicine investigations. This makes it unlikely that smoking would play a part in altering gastric emptying in my patients.

INTRA- AND INTER-SUBJECT VARIABILITY OF GASTRIC EMPTYING

Petring and Flachs (1990) studied ten healthy subjects, five males and five females. Gastric emptying rates were measured scintigraphically following the ingestion of a radiolabelled semi-solid meal, as well as by the paracetamol absorption method. Each subject was studied on four different occasions separated by one week. Intra-subject variability was not significant for any of the scintigraphic or paracetamol absorption measurements. The largest differences were 15% in a male and 18% in one female. Inter-subject variability, on the other hand, was significant for all parameters. The largest inter-subject difference was 35% for the same set of tests. In another study on 6 subjects gastrointestinal transit showed little difference when the same subject was tested on 3 separate occasions but intersubject variations were considerable. For gastric emptying inter-subject variability was 4 to 10 times greater and for oro-

caecal transit 15 to 28 times greater than intra-subject variability (Riley et al 1992). Madsen (1992) also demonstrated considerable inter-subject variability and less intra-subject variability in mean gastric emptying and small intestinal transit times using a ^{99m}Tc -labeled cellulose fibre meal. Collins et al (1983) also found significant inter-subject differences in scintigraphically measured gastric emptying rates of solids and liquids in 19 healthy volunteers.

Brophy et al (1986) demonstrated both intra- and inter-subject variability in gastric emptying of radiolabelled liquid and solid meals in eight healthy subjects who were tested on four different occasions. Solid half emptying times ranged from 29 to 92 minutes (mean of 59 +/- 17) with the half emptying times for liquids ranging between 12 and 37 minutes (mean 24 +/- 8). A nested random effects analysis of variance showed a moderate intra-subject variability for solid and a high intra-subject variability for liquid emptying.

Intra-subject differences are more important in my study than inter-subject ones as the use of each patient as his/her own control will reduce the effects of the latter. The data presented by the groups of researchers who investigated intra-subject variability in gastric emptying is conflicting. The majority of investigators report no or less significant intra-subject than inter-subject differences. But Brophy et al (1986) show significant intra-subject variability for liquid emptying. The reasons for the different results are not known but intra- and inter-subject differences have to be taken into account when performing scintigraphic measurements of gastric emptying in groups of individuals.

SUMMARY

I have summarised certain of the important factors that might influence gastrointestinal motility and gastric emptying in poisoning. A knowledge of the potential effects of therapeutic doses on gastric emptying and motility of the different drug groups that I tested was important to my study. It was also important to be aware of the reported effects of overdoses of these drugs on certain pharmacokinetic and physiologic processes, even though there was relatively little information in this regard. On the basis of the survey of the literature I expected the different drugs to affect gastrointestinal motility differently and to result in different emptying and transit rates. The possible effects of circadian rhythm and stress on gastric emptying were particularly important as I could not control these factors. And it was important for me to establish whether certain iatrogenic measures used in the management of poisoning would alter gastrointestinal motility. Other factors such as age, gender and inter-subject variability were controlled by using each patient as his/her own control.



AN OVERVIEW OF CERTAIN ASPECTS OF POISON MANAGEMENT

A number of controversial areas exist in the field of management of the poisoned patient. The role of gastrointestinal decontamination including gastric lavage, the use of cathartics, laxatives and activated charcoal is constantly under scrutiny. Comparisons are being made regarding the clinical efficacy of the different methods and their adverse effects in attempts to find the best treatment regime for poisoning.

GASTROINTESTINAL DECONTAMINATION

GASTRIC LAVAGE

Adolf Kussmaul is credited with introducing gastric lavage as a method of treatment over a century ago in 1869 (cited in Reid 1970). There continues to be debate over whether emptying the stomach using gastric lavage or induced emesis is of benefit in acute poisoning.

Some feel that there is little, if any, place for evacuating the stomach in these patients (Neuvonen and Olkkola 1988). Neuvonen and Olkkola (1988) hold that gastric emptying might prove effective in patients who have ingested large quantities of poison, because the sheer quantity of drug may overwhelm the capacity of activated charcoal to adsorb it. By adsorbing the drug, activated charcoal reduces the amount of poison available for absorption by the small intestine. Paracetamol poisoning might have this effect (Neuvonen and Olkkola 1988). A further indication for gastric lavage may be poisoning with agents that have a poor affinity for activated charcoal (Neuvonen and Olkkola 1988).

However, if poisons decrease gastric motility, gastric lavage may prove effective when instituted up to several hours post-ingestion (Goulding and Volans 1977, Sharman et al 1975). After a survey of the literature spanning the period 1977 to 1989, Dziukas and Vohra (1991) conclude that all patients seen within 6 hours of a tricyclic overdose should have their stomachs emptied. On the other hand there is evidence which suggests that gastric lavage is only effective when performed within a very short time after ingestion of the poison (Comstock 1981; Kulig et al 1985; Lovejoy and Linden 1991; Jawary et al 1992). Kulig et al (1985) demonstrated that gastric lavage performed more than 1 hour after ingestion has no effect on the clinical outcome. However, when performed in obtunded patients within an hour of ingestion the outcome was significantly better than in patients who did not have lavage (Kulig et al 1985). The fact that only 7.6% of the patients in their study ingested tricyclic antidepressants could have biased the conclusions drawn. Placing less emphasis on the time of ingestion, Krenzelok and Dunmire (1992) and Harris and Kingston (1992) feel that gastric lavage remains an important part of management in the seriously toxic patient and that its use should be based on a thorough clinical assessment.

In contrast, a prospective study by Sullivan showed that gastric lavage in obtunded patients did not significantly alter the length of stay in the emergency department or intensive care unit, or the length of time patients were intubated (Sullivan et al 1990). Gastric lavage was also associated with a higher number of aspiration pneumonias than patients who received activated charcoal or the emetic, ipecacuanha (Sullivan et al 1990). One of the 72 patients on whom gastric lavage was performed in this study developed an oesophageal perforation following that procedure.

Other serious complications of gastric lavage include tracheal lavage, gastric perforation and pulmonary aspiration (Lovejoy and Linden 1991). Arterial oxygen tension was reduced after gastric lavage in patients admitted for drug overdose. The decrease in oxygen tension was greater in smokers and in patients with high plasma tricyclic antidepressant levels (Jorens et al 1991) indicating possible respiratory complications.

A large prospective study on 808 patients demonstrated no benefit from adding gastric lavage to management with activated charcoal in symptomatic patients (Merigian et al 1990). Indeed, the group that received gastric lavage plus activated charcoal showed an increased risk of aspiration pneumonia. All eight patients with aspiration pneumonias were thought to have aspirated during the lavage procedure despite tracheal intubation. Furthermore, patients who had gastric lavage or emesis in addition to activated charcoal were admitted to the intensive care unit more often, had an intubation rate four times that of symptomatic patients who received only activated charcoal, and were more commonly placed on ventilators (Merigian et al 1990). The authors conclude that emesis and lavage are unnecessary in selected asymptomatic patients and that they are of limited clinical benefit in the routine management of symptomatic patients.

Comstock et al (1981) detected a further increase in blood concentrations of sedative-hypnotics in 35.5% of intoxicated patients after lavage. In a retrospective study Serena et al (1994) discovered that patients with acute maprotiline (a tricyclic derivative) intoxication who had gastric lavage fared worse than their unlavaged counterparts who had ingested similar amounts of the drug. This was especially so when the lavage was done more than 1 hour after

ingestion. It must be pointed out that these conclusions were based on a retrospective evaluation of clinical records and relate mainly the blood levels at presentation to the outcome following various forms of management. Watson et al (1989) reported less than 20% recovery of ingested tricyclic antidepressants even with extensive lavage suggesting: that lavage promotes the passage of poison into the small intestine; that the lavage was done after the poison had passed into the intestine; or that the information on the quantity of drug ingested was inaccurate. The study was performed on a small number of patients (13) and an estimated ingested dose was available in only seven patients.

A much more convincing prospective, randomised study was done by Saetta et al (1991) who used radiopaque pellets to demonstrate that gastric lavage increased the rate of anterograde gastric emptying into the small intestine. In the control group which did not undergo a gastric emptying procedure 16.3% of ingested pellets were found in the small intestine compared with 33.3% in the gastric lavage group and 39.3% in the ipecacuanha group. This could cause earlier time to peak or higher peak drug concentrations, thus aggravating the clinical condition of the patient. Moreover, it reduces the opportunity for charcoal adsorption of the drug in the stomach. This study also showed up the inefficiency of the gastric emptying procedures - 51.8% of pellets ingested were retained in the gastrointestinal tract of the gastric lavage treated group and 58.5% of the total number of pellets ingested was retained following ipecacuanha administration.

In another study Saetta and Quinton (1991) performed endoscopic examinations on patients with self-poisoning who had been treated with ipecacuanha induced emesis and a second group who had had gastric lavages. The times between

ingestion and gastric decontamination ranged from 1 to 4.5 hours. Fifteen of the 17 patients (88.2%) who had gastric lavages had residual intragastric solid; tablets were found in ten patients. Four patients had bruising at the cardia of the stomach.

In the group with induced vomiting 38.5% (5 out of 13 patients) had residual solid including tablets (in 3 out of 5) in the stomach.

In summary, therefore, gastric lavage is a psychologically and at times physically traumatic procedure which on the balance of current literature does not appear to affect the clinical outcome of the poisoned patient. Kulig et al (1985) found it useful only in obtunded patients who had the procedure done within an hour of ingesting the poison. This is possibly the sole use for it. However, there are those who feel that it is an indispensable tool in poisonings with serious toxic potential such as tricyclic antidepressant overdoses (Krenzelok and Dunmire 1992; Harrison and Kingston 1992). Others believe that it might be of use in patients who have ingested drugs which delay gastric emptying even when the lavage is performed a number of hours after taking the drug.

Gastric lavage procedures formed an important part of the treatment in a number of patients in my study. The question as to whether the gastric motility and emptying rates are altered by the trauma that may arise following lavage is not answered in the literature.

EMESIS

Parenterally administered apomorphine and orally ingested syrup of ipecacuanha are the 2 drugs used to induce emesis. The former has been shown to act more rapidly, inducing vomiting within 6 minutes. It also results in a greater percentage recovery of gastric contents than ipecacuanha which takes 15-30 minutes to act (Wheeler-Usher et al 1986, Corby et al 1968, MacLean 1973, Robertson 1962, Schofferman 1976). However, apomorphine has to be administered under medical supervision and might cause central nervous system (CNS) and respiratory depression that could aggravate the condition of the patient and confuse the clinical picture (Wheeler-Usher 1986; Klaassen 1985). Syrup of ipecacuanha has been reported to cause diarrhoea and lethargy (Czajka and Russel 1985). Kulig et al (1985) have shown that the use of syrup of ipecacuanha does not alter the clinical course of poisoned patients. This was confirmed in a large prospective study by Sullivan et al (1990). Furthermore, emesis is contraindicated in patients who are obtunded or comatose in whom the gag reflex may be absent (Wheeler-Usher 1986). In addition, ipecacuanha has been shown to increase the rate of anterograde gastric emptying into the small bowel (Saetta and Quinton 1991). This could result in earlier time to peak and/or higher peak drug levels and theoretically worsen the clinical condition.

However, a retrospective study using the American Association of Poison Control Centres data base showed a decrease in the 4-hour paracetamol levels in half of the 455 children with paracetamol poisoning who had been treated with emetics (Bond et al 1993). These patients who received emetics soon after ingestion were compared with a control group that received no decontamination.

Emesis was less effective when it was delayed and had no demonstrable impact when it occurred more than 90 minutes after ingestion.

The use of emetics does not form part of the treatment regime at the Grootte Schuur Hospital Emergency Unit. As such only a small number of patients were given ipecacuanha by referring general practitioners or medical officers based at clinics or outlying hospitals.

ACTIVATED CHARCOAL

In 1963 Holt and Holz proclaimed their belief that in poisoning charcoal was the most effective of the emergency measures "because of its broad spectrum of activity and its exceedingly rapid inactivation of the poison" (Holt and Holz 1963, p313). But thirty years later Vale and Proudfoot (1993) call for more information "before gastric lavage can be abandoned completely in favour of giving activated charcoal..." They claim that there is little evidence to show that morbidity and mortality are reduced by repeated doses of oral activated charcoal.

Activated charcoal is prepared by destructive distillation of various organic materials, usually wood pulp, and is then treated at high temperatures (600-900°C) with steam, carbon dioxide or strong acids to increase its adsorptive capacity (Lee and Roberts 1991). This "activation" creates a complex internal pore structure which expands the surface area from 2-4m²/g to more than 1000m²/g (Vale and Proudfoot 1993). A number of studies and comprehensive reviews indicate that activated charcoal reduces drug absorption and enhances excretion, hence, it is argued, diminishing the toxic load in patients with drug overdose (Jawary et al 1992; Smolinske 1990; McNamara RM 1989; Neuvonen and Olkkola 1988; Olkkola and Neuvonen 1984; Levy 1982; Berlinger et al 1983; Berg et al 1982; Goldberg and Berlinger 1982).

However, other investigators and reviewers continue to express reservations regarding the clinical benefit of activated charcoal (Vale and Proudfoot 1993; Palatnick and Tenenbein 1992; Tenenbein 1991; Merigian 1990; Kulig et al 1985). Problems cited by these investigators include the fact that many studies were done on healthy, fasted volunteers who ingested non-toxic doses of drugs

and large doses of charcoal. In addition, the paucity of clinical studies and the difficulty in evaluating the clinical outcome of patients treated with different treatment regimes make the problem of assessing the clinical benefit of activated charcoal all the more difficult. Whether substantive conclusions regarding the efficacy of activated charcoal can be drawn from subtoxic, volunteer studies is uncertain.

A large prospective study on the effect of gastric lavage in over 800 patients with self-poisoning demonstrated no benefit from a single dose of 50g of activated charcoal administered to asymptomatic patients. It proved of some benefit to symptomatic patients (Merigian et al 1990).

Mechanism of Action

Activated charcoal combats the poison in a number of different ways:

1. Charcoal prevents the absorption of many orally-ingested poisons by adsorbing the portion that remains in the gastrointestinal canal. This mechanism is particularly important in patients who have taken slow release preparations or drugs that are slowly absorbed because they impair gastric motility.
2. Secondly, charcoal adsorbs poisons secreted in bile thus breaking their entero-hepatic cycle.
3. Furthermore, charcoal binds substances that diffuse from the circulation into the gut lumen along a concentration gradient. This gradient is maintained by the

action of the charcoal resulting in continued diffusion and adsorption. In addition to a favourable concentration gradient, blood flow, mucosal permeability and intestinal surface area determine the amount of poison diffusing into the lumen (Vale and Proudfoot 1993). The enteroenteric circulation of the drug is thus interrupted. Activated charcoal therefore increases the elimination rate of drugs already absorbed or given intravenously. This gastrointestinal clearance of the poison by activated charcoal has been referred to as "gastrointestinal dialysis" (Levy 1982, p677).

Drug Adsorption by Activated Charcoal

Activated charcoal adsorbs a wide variety of substances to its vast surface area. Tricyclic antidepressants and antiepileptics are well adsorbed. Unfortunately, paracetamol is only moderately adsorbed and saturation of the charcoal is likely with the latter (Karkkainen and Neuvonen 1986; Neuvonen et al 1978; Neuvonen and Elonen 1980; Neuvonen et al 1983c). It is not clear why this occurs as activated charcoal completely binds paracetamol *in vitro* (Bailey et al 1992).

Although single dose activated charcoal reduces gastrointestinal absorption of nortriptyline it prolongs its elimination time, suggesting desorption from the drug-charcoal complex (Alvan 1973). MDAC may overcome this problem and may also increase the elimination of nortriptyline (Crome et al 1977; Dawling et al 1978; Karkkainen and Neuvonen 1986). Activated charcoal binds amitriptyline and reduces its elimination time. As much as 99% of amitriptyline present in the stomach after healthy volunteers had taken 75mg was adsorbed to 50g of activated charcoal (Karkkainen and Neuvonen 1986). Repeated doses of

charcoal reduced the elimination half-life of amitriptyline by 20%, and its active metabolite, nortriptyline by 40% in these subjects. Charcoal inhibits the absorption of the shorter half-life tricyclic, imipramine, without altering its elimination time (Goldberg et al 1985b). An extensive review on tricyclic poisoning indicated the necessity for all patients to receive activated charcoal (Dziukas and Vohra 1991). They do not make a distinction between single and MDAC.

There is evidence that barbiturates are effectively bound by charcoal. Fifty grams of activated charcoal adsorbed 97% of phenobarbitone (200mg) present in the stomach. Its elimination half-life of approximately 100 hours was reduced to 20 hours by repeated doses of charcoal (Neuvonen and Elonen 1980). Charcoal inhibits the gastrointestinal absorption of phenytoin. Absorption was reduced by 98% when charcoal was administered after 5 minutes and by 80% when given 1 hour after ingestion of 500mg phenytoin (Neuvonen et al 1978). Charcoal also effectively binds carbamazepine. Over 95% of a 400mg dose present in the stomach was adsorbed by 50g charcoal and repeated doses have increased the elimination rate of carbamazepine by 50% in healthy volunteers (Neuvonen and Elonen 1980). The latter effect has also been observed in intoxicated patients (Boldy et al 1987; Heath and Van Loo 1986; Vale et al 1986).

As the elimination half-life of paracetamol is prolonged in severe poisoning repeated doses of charcoal may reduce the absorption of paracetamol and its metabolites thus reducing their hepatotoxicity (Neuvonen and Olkkola 1988). Opioid analgesics are also thought to be adsorbed by charcoal thus reducing gastrointestinal absorption (Neuvonen and Olkkola 1988).

Repeated doses of orally administered activated charcoal increase the elimination from the body of many poisons. This method is regarded as being more effective than gastric lavage or emesis. As a single dose of charcoal is thought to have no serious side-effects it has been recommended for conscious patients at home, at work or at a primary health care centre as a first line of treatment which can be given without fear of compromising the patient or altering further management. As the adsorption capacity of activated charcoal is saturated by large amounts of poison, big stat doses of 50-100g are advised in acute poisoning followed by repeated doses of 20-50g at 4-6 hour intervals (Neuvonen and Olkkola 1988).

Gastrointestinal contents like food might reduce the adsorption of drugs to the activated charcoal by competing for binding sites. But it is possible that the gastric emptying delay associated with the presence of food might give the charcoal more time for effective adsorption of the poison (Olkkola and Neuvonen 1984b). This effect may, however, be counteracted by desorption of the poison from the charcoal. Poisons are known to bind reversibly to activated charcoal (Neuvonen and Olkkola 1986; Neuvonen et al 1978; Bainbridge et al 1977; Levy and Tsuchiya 1972). The half-lives of certain drugs have increased when taken with a single dose of charcoal (Alvan 1973). This suggests desorption of the drug from the charcoal with subsequent absorption into the circulation.

Regimes which incorporate repeated dosing with activated charcoal increase its efficacy and reduce the risk of desorption (Crome et al 1977; Dowling et al 1978). The sooner the activated charcoal is administered after drug ingestion, the greater its efficacy in preventing absorption. As the rate of absorption of agents taken orally is determined by the rate at which these pass from the

stomach to the intestine (Nimmo 1979), factors that delay gastric emptying will permit effective binding by the charcoal even when the latter has been administered several hours after ingestion. This applies to patients who have taken life-threatening overdoses in whom drug absorption may be considerably prolonged (Rosenberg et al 1981). However, if the bulk of the drug has passed into the small intestine and inhibits gastric emptying then the administration of charcoal will be less effective.

Single Or Multiple Dose Treatment?

Some clinicians propose a single large dose of activated charcoal given orally, or through a nasogastric tube in the obtunded patient. While calling for further studies to determine proper doses, Vale and Proudfoot (1993) recommend a dose of 150-200 g to severely poisoned patients. They maintain that the total dose is more important than the frequency of dosing (Vale and Proudfoot 1993). Citing the lack of clinical evidence to support the use of MDAC and the mounting reports of morbidity and mortality with that regime, Palatnick and Tenenbein (1992) recommend a single large dose of 25-50 g for children under 5 years and 50-100 g for older children and adults. They reason that for mass action to be effective, large doses are needed to enhance adsorption to, and to prevent desorption from, the activated charcoal. Larger quantities should be given to patients who have ingested large gram amounts of a drug, for example, in cases of severe paracetamol poisoning (Palatnick and Tenenbein 1992). In a review of recent literature Jawary et al (1992) conclude that patients be treated with a single dose of activated charcoal if seen within four hours of toxin ingestion.

A number of others support the use of MDAC therapy (Boldy et al 1986; 1987; Weidle et al 1991; Dolgin et al 1991). They claim that MDAC is necessary to ensure a sufficiently high charcoal-to-poison ratio and to overcome the problems of low affinity of ingested poisons to charcoal, reversibility of adsorption and varying rates of release from different pharmaceutical formulations (Neuvonen and Olkkola 1988). Although repeated doses of activated charcoal increased drug elimination in both volunteers (Neuvonen and Elonen 1980; Swartz and Sherman 1984; Mauro et al 1987; Ilkhanipour et al 1992) and poisoned patients (Boldy et al 1986; 1987; Weidle et al 1991; Dolgin et al 1991) there is little proof that MDAC reduces morbidity and mortality in poisoned patients.

The gastric emptying rate may provide an important clue in this regard. If the rate is retarded in poisoning a single, large dose of activated charcoal may be sufficient to neutralise the residual toxin in the stomach. If, on the other hand, gastric emptying remains within normal limits or is enhanced, multiple doses could bind the toxin in the gastrointestinal lumen and break enterohepatic and enteroenteric cycles.

Although activated charcoal has been reported to cause vomiting, constipation and diarrhoea in some patients, it was initially thought to be relatively safe (Neuvonen and Olkkola 1988; Nau et al 1962, 1958a&b). However, reported complications now include pulmonary aspirations of charcoal and gastric contents, including fatal episodes (Benson et al 1989; Harsch 1986; Pollack et al 1981), and intestinal obstruction following multiple doses of activated charcoal (Ray et al 1988; Anderson and Ware 1987; Watson et al 1986).

While some argue that MDAC is the most effective form of treatment in poisoning others disagree. The reports of complications following MDAC and the lack of evidence as to its clinical efficacy continue to spawn many questions about its role in the management of poisoning (Vale and Proudfoot 1993; Palatnick and Tenenbein 1992; Tenenbein 1991).

Although the matter remains unresolved, the consensus of opinion appears to favour the use of single doses of activated charcoal, with multiple doses in specific situations, over that of the traditional methods of gastric emptying - gastric lavage and emesis in cases of poisoning. However, there are those who continue to advocate the use of both gastric lavage and activated charcoal in patients with life-threatening overdoses (Krenzelok and Dunmire 1992).

Activated charcoal is part of the routine management in patients who present with poisoning to the GSH Emergency Unit. More severe cases of poisoning receive a multiple dose regime of activated charcoal. Patients presenting with tricyclic poisoning undergo gastric lavage before having multiple doses of charcoal.

CHARCOAL-PURGATIVES AND SORBITOL COMBINATIONS

Charcoal-cathartic preparations are commonly used in the management of acute poisoning. A charcoal-sorbitol suspension is used in many institutions. The rationale for the use of charcoal-cathartic preparations is simple. Rapid transit of the poison through the small intestine should, theoretically, reduce desorption from the activated charcoal-poison complex and, therefore, absorption; as long as hyperperistalsis and increased fluid secretion do not enhance desorption.

Krenzelok et al (1985) found that the osmotic saccharide, sorbitol (70%), caused stooling in 0.9 hours in normal volunteers as compared with 4.2 hours for magnesium citrate and 9.3 hours for magnesium sulphate. The mean gastrointestinal transit time for charcoal alone was 23.5 hours. Gaudreault et al (1985) using simulated overdoses in animals reported a decrease in drug absorption and improved survival rates using charcoal and magnesium citrate. Keller and his co-workers (1990) demonstrated a 14.2% decrease in salicylate absorption after treating patients with a charcoal-sorbitol mixture. Furthermore, Goldberg et al (1987) and Berg et al (1987) have shown that the addition of sorbitol to the activated charcoal decreases serum concentrations of theophyllin and phenobarbitone respectively.

In a review on the role of cathartics and laxatives Shannon and his co-workers (1986) argue in favour of their continued use on the basis that they accelerate gastrointestinal transit thereby expediting expulsion of the reversible drug-charcoal complex. Potential advantages are increased contact between the drug and the activated charcoal due to increased intestinal motility and the prevention

of constipation associated with the use of activated charcoal (Shannon et al 1986).

In contrast, a number of studies have not demonstrated any real clinical benefit nor shown decreased drug absorption from the combined use of purgatives and charcoal (McNamara et al 1988; Neuvonen and Olkkola 1986; Galinsky and Levy 1984; Easom et al 1982; Sketris et al 1982; Mayersohn et al 1977). Although Berg et al (1987) have suggested that sorbitol-induced diarrhoea might have accelerated the onset of the effect of charcoal on the elimination of intravenously administered phenobarbitone, there was little overall benefit from sorbitol. In a study to determine the effect of charcoal and charcoal-sorbitol on the pharmacokinetics of phenytoin, Rowden et al (1990) found no difference between the 2 regimes. Sorbitol, however, resulted in more gastrointestinal adverse effects.

A single dose of 10g of sorbitol was reported to cause abdominal symptoms in 32% of 124 healthy adults (Jain et al 1987). Sorbitol given in large amounts in repeated doses of charcoal may cause serious gastrointestinal and systemic side effects. Morbidity and mortality have been associated with charcoal-cathartic use. Severe diarrhoea resulting in dehydration and electrolyte imbalances have been reported with the use of activated charcoal-sorbitol mixtures (Caldwell et al 1987; Farley 1986; Keller et al 1990; McCord and Ijun 1987; McNamara 1987). Two cases of intestinal pseudo-obstruction, one fatal, following the use of charcoal and sorbitol in patients with theophyllin poisoning have been reported (Longdon and Henderson 1992). Severe abdominal cramps and hypermagnesaemia have been reported with the magnesium cathartics and

an iatrogenic death has occurred with the use of sorbitol and magnesium sulphate during treatment for salicylism (Jones et al 1986; Brent et al 1989).

The lack of evidence for its clinical efficacy and the increasing number of adverse reactions being reported casts doubt on the use of charcoal-cathartic mixtures other than in selected cases. Activated charcoal without sorbitol is preferred as a first-line treatment for poisoning.

SUMMARY

In summary, therefore, the following points can be made:

1. Poisoning is a significant problem both internationally and locally and has serious clinical, social and economic implications.
2. Different methods have been used to measure gastric emptying, motility and intestinal transit times in healthy volunteers and patients suffering from various disorders. Scintigraphy is a reliable method for determining gastric emptying and gastrointestinal motility and transit times while imposing a low radiation burden on the patient.
3. A number of factors could influence gastric emptying and gastrointestinal motility in patients with poisoning. The tricyclic antidepressants are known to diminish gastrointestinal motility in *therapeutic* doses. Its effects on gastric emptying appear less certain. The opioids are reported to delay gastric emptying and small intestinal transit in *therapeutic* doses. There is little evidence to suggest that the anticonvulsants and paracetamol alter gastric emptying and gastrointestinal motility. To the best of my knowledge no study has been done measuring gastric emptying rates and motility and small intestinal transit times in patients with *poisoning*. What little information there is regarding the effects of overdose in poisoning is based on very small numbers of observations in animals and odd case reports in humans. There is little convincing evidence that drug overdose significantly alters gastric emptying and gastrointestinal motility.

4. The potential effects on gastric emptying of factors like gender, age, stress, and circadian rhythm have been documented in healthy subjects under controlled conditions but these have rarely been tested in the clinical setting.

5. Information is scant on whether the methods of gastric decontamination - emesis, gastric lavage and activated charcoal - alter gastrointestinal motility and gastric emptying.

6. Current therapeutic measures for poisoning are the matter of ongoing debate. The merits and demerits of emetics, gastric lavage and activated charcoal in poison management are the subject of a variety of opinions. A broad consensus favours the use of activated charcoal in most cases of poisoning. However, whether this is administered in one large dose or in multiple doses is also the subject of debate. As gastric decontamination forms an essential part of poison management altered gastric motility and emptying might have profound implications for treatment.

A study (Part 1) was, therefore, set up to evaluate gastric emptying and gastrointestinal motility in patients who had ingested overdoses of certain common poisons. Each patient was used as his/her own control in order to eliminate variables such as age, gender and other intra-individual differences. However, studying patients in the clinical setting does impose certain constraints which may be difficult to overcome. For example, patient management cannot be altered to suit the study conditions. The attending physician decides whether patients require gastric lavage, activated charcoal or both of these. Some patients may be given antidepressant or anticonvulsant treatment before the control study can be done.

The second part (Part 2) of the study was planned after the results of the first part were available to investigate the effect of sorbitol on gastric emptying and intestinal transit in poisoning. This osmotic laxative has been found to reduce gastrointestinal transit times but its effect on gastric emptying is unknown.

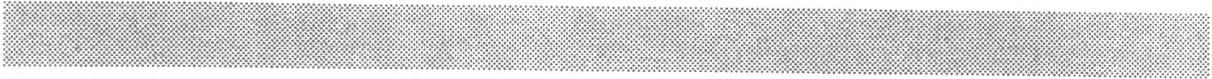
The paracetamol control study (Part 3) was planned after results on the effects of paracetamol poisoning on gastric emptying and gastrointestinal motility were available from Part 1.

On the basis of the review of the literature and the clinical experience of the physicians the following null hypotheses were formulated for the study:

1. Poisoning does not prolong gastric emptying.
2. Gastric emptying times do not vary according to the drug taken.
3. Gastric motility is not diminished by poisoning.
4. Small intestinal transit times are not prolonged by poisoning.
5. Sorbitol does not reduce gastric emptying times in poisoning.
6. Sorbitol does not diminish small intestinal transit times in poisoning.



PART ONE



PATIENTS AND METHODS

The study was approved by the Ethics and Research Committee of the University of Cape Town in May 1992.

I began imaging patients in August 1992 and by October 1993 a total of 108 patients had been studied. These patients received standard hospital management that included gastric lavage when indicated, oral activated charcoal in all, the antidote, N-acetylcysteine in paracetamol toxicity, and supportive medical treatment as required. The only three patients with phenobarbitone poisoning were excluded on the basis of their small number. And one patient with paracetamol poisoning was excluded as she was being treated with a powerful anticholinergic, clozapine, when the control study was done. The results of the excluded patients are tabulated in **appendix 1**. This left a total of 104 patients. Of these 86 patients returned for a follow-up study at least seven half-lives of the drug later when the drug levels were absent or negligible. One control study was unsuccessful because of technical problems leaving 85 for analysis.

SURVEY OF EMERGENCY UNIT ADMISSION RECORDS

A retrospective survey of the Emergency Unit admission records was undertaken to determine the most frequent causes of poisoning at the hospital. Six different weeks were selected at random from records of the following periods: November 1990, February 1991 and January 1992. All poisons that could be identified on patient admission were counted and divided into groups. This survey, along with discussions with the clinicians, determined the groups of drugs that patients had to take to be selected for the study.

COMPUTER PROGRAMMES

3.1 Statgraphics Version 5

The statistical analysis was done using this computer package.

PATIENT SELECTION

DIFFERENT DRUG GROUPS

Patients who had taken overdoses of the following four groups of poisons were selected for the study :

1. Tricyclic antidepressants;
2. Anticonvulsants;
3. Paracetamol;
4. Opioid-paracetamol mixtures. these are referred to as the opioid group.

Patients who had ingested combinations of these or additional drugs were also selected. The tricyclic antidepressants, anticonvulsants, paracetamol and opioid groups were chosen because they are amongst the most frequent causes of poisoning at Groote Schuur Hospital.

No formal randomisation process was considered necessary and the nursing sister or clinician on duty informed us of every patient that presented with a history of having ingested excessive amounts of the drugs in question. However, the system suffered temporary breakdowns during periods of staff changes, due to very occasional lapses on the part of the staff during very busy periods, and when the chief investigator was away on vacation.

DETERMINING THE TYPE OF DRUG INGESTED

The following steps were taken to determine the type of drug ingested:

1. a careful history was taken from the patient and/or the person who accompanied the patient to hospital;
2. inspection of packet or container labels which were brought along by most patients or their attendants;
3. plasma drug levels were performed on all patients;
4. urinary opiate levels were done on the majority of patients.

EXCLUSIONS

Patients were excluded from this study for the following reasons:

1. Pregnancy
2. Those who refused informed consent. These represented a small minority of patients (3% of the total number of patients approached).
3. Those who had been given sorbitol were excluded from the first part of the study. This occurred only in 5 patients who were given the laxative at a day hospital or clinic.

PATIENT MANAGEMENT AND REFERRAL

When the patients arrived at the Emergency Unit (EU) they received standard clinical management which included the following measures.

1. A history was taken which included attempts to determine the type and quantity of poison taken and the time of ingestion.
2. Gastric lavage was performed in all cases in whom the clinician deemed it necessary. In general the protocol followed meant that patients who had ingested tricyclic antidepressants and carbamazepine within 6 hours of presentation to the Emergency Unit and those who had ingested other poisons and presented within 2 hours, had gastric lavages.
3. The administration of activated charcoal in 200 - 300ml of water. No sorbitol was added. (The activated charcoal was manufactured by Lurgi [Frankfurt] and has a total surface area of $1400 \pm 100 \text{ m}^2/\text{g}$, and a particle size of $<40 \mu\text{m}$).
4. The antidote, N-acetylcysteine was given for paracetamol toxicity. It was the only antidote used in my patients.
5. Drug levels were measured in blood and urine.
6. The investigator was informed of the patient by the nursing sister or attending doctor.

7. Patients who were severely ill were transferred to the intensive care unit (ICU) after the initial management was carried out in the emergency unit. Scintigraphy was performed in the ICU with a mobile camera.

8. All other patients were transferred to the nuclear medicine department (NMD) where the scintigraphy was commenced in the shortest possible time. Patients admitted to the ICU were imaged there with a mobile camera.

9. Informed consent was obtained for the study from every patient or from a close relative where this was not possible because of confusion or coma. Informed consent was obtained from every patient for the control study.

PERFORMANCE OF THE GASTROINTESTINAL SCINTIGRAPHY

PREPARATION OF THE LIQUID TRACER

The liquid tracer consisted of 18-22 MBq of $^{99m}\text{Tc-Sn}$ colloid mixed in 10ml of water. The radiopharmaceutical was freshly prepared for each study. The tin colloid vial consisting of a sterile lyophilised powder containing 1.0mg of sodium fluoride and 0.13mg of stannous fluoride was obtained from the Atomic Energy Corporation of South Africa and stored in a refrigerator.

After allowing the contents of the vial to reach room temperature, the latter was reconstituted with sodium pertechnetate- ^{99m}Tc generator eluate using aseptic technique. The vial was inverted gently several times to dissolve the lyophilised powder and then allowed to stand at room temperature for at least 20 minutes. The vial was carefully inspected to ensure that it was free from particulate matter. A dose of 18-22 MBq of $^{99m}\text{Tc-Sn}$ colloid was drawn up to which 10 millilitres of water were added. The radiopharmaceutical was ready for administration to the patient.

ACTIVATED CHARCOAL

Patients were given to drink a slurry consisting of 25 or 50g of activated charcoal (AC) and 200 to 300ml of water respectively.

Each patient was given the liquid tracer containing approximately 20 MBq of $^{99m}\text{Tc-Sn}$ colloid in water which was "washed down" by 10ml of water. This was administered orally to conscious patients in the sitting position, and through a nasogastric tube in the obtunded.

The study was performed with the patient lying supine.

Small point markers were placed on the patient's skin over the xiphisternum and on the superior border of the umbilicus.

The detector was placed anterior to the abdomen for the marker and initial image and then a posterior image of the abdomen was taken immediately afterwards.

The exact time that the patient drank the radiopharmaceutical was recorded, and data collection was started 1 minute afterwards and continued for up to 5 hours. The exact time period depended on the patient's clinical condition. A minority of studies were stopped early because deterioration in the patients' condition required urgent clinical intervention.

No additional fluids or meals were taken until the study was complete. Smoking was not permitted.

DATA ACQUISITION

Large-field-of-view (lfov) Elscint Apex 415 and 410 scintillation gamma cameras equipped with a low energy general purpose (medium resolution, medium sensitivity) parallel hole collimators interfaced to a computer were used for data collection in patients in the nuclear medicine department. Patients in the ICU were imaged on a General Electric 300a mobile camera fitted with a low energy general purpose parallel hole collimator. A parallel hole collimator was chosen because it showed significantly less variation in response from the centre to the periphery than the diverging collimator although this meant having to do two images instead of one on a number of patients. The tests performed on these collimators are described in **appendix 2**. These patients were too ill to make the journey to the nuclear medicine department and had to be scanned on the only mobile gamma camera available. Thus two different camera systems were used.

Static 60 second images were taken at: 1, 15, 30, 45 and 60 minutes in the first hour. Subsequent images were taken at 30 minute intervals for 60 seconds each for the next four hours.

Prior to each anterior image a marker picture was obtained for 10 seconds. The markers were then removed and the anterior image was acquired with the patient in the same position. This was followed by a posterior image of the abdomen with the same acquisition time (60 seconds) as the anterior image. In the ICU marker and anterior images were taken. No posterior images were done as the detector could not fit under the ICU bed and it proved nigh on impossible to turn patients who were connected to respirators, monitors and intravenous lines.

The smaller fov of the mobile camera necessitated an upper and a lower image of the abdomen so that all the activity could be included. Marker pictures were followed by 60 second images which overlapped slightly at their lower and upper borders respectively. This allowed for accurate calculation of the total number of counts in the abdomen.

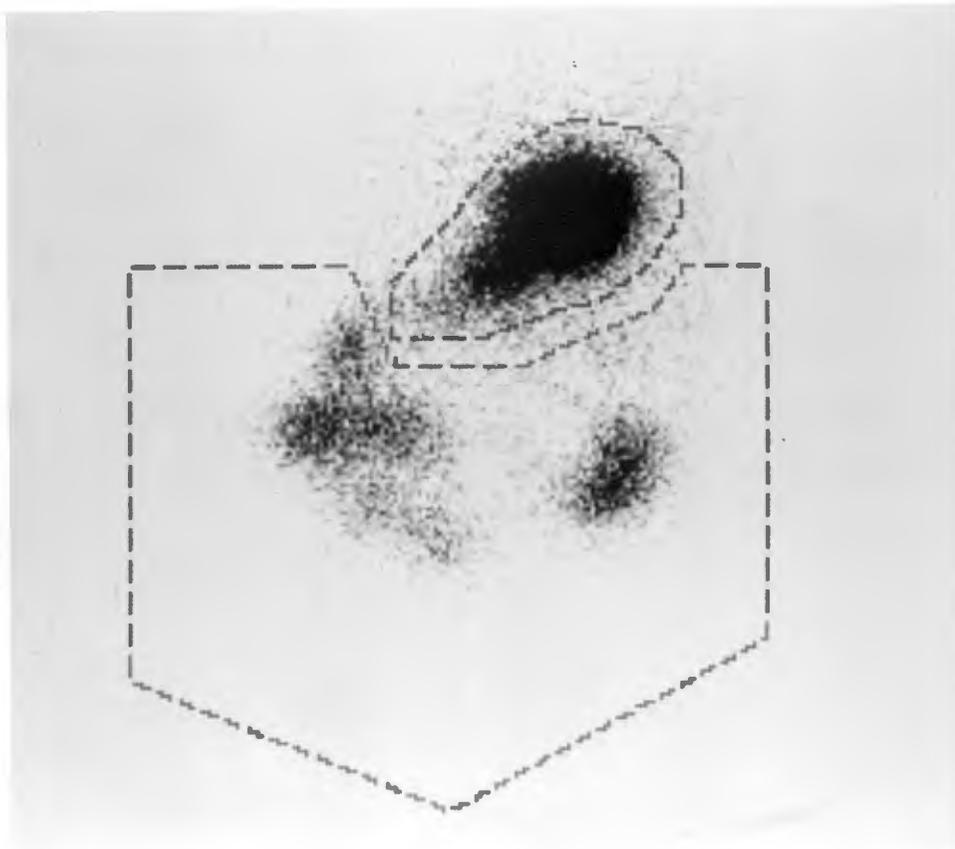
Two - 10 minute dynamic studies were performed, the first between the 15 and 30 minute and the second between the 45 and 60 minute images. A period of 5 minutes was allowed for patient positioning and for setting the camera to dynamic mode. Dynamic acquisition occurred at 5 seconds per frame and was done with the detector in the anterior position.

DATA ANALYSIS

REGION OF INTEREST (ROI) SELECTION

Using the computer display and the static images, an ROI was drawn to include the whole stomach, but excluding the intestines. A second ROI was drawn to include the intestines (see **Figure 1**). The stomach ROI was altered to accommodate the distribution of radioactivity in that organ. Counts were measured in both ROIs and the total number of counts was calculated by adding together counts from the 2 ROIs. ROIs were drawn on both the anterior and posterior images.

Figure 1. Regions of interest (ROIs) drawn to include the stomach and the intestine so as to calculate gastric counts as a proportion of total counts.



TIME-ACTIVITY CURVES

Gastric emptying rates were calculated from two data sets:

1. Geometric Means of anterior and posterior counts
2. Anterior Counts only

8.2.1 Geometric Means

This was calculated by using the formula:

$$\frac{(\text{ant counts stom} \times \text{post counts stom})^{1/2}}{(\text{ant counts tot} \times \text{post counts tot})^{1/2}} \times 100$$

8.2.2 Anterior Counts:

This was calculated by the formula:

$$\frac{\text{Ant counts stom}}{\text{Ant counts tot}} \times 100$$

A histogram/time-activity curve was generated for each study expressed as the proportion of activity retained in the stomach (i.e. as a percentage of the total activity as derived from the above formulae) versus time. The main parameter derived from these curves was the time it took for 50% of the activity to empty from the stomach - $T^{1/2}$.

EXTRAPOLATIONS

Certain patients failed to empty half of the gastric activity by the end of the imaging time. Therefore, in 14 studies simple extrapolation had to be used to determine gastric emptying half-times.

Statistical comparisons were made between the gastric emptying half-times calculated for the studies following overdose ingestion and those at control.

INTEGRATION - AREA UNDER THE CURVE

The areas under the time-activity curves were determined for each study using a special programme written by Dr S. Isaacs of the Medical Informatics Department at Groote Schuur Hospital. Statistical comparisons were made between the areas derived for the studies following overdose and those at control.

CONTROL STUDIES

A repeat study was performed on the majority of patients (81.73%). Certain patients failed to return despite a number of reminders. The control study was conducted at least seven half-lives of the drug later when there was no measurable trace of the drug left in the blood or when the levels were negligible. But certain patients had to resume treatment on antidepressant or anticonvulsant medication before the control studies were done. In these patients blood taken at the time of the control studies contained therapeutic levels of the drug. The control studies were done in the following way:

Patients were given a date on which to return to the Nuclear Medicine Department and were told to fast for a 4 hour period before the study was scheduled to start. The starting time varied from study to study but was usually between 10h30 and 12h00. No meals or smoking were permitted during the study period which lasted for 5 hours.

Patients received 25 or 50g of activated charcoal in 200 to 300ml of water - the same dose to the one they had for the first study - 45 to 60 minutes before taking the radiopharmaceutical. This was the approximate time between the administration of activated charcoal in the first study and commencement of imaging.

Blood and urine samples were taken for measuring drug levels.

Approximately 20 MBq of $^{99m}\text{Tc-Sn}$ colloid in 10ml of water was taken orally followed by a further 10ml of water.

The time of administration was carefully noted.

Data was acquired and processed in precisely the same way as for the initial study.

Gastrointestinal scintigraphy was performed by a LFOV Elscint Apex 400 or 415 gamma camera fitted with a low energy general purpose collimator.

None of the studies were done on the mobile camera as all the patients were imaged in the department during the daytime when the mobile camera was in clinical use.

ANALYSIS OF THE DYNAMIC STUDIES: GASTRIC MOTILITY EVALUATION

RATIONALE

A visual evaluation was made of two - 10 minute dynamic studies performed in the first hour of imaging. The dynamic studies were started at 15 and 45 minutes following ingestion of the radiopharmaceutical. Based on the literature review of gastric emptying half-times of liquids I expected sufficient radioactivity to be present at least on the first set of dynamic images for adequate visual assessment.

This relatively simple method of assessing gastric motility was chosen for the following reasons:

Firstly, the method had to be sufficiently robust to be carried out on seriously ill patients by a mobile camera in the intensive care unit.

Secondly, the nuclear medicine department at Groote Schuur Hospital is not equipped to carry out many of the sophisticated antral motility tests described in the section: "Measuring gastrointestinal motility - Radionuclide scintigraphy" in the section on "Normal Gastric Emptying and Motility". Moreover, an initial examination of images of patients at presentation with gastric emptying delay showed a marked absence of activity in the antral region making an evaluation of motility in this area virtually impossible. This pattern of distribution is discussed in greater detail in the section on "Distribution of the radiolabeled meal in the stomach".

The reliability of the method was tested using intra- and inter-observer studies.

METHOD

Two dynamic studies at 5 seconds per frame for 10 minutes each were performed on each patient within the first hour of imaging: during the 15 to 30 minute and 45 to 60 minute periods. These studies were analysed as follows:

1. The images were displayed on the terminal and 2 temporal smoothing functions were performed.

2. The dynamic study was then played in cine mode at 3 different speeds: a very slow rate to view each image individually; a slow rate of 1 second per frame; and a fast rate of 0.2 seconds per frame.

3. The contractility of the stomach was carefully observed. Contractions were scored on the following basis:

0 = no contractions seen

1 = weak contraction

2 = weak to moderate contraction

3 = moderate strength contraction

4 = strong contraction

5 = very strong contraction with marked distortion of the gastric wall.

The scores for each contraction were added and these, in turn, were added to the scores obtained from the second dynamic study thus deriving a total contraction score.

4. These observations were recorded on a diagram of the gastrointestinal tract (see **appendix 3**) and then transferred to a computer spread sheet. A statistical

comparison was made between the gastrointestinal motility during the initial study and that of the control study.

RELIABILITY OF THE GASTRIC MOTILITY SCORING METHOD

The scoring method set out above was tested for reliability in the following way:

Thirty dynamic studies were chosen randomly. These consisted of 14 studies done following drug overdose and 16 control studies. The studies were taken from all the different drug groups.

The author reviewed the thirty studies in the manner described above and recorded the scores for each study. This was performed "blind" as the investigator was unaware of patient names, gastric emptying data and any previous scores. The author examined the same set of studies in a different order 6 weeks later. This intra-observer study was carried out prior to the author evaluating the rest of the dynamic studies in the overdose and control groups. The dynamic studies were reviewed after the rest of the data analysis.

Subsequent to the study being completed three other observers: a senior consultant, a registrar and a chief technologist were asked to score the same 30 studies independently. As none of them was familiar with gastric motility studies the author gave a short explanation of how to score the dynamic studies. This "tutorial" lasted approximately fifteen minutes. An additional "hands-on" demonstration lasting approximately one hour was given to the technologist. Each observer read the studies without any of them having any prior knowledge of the scores obtained by the author.

The results were compared statistically to test for:

1. intra-observer reliability in the case of the author;
2. inter-observer reliability between all of the observers including the author.

DISTRIBUTION OF THE RADIOLABELED MEAL IN THE STOMACH

The static images of each study were viewed and the dominant patterns of distribution of the activity were noted. Three patterns emerged. The distribution of the activity in the stomach was either predominantly in the proximal half, the proximal two-thirds (fundus and corpus) or evenly distributed throughout the stomach. The distribution was classified on the basis of whether the bulk of activity resided in one or other of these compartments. The length of time for which the dominant pattern was maintained was recorded. Transient changes in pattern were not considered.

The distribution patterns were analysed in terms of:

1. the times for which the pattern was maintained;
2. gastric emptying half-times in order to determine whether a relationship existed;
3. a comparison between overdose and control studies.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT TIMES

A visual analysis was made of the passage of radioactivity through the gastrointestinal tract. The sequential images taken during the study were carefully observed so as to identify and follow the leading edge of radioactivity.

METHOD

1. Two times of entry were identified -

- 1.1 the mouth - the time at which the radiopharmaceutical was ingested;
- 1.2 the duodenum - the time at which the leading edge of the radioactivity left the stomach and entered the proximal duodenum.

2. The time of exit from the small intestine was identified as the time it took for the leading edge of radioactivity to reach the terminal ileum. If the radioactivity had not traversed the entire small bowel, the approximate region that it reached on termination of the study was recorded.

3. Oro-caecal and small intestinal transit times were determined by subtracting the oral and duodenal times from the time it took the radioactivity to reach the terminal ileum.

4. The terminal ileum was chosen as the point of exit from the small intestine because the radioactivity failed to reach the large intestine in many of the patients at presentation. Prolonged hold-up of activity in the ileum proximal to the ileo-caecal valve presented a problem in many patients.

5. The terminal ileum was identified by the following:

- 5.1 its pelvic situation - in the region of the right iliac fossa;

5.2 the progression of radioactivity stopped and accumulated for varying periods in this area before passing into the large bowel. This region was identified and then the previous images were again carefully studied to ascertain when the leading edge of radioactivity had arrived there.

6. When the radioactivity failed to reach the terminal ileum the time at which the study was terminated was regarded as the exit time.

7. Comparisons were made between the transit times following overdosage and those at control.

RESULTS

RESULTS OF SURVEY OF THE EMERGENCY UNIT RECORDS

A six week survey of Emergency Unit records was undertaken to find out which were the most frequent causes of poisoning. A total of 67 patients had causative agents recorded in the registers. Table 3 shows the frequency of the different drug groups implicated in poisoning.

TABLE : 3

FREQUENCY OF DRUG GROUPS IMPLICATED IN POISONING.

	Drug Groups	Frequency (%)
Tricyclics	12	18
Anticonvulsants	6	9
Paracetamol	10	15
Opioids	9	13.4
Other	30	44.8
TOTAL	37	55.2

RELIABILITY OF MOTILITY SCORING SYSTEM

INTRA-OBSERVER RELIABILITY

The test-retest reliability coefficient for the set of studies scored twice by the author was $R = 0.88$. The test-retest reliability coefficient for the for the number of contractions was 0.91. This shows good intra-observer reliability. Table 4 shows the different mean scores and the average number of contractions noted per study by the different observers.

TABLE: 4

INTER-OBSERVER RELIABILITY

	Average scores	Average no. of contractions/study
the author (two x 30 studies)	4.5	1.65 (+/-1.42)
consultant	8.5	2.7 (+/-1.91)
registrar	6.1	3.8 (+/- 1.45)
technologist	3.3	1.3 (+/- 1.20)

There were significant differences between the author and the consultant ($p = 0.03$; Two-sample analysis) but not between the author and the technologist ($p = 0.21$; Two-sample analysis). Regression analysis for number of contractions showed a correlation coefficients of 0.57 for the author and the consultant and 0.68 for the author and the technologist. **Figure 2** demonstrates the slope between the overdose and control scores to be very similar for both the author and the consultant. The slope of the technologist's was similar to these two. All showed the

expected steep incline from the overdose to the control scores. The higher scores obtained by the consultant was due to a higher number of contractions scored and a slightly higher average score per contraction (3.1) than the investigator (2.7) and the technologist (2.54). The registrar scored many more contractions with the lowest average score per contraction of 1.6.

Figure 2. Demonstrates scores obtained after overdose than at follow-up for the author (1), the registrar (2), the technologist (3) and the consultant (4).

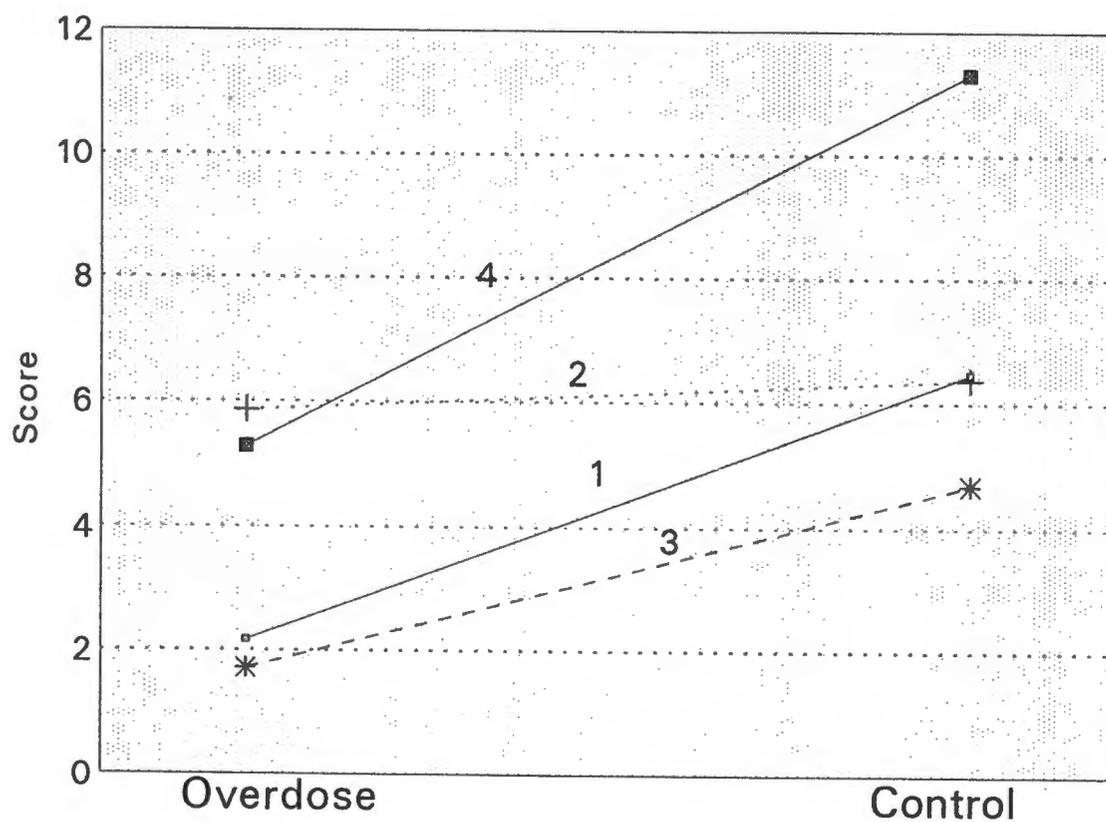


Table 5 demonstrates lower scores for studies after overdose when compared with follow-up studies for all observers.

TABLE : 5

OVERDOSE VERSUS CONTROLS: MEAN SCORES

	Mean score Overdose	Mean score Control
Author	2.17	6.46
Consultant	5.28	11.31
Registrar	5.86	6.37
Technologist	1.71	4.69

There were significant differences between the overdose studies ($n = 14$) and the controls ($n=16$) ($P < 0.00001$). All the observers scored the control studies higher than those at overdose. The consultant recorded the biggest differences between the overdose and controls and the highest scores for latter. The registrar recorded the smallest differences between these two groups. The author found significant mean differences between the two groups but somewhat less than those recorded by the consultant.

OVERALL DESCRIPTION OF THE SAMPLE

The analysis will give:

1. a general description
2. detail regarding the differences between studies after overdose and those at control for each drug.
3. an overall view of gross differences between studies after overdose and those at control.

Table 6 shows the number of patients by drug group and gender.

TABLE : 6

PATIENT NUMBERS BY DRUG GROUP AND GENDER

DRUG	TOTAL PAT.NO.	MALE	FEMALE	CONTROLS
TCA	31	5	26	26 (83.9%)
CBZ	15	5	10	11 (73.3%)
PHE	12	6	6	7 (58.3%)
PAR	29	7	22	26 (89.7%)
OPI	17	4	13	15 (88.2%)
TOTALS	104	27	77	85 (81.7%)

TCA = Tricyclic antidepressants

CBZ = Carbamazepine

PHE = Phenytoin

PAR = Paracetamol

OPI = Opioid

Therefore, 19 patients did not have control studies. All, with one exception (an opioid control study which was unsuccessful for technical reasons) failed to return.

EXCLUSIONS

A total of 108 patients were scanned. The following exclusions were made:

Three patients with phenobarbitone overdose were excluded from the analysis for the following reasons:

they were the only patients who had taken phenobarbitone making the sample size very small;

the coefficient of variation of the mean gastric emptying half-times was excessively high (139.3%) according to established criteria (Davies and Goldsmith 1972).

One patient was excluded from the paracetamol group because she was given clozapine, a powerful anticholinergic, prior to having the control study done.

AGE AND GENDER

A total of 104 patients were investigated of whom 77 were female and 27 male. The mean age for the entire group was 29.3 +/- 10.9 years. The mean age for females = 28.9 +/- 11.5 compared with males = 30.7 +/- 9.4 years. Age ranges were:

females 14 - 66, males 14 - 51 years. There was no significant difference between females and males regarding age: the two-sample test produced a p value = 0.45.

The vast majority of patients are under 40 years of age with the the biggest single category being the 20 - 30 year group. Young females predominate. Teenage girls form a far larger group than their male counterparts. There are almost twice as many women in the 20 - 30 year group than men despite the fact that this forms the largest male category.

AGE AND GENDER BY DRUG GROUP

TRICYCLIC ANTIDEPRESSANTS

There were 26 females and 5 males in this group. The mean age was 35.7 +/- 11.9 years. The mean age for females was 36.3 +/- 12.5 and males 32.8 +/- 7.9 years. Patients who ingested tricyclic antidepressants were significantly older than patients in the entire group ($p = 0.0006$; two-sample analysis).

There was no significant gender difference between the group of patients that ingested tricyclic antidepressants and the whole group of the patients ($p = 0.26$ two-sample analysis).

CARBAMAZEPINE

There were 10 females and 5 males in this group. The mean age for the group was 27.7 +/- 10.9 years. The mean age for females was 22.3 +/- 6.7 and males 38.4 +/- 10 years. There was no significant age difference between patients who ingested carbamazepine and all the patients ($p = 0.58$; two-sample analysis).

There was no significant gender difference between this group of patients and the entire group ($p = 0.55$; two-sample analysis).

PHENYTOIN

There were 6 females and 6 males in this group. The mean age was 31.8 ± 8.3 years. The average age of the females 32.3 ± 10.2 and males 31.2 ± 6.9 years. There no significant age difference between this group and the entire group of patients ($p = 0.46$; two-sample analysis).

There was no significant gender difference between this group and the entire patient population ($p = 0.08$; two-sample test).

PARACETAMOL

There were 22 females and 7 males in this group. The mean age was 24.2 ± 8.0 years. The average age for the females was 24.7 ± 8.8 and males 22.7 ± 5.3 years. The age of this group was significantly lower than the whole group of patients ($p = 0.02$; two-sample analysis).

No significant gender difference was found between the group that ingested paracetamol and the entire group of patients ($p = 0.84$; two-sample analysis).

OPIOIDS

There were 13 females and 4 males in this group. The mean age was 26.2 ± 10 years. The mean age of the females was 24.5 ± 9 and males 31.8 ± 12.3 years. There was no significant age difference between this group and all of the patients ($p = 0.27$; two-sample analysis).

There was no significant gender difference between the patients in this group and the entire group ($p = 0.83$; two-sample test).

CONTROLS

Out of a total of 104 patients investigated in the first part of the study 18 patients failed to return for their control studies. One control study was technically unsatisfactory. The average age for the males ($n = 8$) who failed to return for their control studies was 29.5 ± 14.9 years, and for the females ($n = 10$), 27.7 ± 12.1 years. The mean ages do not differ significantly from that of the entire group of patients. However, there is a proportionately larger number of males who did not return for control studies.

DRUG INGESTION TO SCANNING TIME

The mean time between drug ingestion and the commencement of gastric scintigraphy was 14.7 +/- 10.06 hours (range = 2 to 51 hours).

DURATION OF GASTRIC SCINTIGRAPHY

Patients were scanned for the times indicated in Table 7. Sixty-seven patients were imaged for the full 5 hours or longer while a total of 91 out of the 104 patients had scanning times of longer than 4 hours.

TABLE: 7

DURATION OF SCAN

Number	Scan Duration (minutes)
67	300
24	240 - 299
3	210 - 239
10	< 210

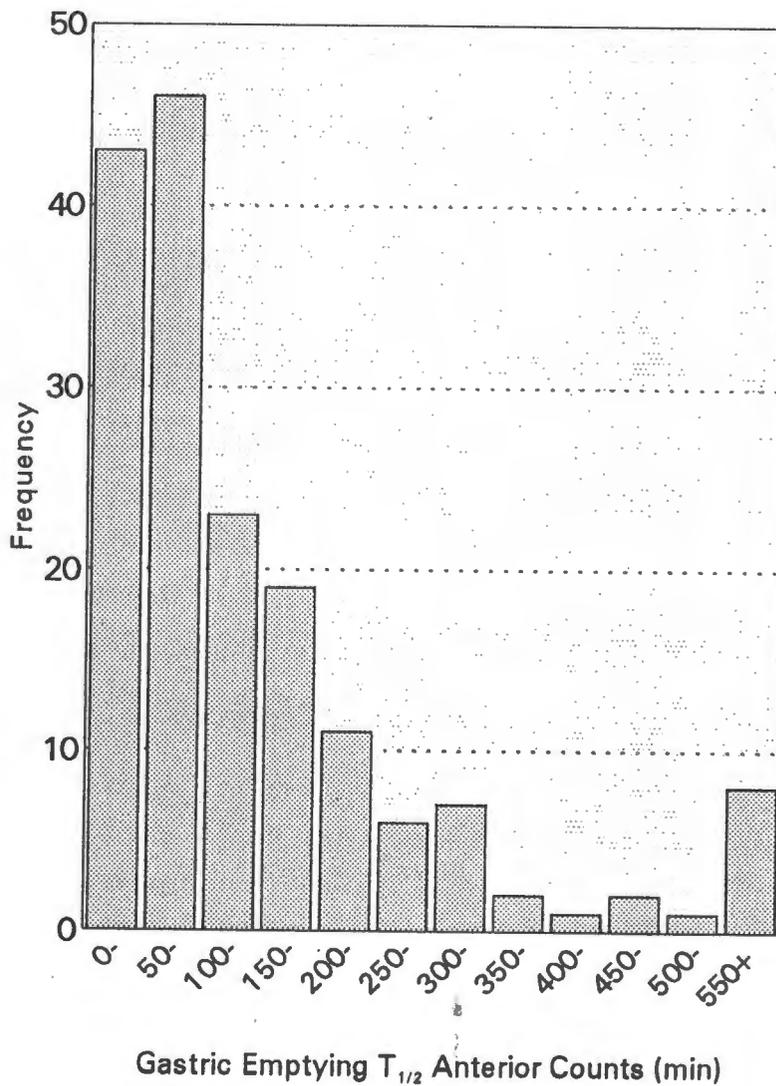
Range: 1.5 to 6 hours.

FREQUENCY DISTRIBUTIONS OF GASTRIC EMPTYING HALF-TIMES ($T_{1/2}$)

GASTRIC EMPTYING $T_{1/2}$ ANTERIOR AT OVERDOSE

Figure 3 presents the frequency distribution of gastric emptying half-times using anterior data. The distribution appears positively skewed.

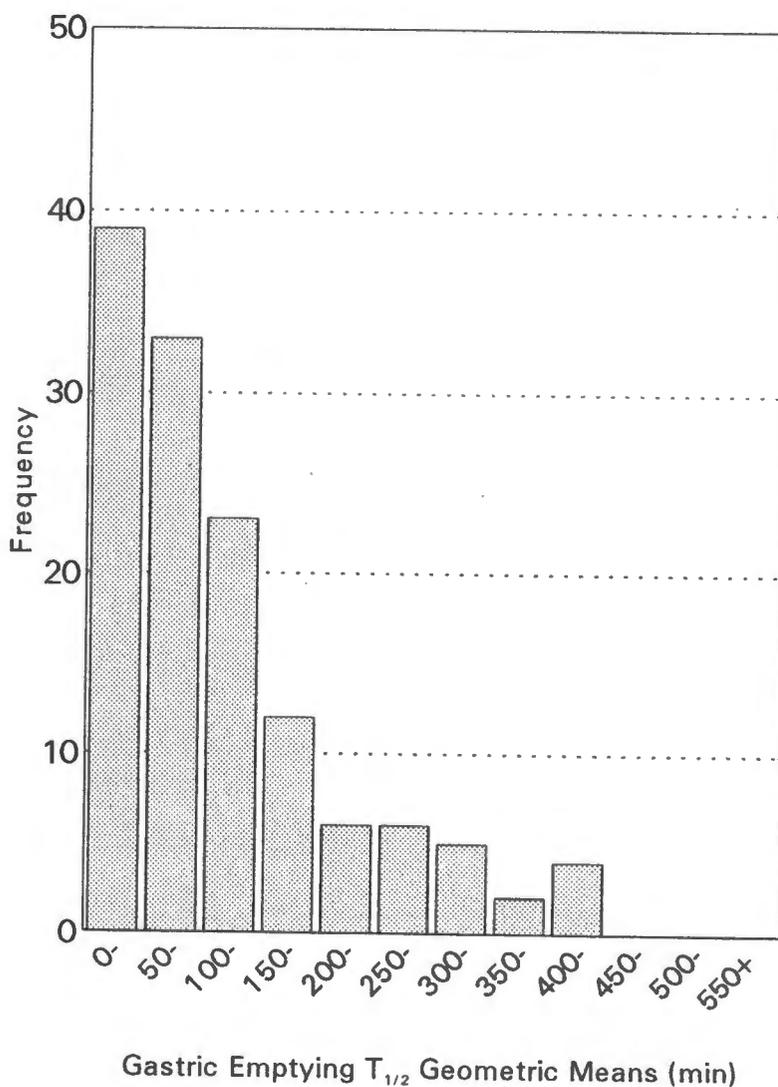
Figure 3. Histogram demonstrating the frequency distribution of gastric emptying half-times calculated from anterior counts after overdose.



GASTRIC EMPTYING $T_{1/2}$ GEOMETRIC MEAN

Figure 4 presents the frequency distribution of geometric mean corrected gastric emptying half-lives. The distribution curve is skewed to the right.

Figure 4. Histogram showing the frequency distribution of gastric emptying half-times calculated from geometric means after overdose.

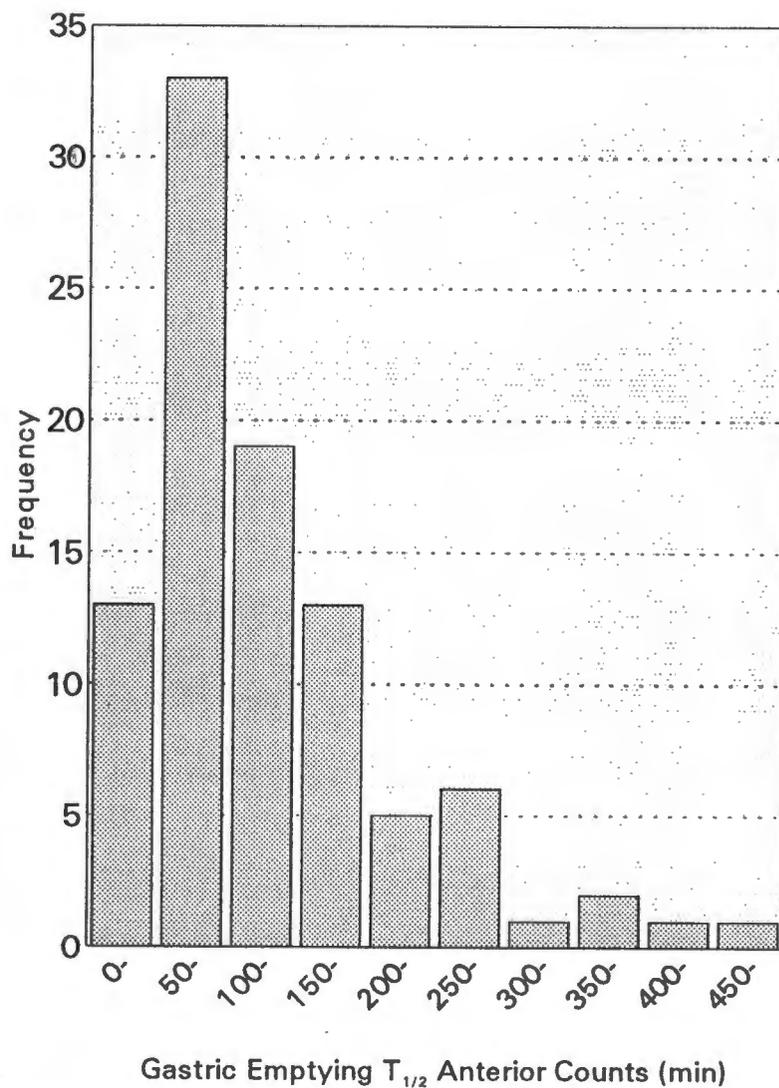


AT CONTROL

GASTRIC EMPTYING $T_{1/2}$ ANTERIOR

Figure 5 presents the frequency distribution of gastric emptying half-times derived from the anterior data of the control studies. The curve appears positively skewed.

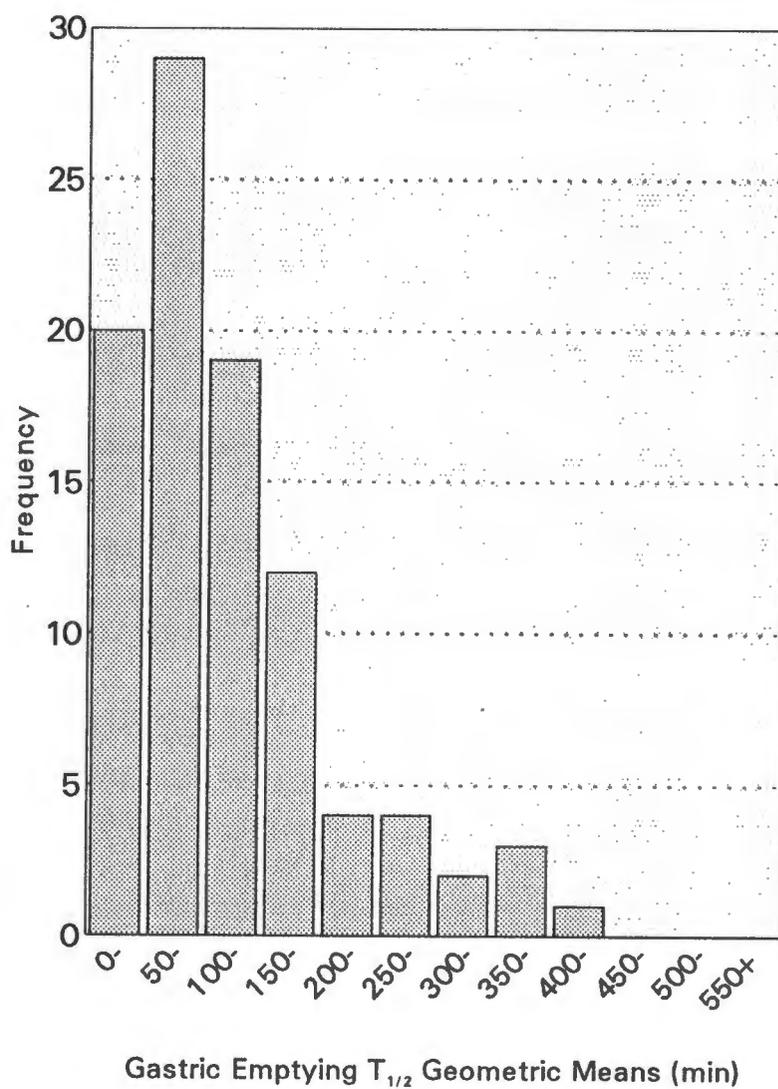
Figure 5. Histogram presenting the frequency distribution of gastric emptying half-times calculated from anterior counts at follow-up.



GASTRIC EMPTYING $T_{1/2}$ GEOMETRIC MEAN

Figure 6 presents the frequency distribution of the geometric mean corrected gastric emptying half-times of the control studies. The distribution also appears skewed to the right.

Figure 6. Histogram presenting the distribution of gastric emptying half-times calculated from geometric means at control.



GASTRIC EMPTYING HALF-TIMES

GEOMETRIC MEANS AND ANTERIOR COUNTS

Patients who were admitted to the intensive care unit were imaged on a mobile camera. Posterior images were not done for the following reasons:

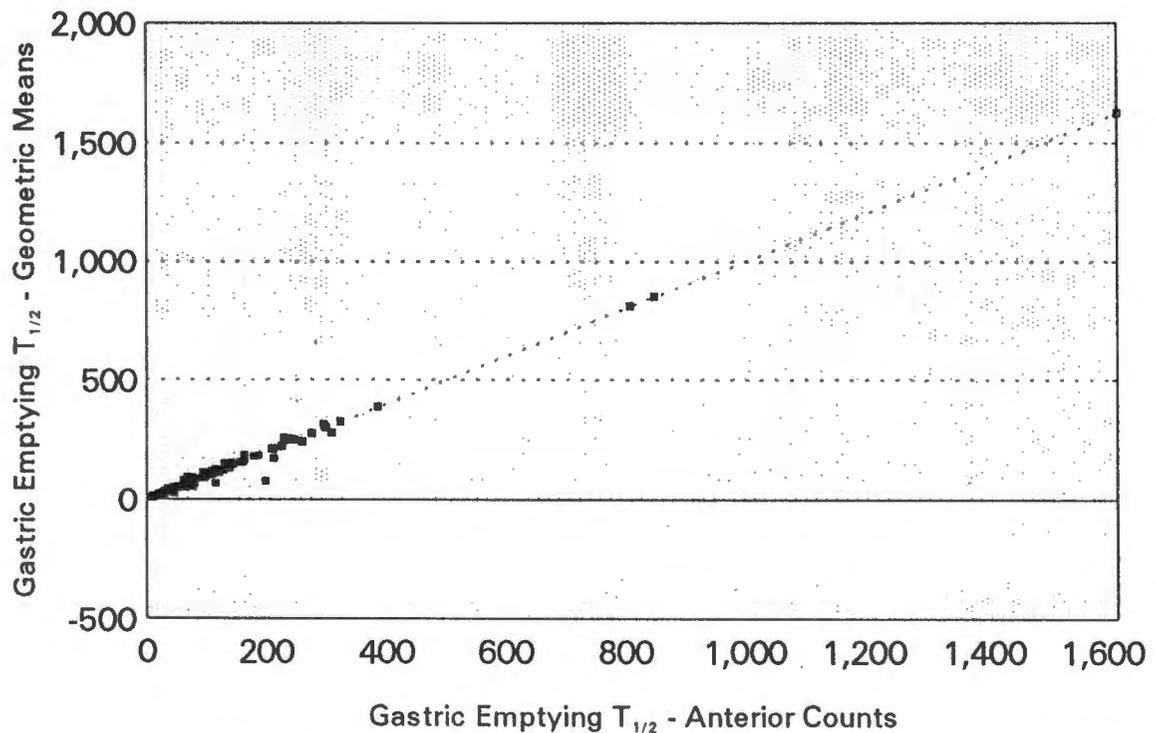
The camera head could not fit under the intensive care unit bed.

As these patients were on monitors and respirators they could not be turned.

Therefore, gastric emptying half-times were obtained using only the counts from the anterior images. The rest of the patients and all the controls had gastric emptying times measured using both geometric means and anterior counts.

It was, therefore, considered necessary to establish whether a relation existed between gastric emptying half-times derived from geometric means and those derived from the anterior counts. A very good correlation was obtained between these 2 measures. Simple regression analysis using gastric emptying half-times derived from geometric means versus half-times from anterior counts alone at overdose found a reliable slope of 0.993 ($p < 0.00001$), with a somewhat uncertain intercept 4.02 ($p = 0.099$) (**Figure 7**). The correlation value $r = 0.997$.

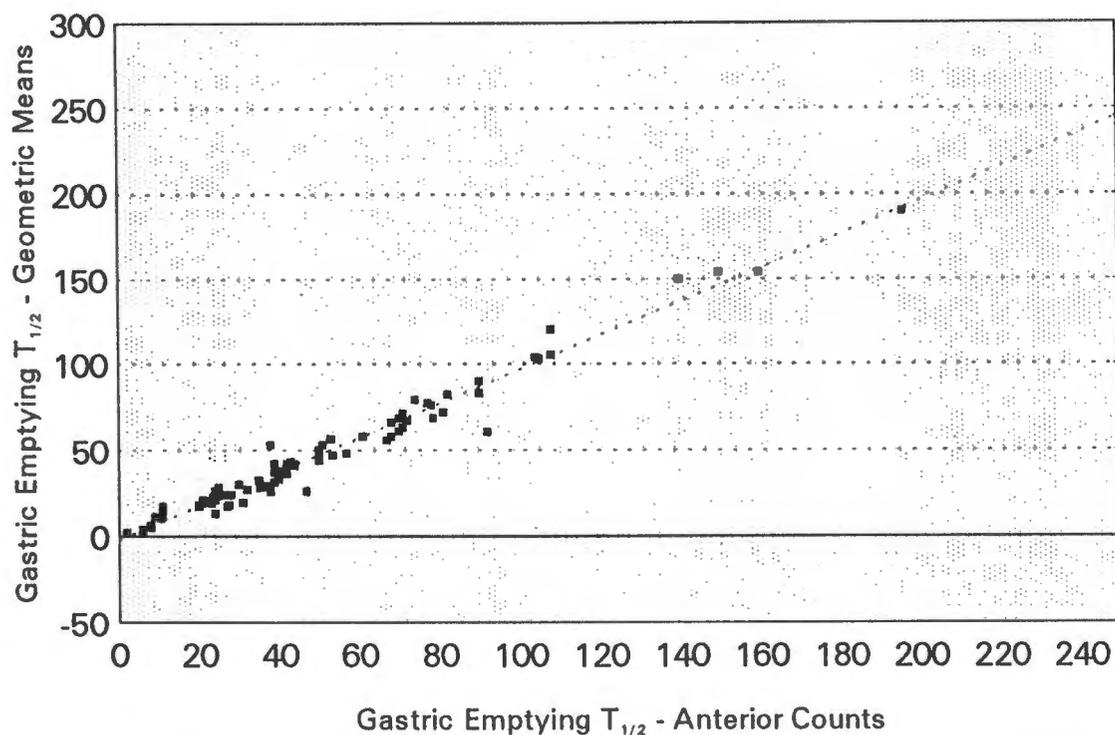
Figure 7. Scatter diagram illustrating the correlation between gastric emptying half-times (minutes) calculated from geometric means and half-times calculated from anterior counts alone after overdose.



When the half-times derived from geometric means were regressed on those from anterior counts in the control group both the slope 0.980 ($p = 0.0006$) and the intercept 3.86 ($p < 0.0001$) were found to be reliable (**Figure 8**).

Correlation value $r = 0.986$.

Figure 8. Scatter diagram showing the correlation between gastric emptying half-times (minutes) at follow-up calculated from geometric means and those calculated from anterior counts at control.



As there was an almost perfect linear correlation between the gastric emptying half-times derived from geometric means and those from anterior counts, all further analyses were done using the gastric emptying half-times determined from anterior data alone.

COMPARING GASTRIC EMPTYING HALF-TIMES AFTER OVERDOSE AND AT CONTROL

The Mann-Whitney U and Kruskal-Wallis tests were used to compare gastric emptying half-times after overdose and at control for each of the drug groups and the entire sample.

A number of variables - including age, gender, and drug level were subjected to statistical analyses to determine their relationship to gastric emptying half-times. Multiple regression analyses were used.

TRICYCLIC ANTIDEPRESSANTS

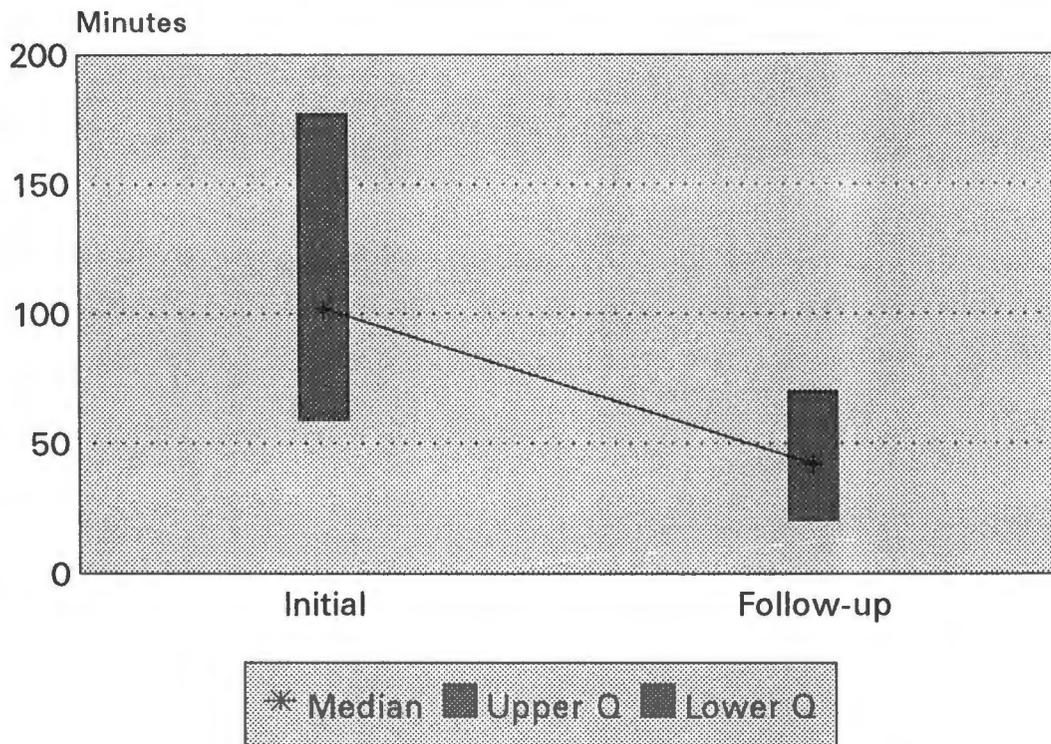
The gastric emptying half-times in minutes were:

AFTER OVERDOSE:	103 (median),	62.5 - 188 (IQR)
AT CONTROL:	46 (median),	21 - 71 (IQR)

IQR = interquartile range

Comparison of the gastric emptying half-times after overdose and at control shows highly significant differences ($p < 0.0002$; Mann-Whitney U test). (See **Figure 9**).

Figure 9. A comparison of gastric emptying half-times following tricyclic antidepressant overdose and those at follow-up in the same patients.



Fifteen of the 31 patients had gastric emptying half-times greater than 120 minutes. Of these 6 gastric emptying half-times were longer than 300 minutes and 1 longer than 240 minutes. Four patients had differences in gastric emptying half-times of more than 230 minutes when comparing the studies after overdose with the follow-up, and differences were greater than 100 minutes in 6 patients and more than 60 minutes in a further 6.

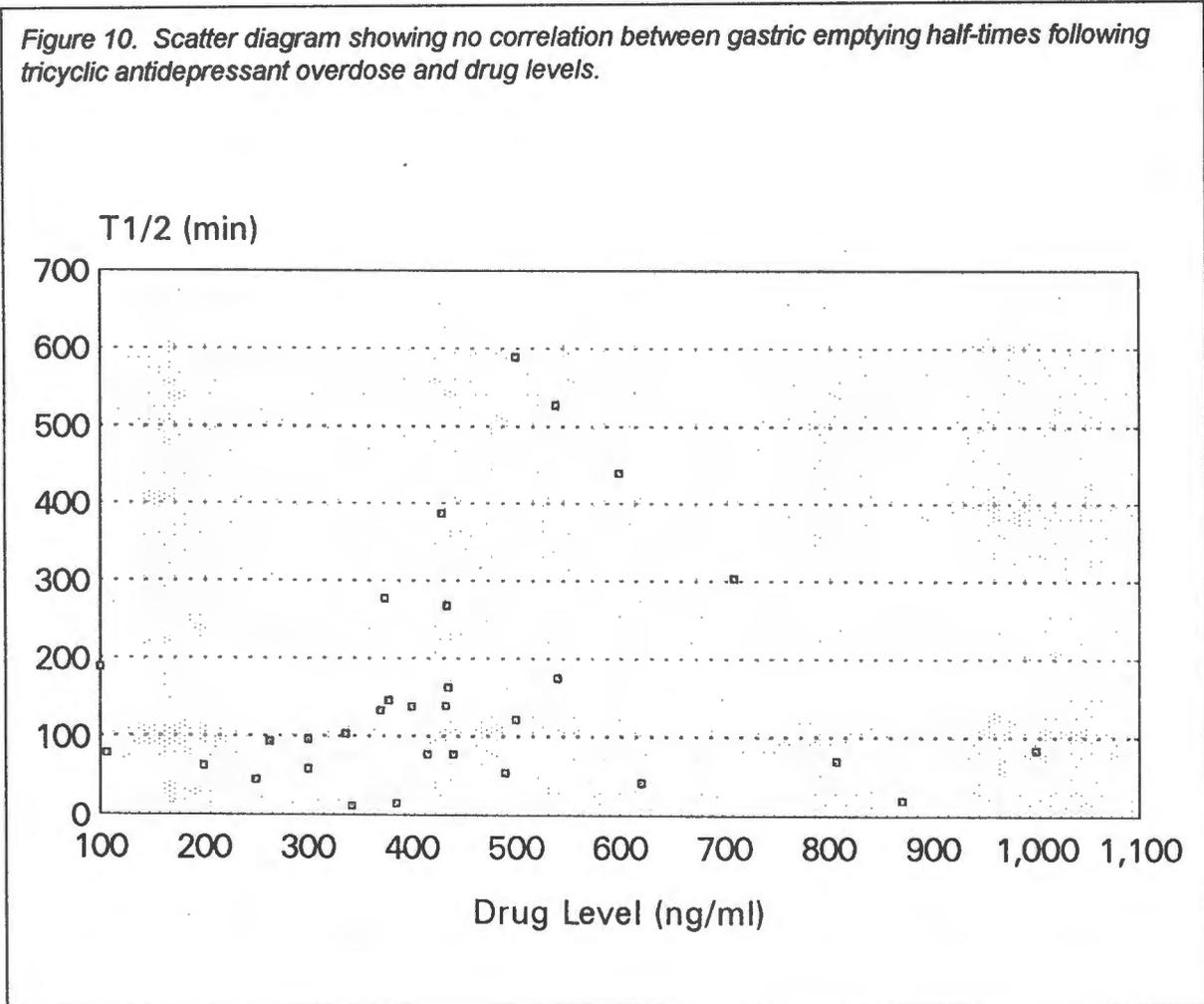
MULTIPLE REGRESSION ANALYSIS

After Overdose:

Multiple regression analysis was used to assess the relationships of the following variables to gastric emptying half-times: age, gender and drug level. None of these

variables were found to influence significantly the gastric emptying half-times following tricyclic overdose (age: $p = 0.87$; gender $p = 0.50$; drug level $p = 0.50$). Simple regression analysis confirmed the poor correlation between gastric emptying half-times and drug levels ($r = 0.114$). (See Figure 10).

Figure 10. Scatter diagram showing no correlation between gastric emptying half-times following tricyclic antidepressant overdose and drug levels.



At Control

The variables age, gender and drug level did not significantly influence gastric emptying half-times ($p = 0.94, 0.08, 0.81$, respectively).

CARBAMAZEPINE

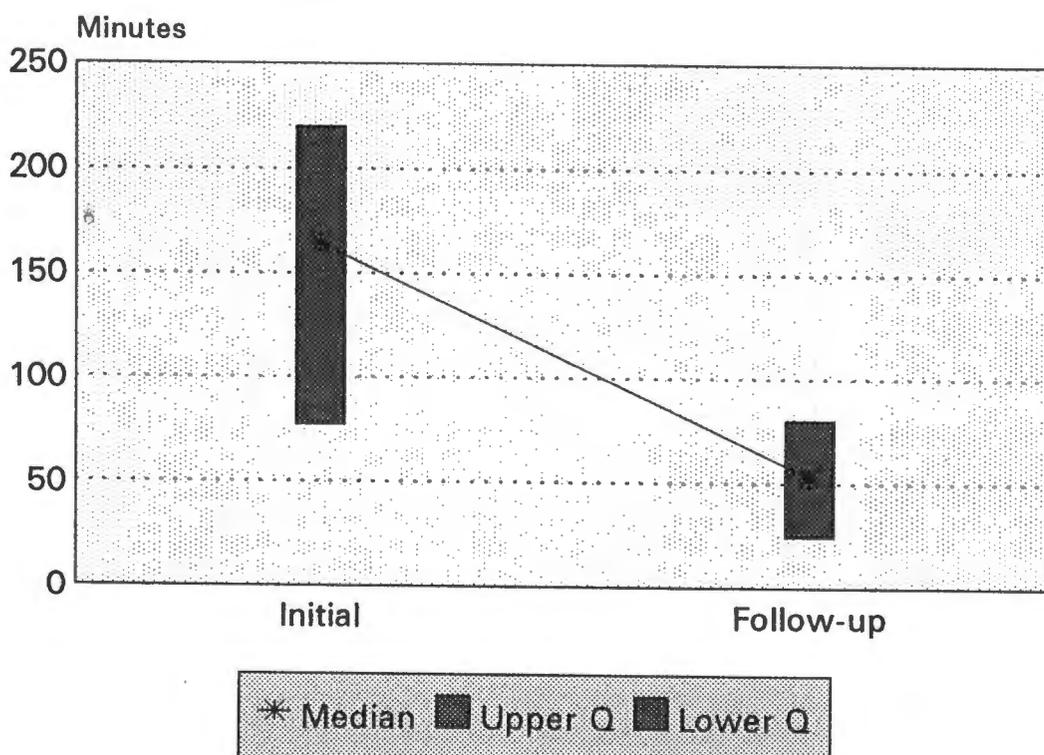
The gastric emptying half-times in minutes were:

AFTER OVERDOSE: 164 (median), 78 - 227 (IQR)

AT CONTROL: 53 (median), 25 - 82 (IQR)

Comparison of gastric emptying half-times after overdose with those at control shows highly significance differences ($p = 0.005$; Mann-Whitney U test). (See **Figure 11**).

Figure 11. A comparison of gastric emptying half-times after carbamazepine overdose and half-times in the same patients at control.



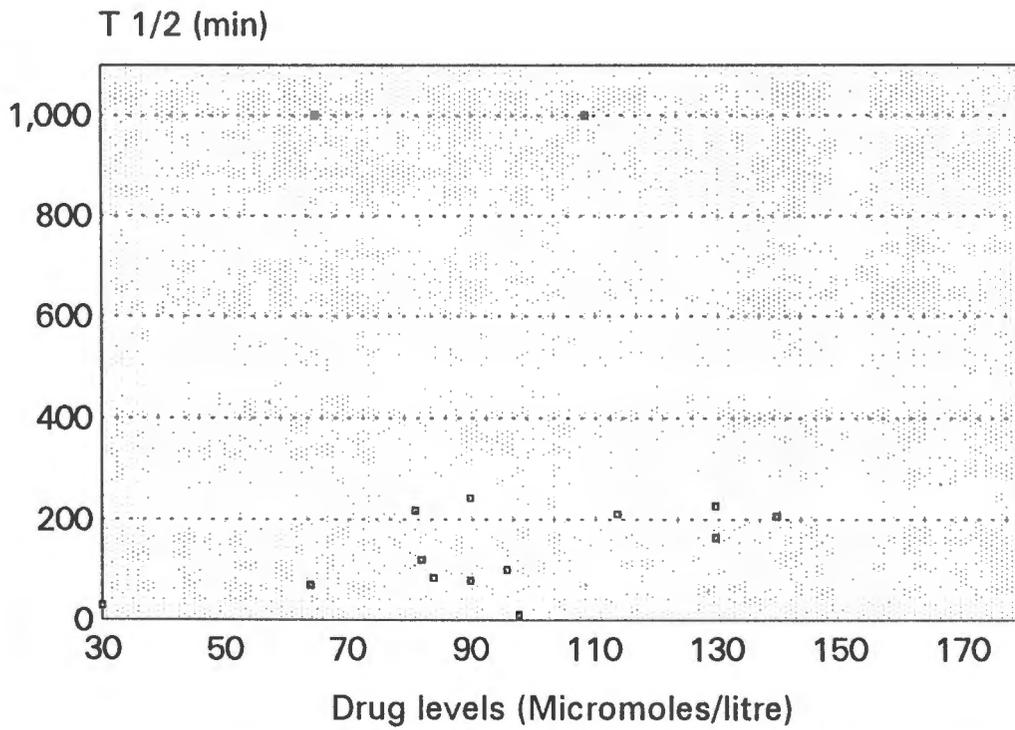
Nine of the 15 patients in this group had gastric emptying half-times longer than 120 minutes. Two of these had gastric emptying half-times of more than 300 minutes and 5 had emptying half-times longer than 200 minutes. Differences between the initial and follow-up groups were greater than 180 minutes in 3 patients, more than 150 minutes for another and over 90 minutes for a further 3.

MULTIPLE REGRESSION ANALYSIS

After Overdose

The following variables were entered into multiple regression analyses to assess their respective influence on gastric emptying half-times: age, gender and drug level. None of these variables were found to have a significant influence: age ($p = 0.44$), gender ($p = 0.30$), and drug level ($p = 0.97$). Simple regression analysis also failed to show a correlation between gastric emptying half-times and drug levels ($r = -0.06$). (See **Figure 12**).

Figure 12. Scatter diagram showing no correlation between gastric emptying half-times and drug levels following carbamazepine overdose.



At Control

Age ($p = 0.79$), gender ($p = 0.47$) and drug level ($p = 0.25$) did not influence significantly the gastric emptying half-times at control.

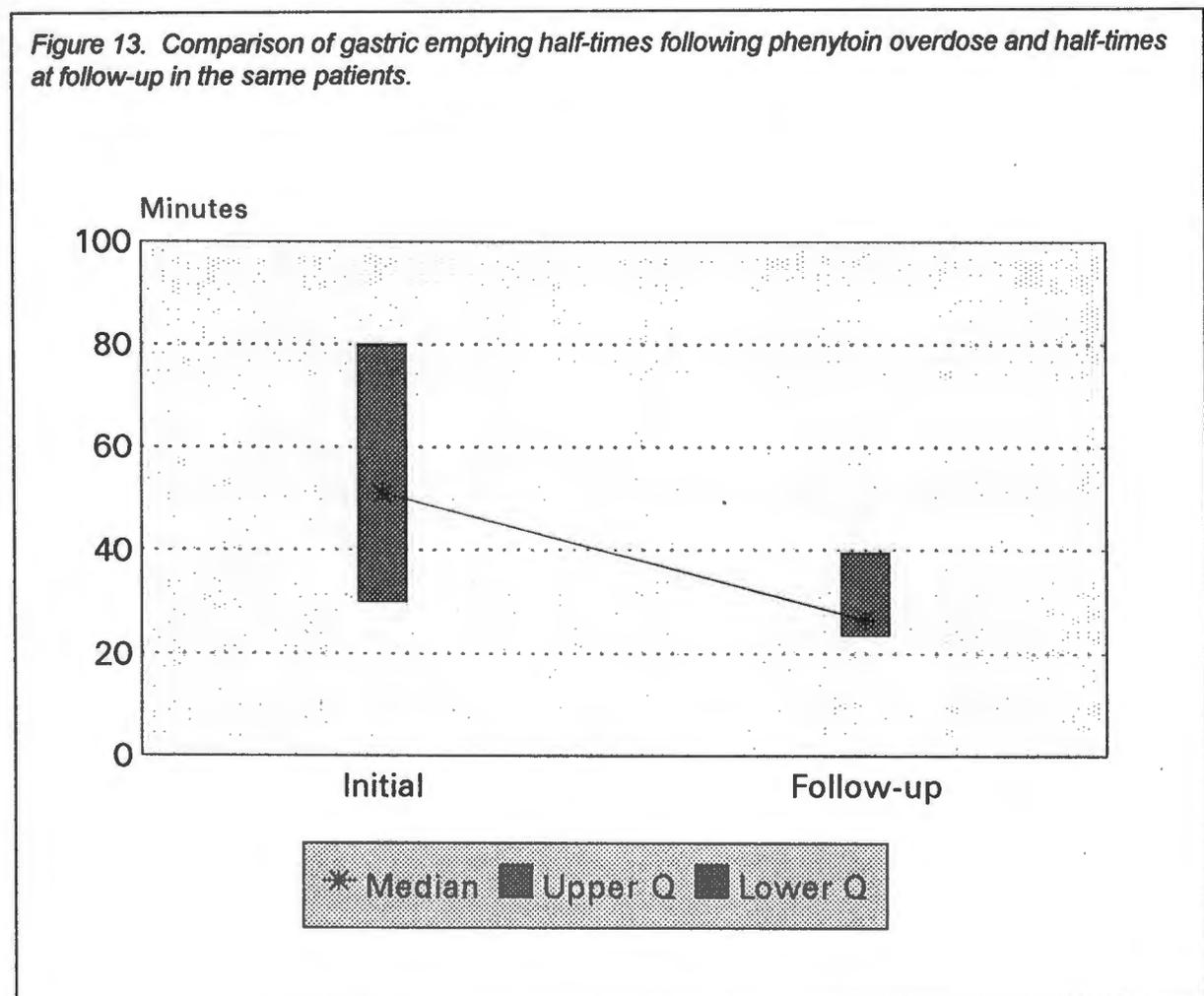
PHENYTOIN

The gastric emptying half-times in minutes were:

AFTER OVERDOSE: 52 (median), 32.5 - 95 (IQR)

AT CONTROL: 27 (median), 24 - 40 (IQR)

A comparison of gastric emptying half-times determined after overdose with those at control showed a tendency to be longer after overdose than at control ($p = 0.069$; Mann-Whitney U test). (See **Figure 13**).



Of the 12 patients in this group 1 patient had a gastric emptying half-time of over 300 minutes, another a half-time of over 240 minutes and a third had a

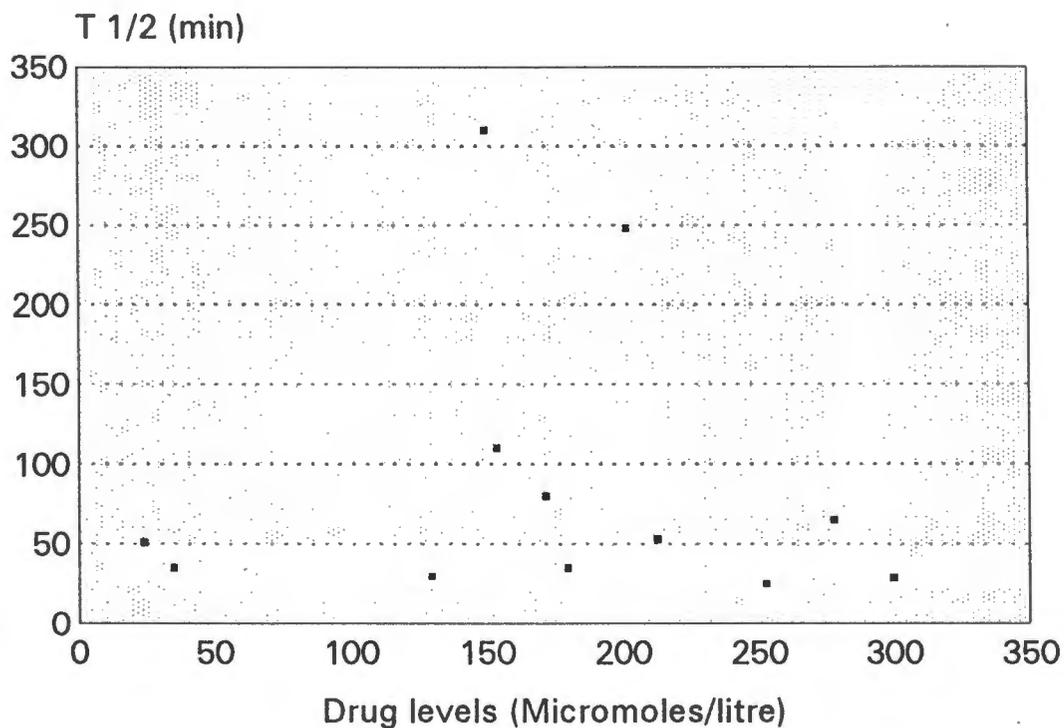
half-time of 110 minutes. Differences between the test (after overdose) and follow-up studies were greater than 200 minutes in 2 patients.

MULTIPLE REGRESSION ANALYSIS

After Overdose

The following variables were analysed and showed no significant relation to gastric emptying half-times: age ($p = 0.23$), gender ($p = 0.84$) and drug level (0.99). The r value = -0.026 (simple regression analysis). (See **Figure 14**).

Figure 14. Scatter diagram demonstrating no correlation between gastric emptying half-times and drug levels after phenytoin overdose.



At Control

The same set of variables made no significant contribution to gastric emptying at control. Drug level ($p = 0.16$), age ($p = 0.91$), gender ($p = 0.32$).

PARACETAMOL

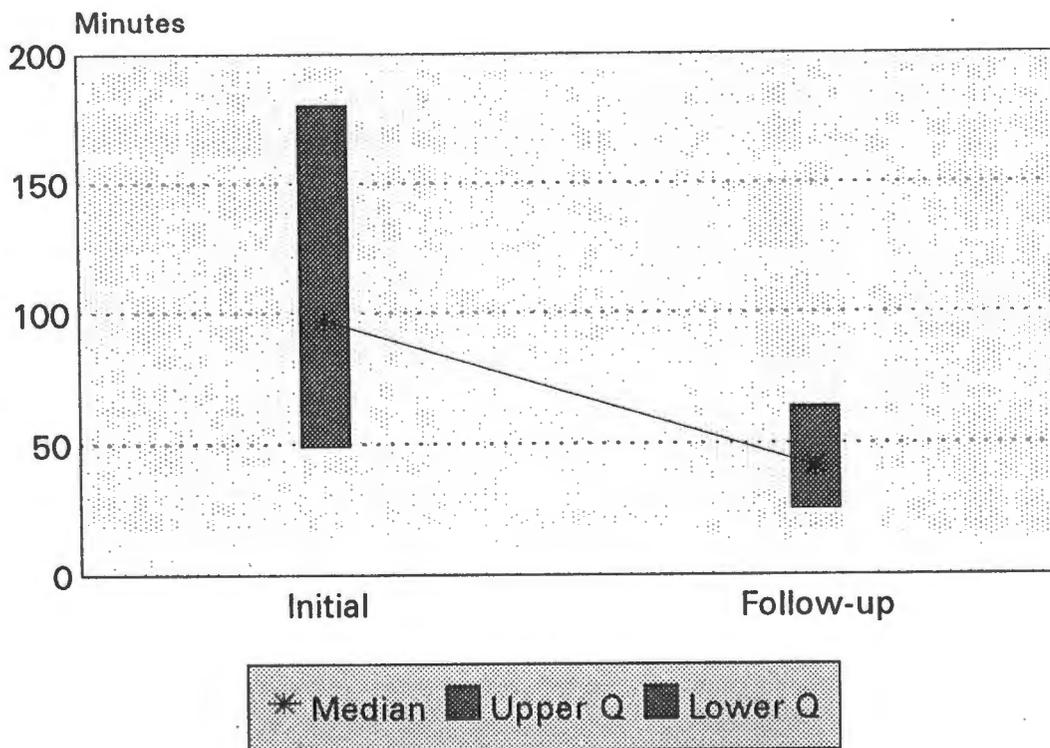
Gastric emptying times in minutes were:

AFTER OVERDOSE: 98 (median), 55 - 180 (IQR)

AT CONTROL: 42 (median), 25 - 70 (IQR)

A comparison between the gastric emptying half-times after overdose and at control shows a highly significant difference ($p = 0.00173$; Mann-Whitney U test). (See **Figure 15**).

Figure 15. Comparison of gastric emptying half-times following paracetamol overdose and half-times at follow-up in the same patients.



Thirteen of the 29 patients who ingested overdoses of paracetamol had gastric emptying half-times of over 120 minutes. Of these 2 were over 300 minutes, 4 longer than 240 minutes and 7 longer than 120 minutes. In 3 patients

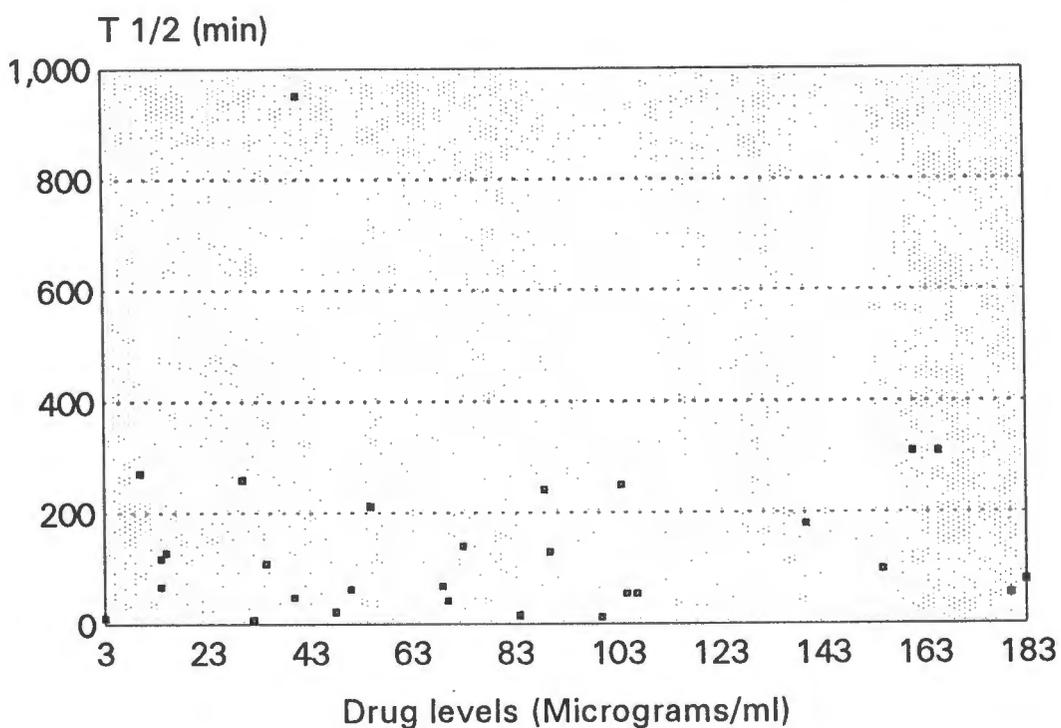
differences between the initial and follow-up studies were greater than 200 minutes, 4 others had differences of more than 120 minutes and a further 6 of more than 60 minutes.

MULTIPLE REGRESSION ANALYSIS

After Overdose

Drug level ($p = 0.27$) showed no significant relationship to gastric emptying half-times following paracetamol overdose. The correlation coefficient, $r = 0.15$ (See Figure 16). Age ($p = 0.49$) and gender ($p = 0.87$) had no significant relationship to gastric emptying.

Figure 16. Scatter diagram showing no correlation between gastric emptying half-times and drug levels following paracetamol overdose.



PARACETAMOL TOXICITY

The paracetamol group is special in that overdoses can be ingested without the patient necessarily having blood levels that are potentially hepatotoxic. In addition, those patients who were thought to have ingested potentially hepatotoxic amounts of paracetamol or who had blood levels that fell within the potentially hepatotoxic range were given N-acetylcysteine (parvolex) intravenously. However, it must be noted that not all toxic patients received the antidote before imaging began. In certain patients the antidote was begun after imaging started, and in others after the scan had been completed. Four patients had no N-acetylcysteine during the study; in 1 the antidote was started 2 hours and in another 70 minutes after imaging began.

A COMPARISON OF GASTRIC EMPTYING T_{1/2} IN PATIENTS WITH TOXIC VERSUS NON-TOXIC DRUG LEVELS

There are marked differences between the medians of gastric emptying half-times of patients with toxic drug levels (141 minutes; IQR 98 - 242; n = 13) and patients who had non-toxic levels (55 minutes; IQR 18.5 - 112.25; n = 16). The Mann-Whitney U test shows a significant difference in gastric emptying half-times between these 2 groups (p = 0.002). Table 8 shows the drug levels at the estimated time post-ingestion and gastric emptying half-times in the patients who were regarded by the attending clinician as being within the potentially toxic range. As indicated in Table 8 nine out of the 13 patients were receiving N-acetylcysteine during the entire imaging procedure, in 2 others the antidote was started at 70 and 120 minutes after scanning begun and in a further 4 patients N-acetylcysteine was not administered throughout the procedure.

TABLE: 8

GASTRIC EMPTYING HALF-TIMES IN PARACETAMOL TOXIC PATIENTS

DRUG LEVEL	HOURS POST-INGESTION	G E T½	N-ACETYLCYSTEINE
104	11	240	70 min into scan
140	4	180	No
44	14	145	No
30	19.5	77	Yes
89	17	253	Yes
15	24	121	Yes
166	4	>300	Yes
155	6	95	2hr into scan
161	4	>300	No
14	13	62.5	Yes
14	26	153	Yes
183	4	74	No
41	16	106	Yes

* This patient was still N-acetylcysteine when the control study was done. The gastric emptying half-time at the time of the second study was 60 minutes.

At Control

Paracetamol was not present in any of the blood samples done at the time of the control study. Other variables age ($p = 0.68$) and gender ($p = 0.99$) showed no significant relation to the gastric emptying half-times.

OPIOIDS

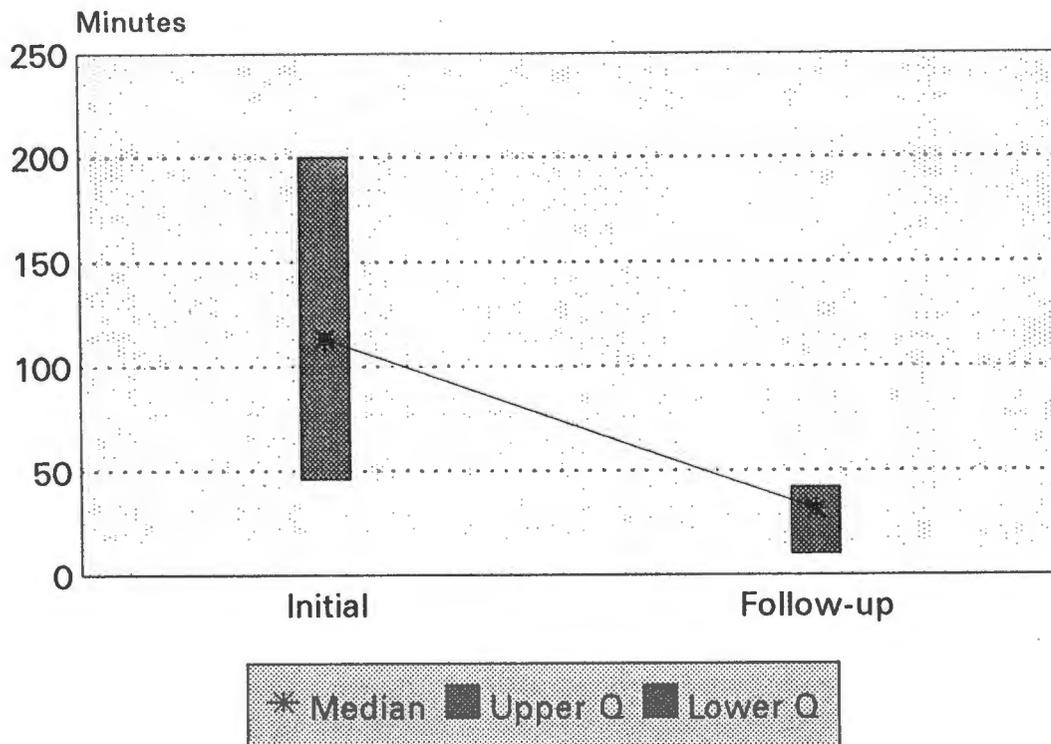
Gastric emptying half-times in minutes were:

AFTER OVERDOSE: 115.0 (median), 69 - 213 (IQR)

AT CONTROL: 34.5 (median), 21 - 43 (IQR)

A comparison between the gastric emptying half-times after overdose and at control demonstrated a significant difference ($p = 0.00170$; Mann-Whitney U test). (See **Figure 17**).

Figure 17. Comparison of gastric emptying half-times at presentation following opioid overdose and those at control in the same patients.



Eight of the 17 patients in this group had gastric emptying half-times of over 120 minutes. Of these 1 half-time was longer than 300 minutes, and 3 longer

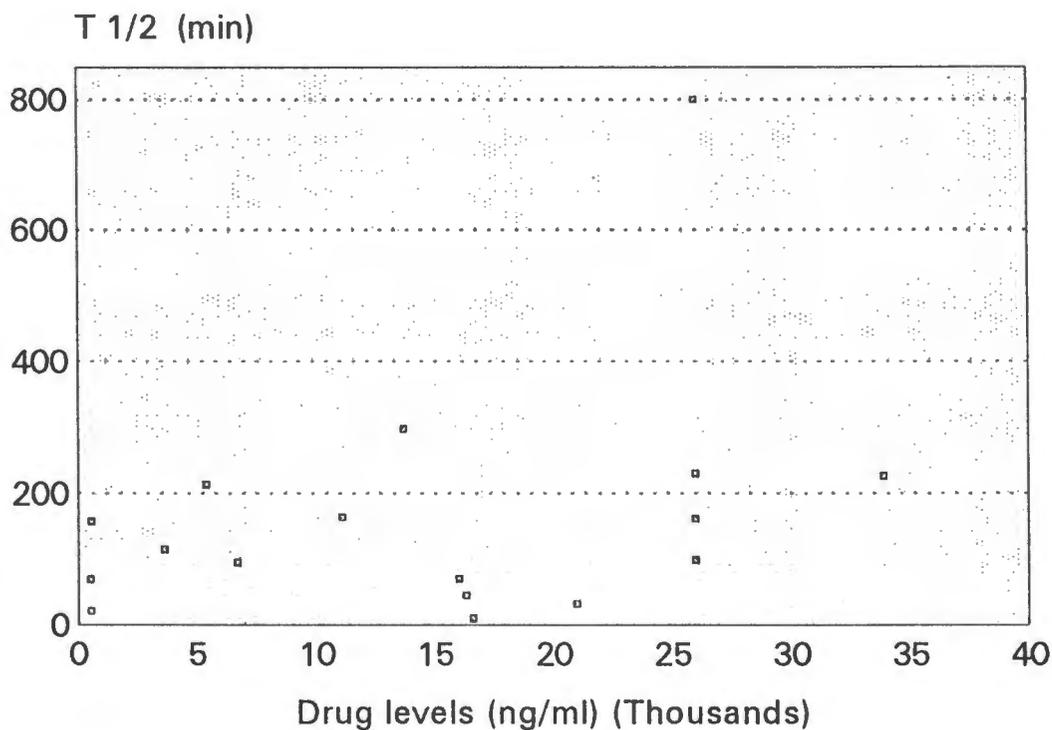
than 230 minutes. Differences between the test and follow-up studies were greater than 120 minutes in 4 patients and over 60 minutes in another 3.

MULTIPLE REGRESSION ANALYSIS

After Overdose

All the variables tested showed no significant relation to gastric emptying half-times after overdosage: age ($p = 0.36$), gender ($p = 0.55$), drug level ($p = 0.19$). Simple regression analysis found a correlation value, $r = 0.346$, $p = 0.17$). (See **Figure 18**).

Figure 18. Scatter diagram showing the relationship between gastric emptying half-times and drug levels after opioid overdose.



At Control

None of the variables had any significant relation to gastric emptying half-times: age ($p = 0.76$), gender ($p = 0.66$), drug level ($p = 0.98$).

THE ENTIRE GROUP OF PATIENTS

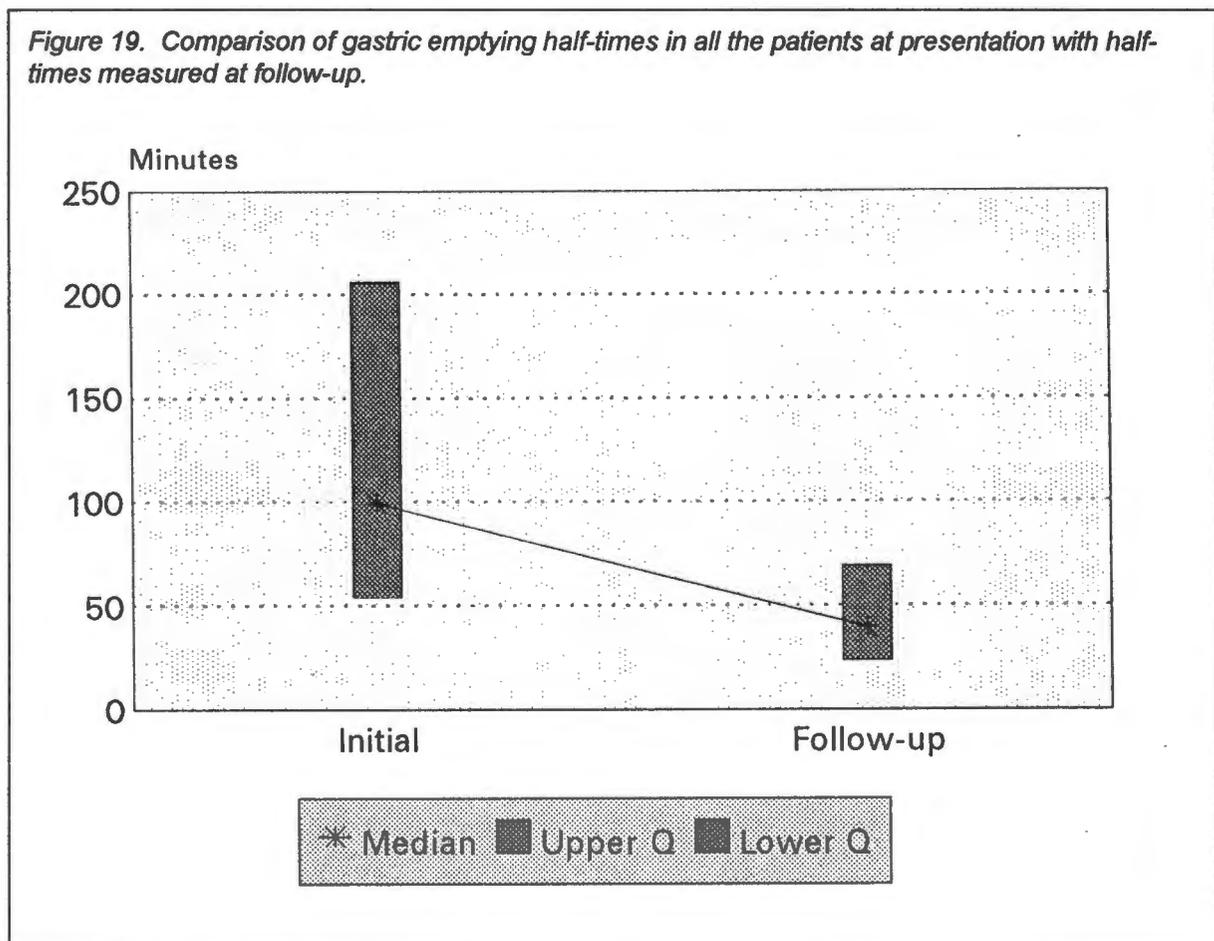
The results obtained for the entire group of 104 patients are detailed below.

Gastric emptying half-times in minutes were:

AFTER OVERDOSE: 99.5 mins (median), 54.5 - 208.25 (IQR)

AT CONTROL: 40 mins (median), 24 - 70 (IQR).

A comparison between these two sets of data shows a highly significant difference ($p < 0.00001$; Mann-Whitney U test). (See **Figure 19**).



Twelve patients had gastric emptying half-times of over 300 minutes, another 14 had half-times of over 200 minutes and 21 other patients had half-times of over 120 minutes.

It has been shown, therefore, that gastric emptying half-times measured after overdose are significantly prolonged (somewhat less pronounced in the group that took phenytoin) when compared with control studies performed on the same patients. **The first hypothesis that poisoning does not prolong gastric emptying is rejected.**

STANDARDISED DRUG LEVELS

Drug levels for the different groups were measured in different units. A form of standardisation was necessary, therefore, to determine the influence of drug levels on gastric emptying half-times and small intestinal transit times when combining patients who had ingested different drug types. The following formula was used:

$$Z_i = (X_i - \bar{X})/SD$$

where: X_i = the individual measurement

\bar{X} = the mean of the sample of the specific drug group and

SD = the standard deviation of the specific drug group.

The "standardised drug levels" allowed for an evaluation of the relationship between drug levels and gastric emptying and small intestinal transit times and was used only when making a global assessment of the entire group of patients by multiple regression analysis. Standardised drug levels were not used for analysis in the individual drug groups.

MULTIPLE REGRESSION ANALYSIS

The following variables were entered into multiple regression analysis to assess their respective influences on gastric emptying half-times: the different drug groups; age; gender and standardised drug levels. None of the variables showed a

significant relationship to gastric emptying half-times after overdose: the different drug groups ($p = 0.36$), age ($p = 0.51$), gender ($p = 0.96$) and standardised drug levels ($p = 0.24$).

The coefficient of determination, R-Squared was 0.025 for all the variables tested. Therefore, all the variables tested accounted for only 2.5% of the variance in the gastric emptying half-times. Unknown and untested factors could thus be responsible for the variance in gastric emptying.

At control gender was found to be the only variable with correlate significantly with gastric emptying half-times ($p = 0.033$). The other variables showed no significant relationship.

THE CONTROL GROUP

Certain patients had therapeutic drug levels in the blood at the time of the control study as they had already restarted treatment. I therefore compared members of the control group who had drug levels > 0 ($n = 19$) with those with levels $= 0$ ($n = 66$) and found no significant difference in gastric emptying half-times between the two groups. Kruskal-Wallis one way analysis of variance produced a p value $= 0.20$.

THE EFFECTS OF THE DIFFERENT DRUG GROUPS

THE EFFECTS OF THE DRUG GROUPS ON THE OVERDOSE GROUP

One-way Analysis of variance (ANOVA) found no difference between the effects of the different drug groups on the gastric emptying half-times following overdose. P value = 0.13.

THE EFFECTS OF DIFFERENT DRUG GROUPS ON THE CONTROL GROUP

No difference was found in the relative influence of the different drug groups on the gastric emptying half-times of the control group. P value = 0.30.

THE EFFECTS OF DIFFERENT DRUG GROUPS ON THE DIFFERENCES: OVERDOSE MINUS CONTROL GASTRIC EMPTYING HALF-TIMES.

No differences were found when comparing the effects of the various drugs on gastric emptying half-time differences. P value = 0.16.

The null hypothesis that gastric emptying times do not vary according to the drug taken at overdose levels is therefore accepted.

THE EFFECTS OF GASTRIC LAVAGE

The Mann-Whitney U test showed a tendency to differ in gastric emptying half-times between the group that had gastric lavage and those who did not ($p = 0.077$). The gastric emptying half-times median for the group who had gastric lavage was 131 minutes (IQR = 69 - 211.75; $n = 56$) compared with the median of 87.5 minutes (IQR = 41.5 - 178.25; $n = 48$) for those patients not lavaged. This difference is probably

due to the fact that the more seriously ill patients were lavaged more readily than the rest.

ALTERED LEVEL OF CONSCIOUSNESS

Thirty-one patients were obtunded and/or confused. Twenty of these had ingested tricyclic antidepressants, 8 took carbamazepine and 3 phenytoin overdoses. Gastric emptying half-times for the group with the altered consciousness were significantly longer than for the rest of the patients ($p = 0.0040$, $n = 73$) and for the group taken as a whole ($p = 0.0345$, $n = 104$; Mann-Whitney U test). The median of the gastric emptying half-times for patients with altered consciousness was: 163 minutes (IQR = 78 - 310 minutes) compared with that of 89.5 minutes (IQR = 45 - 168.5 minutes) for those with normal consciousness.

SUMMARY:

1. The excellent linear correlation between gastric emptying half-times calculated from geometric means and those derived from anterior counts alone enabled me to use gastric emptying times calculated from the anterior data.
2. Significant differences were found between gastric emptying half-times after overdose and those at control using gastric emptying half-times based on time-activity curves.
3. Gastric emptying half-times of studies following overdose were markedly prolonged. A total of 47 patients had gastric emptying half-times of over 120 minutes. Of these 12 had half-times of over 300 minutes, 14 of over 200 minutes and 21 of over 120 minutes.
4. There was no significant difference in the effects of the different drug groups on gastric emptying half-times.
5. Gastric emptying half-times showed a tendency to be longer in patients who were lavaged than in those who were not lavaged.
6. Patients with toxic levels of paracetamol had significantly longer gastric emptying times than the other patients who ingested paracetamol overdoses.
7. Drug level showed no correlation with gastric emptying half-times.
8. No significant difference in gastric emptying half-times were found between patients at control who were on therapeutic doses of drugs and those not taking any drugs.

9. Patients with altered levels of consciousness had significantly longer gastric emptying half-times when compared with the rest.

10. None of the variables tested for - age, gender and different drug groups influenced significantly the gastric emptying half-times in patients with overdose.

11. In a regression all the variables tested explained less than 5% of the variance in gastric emptying half-times at overdose.

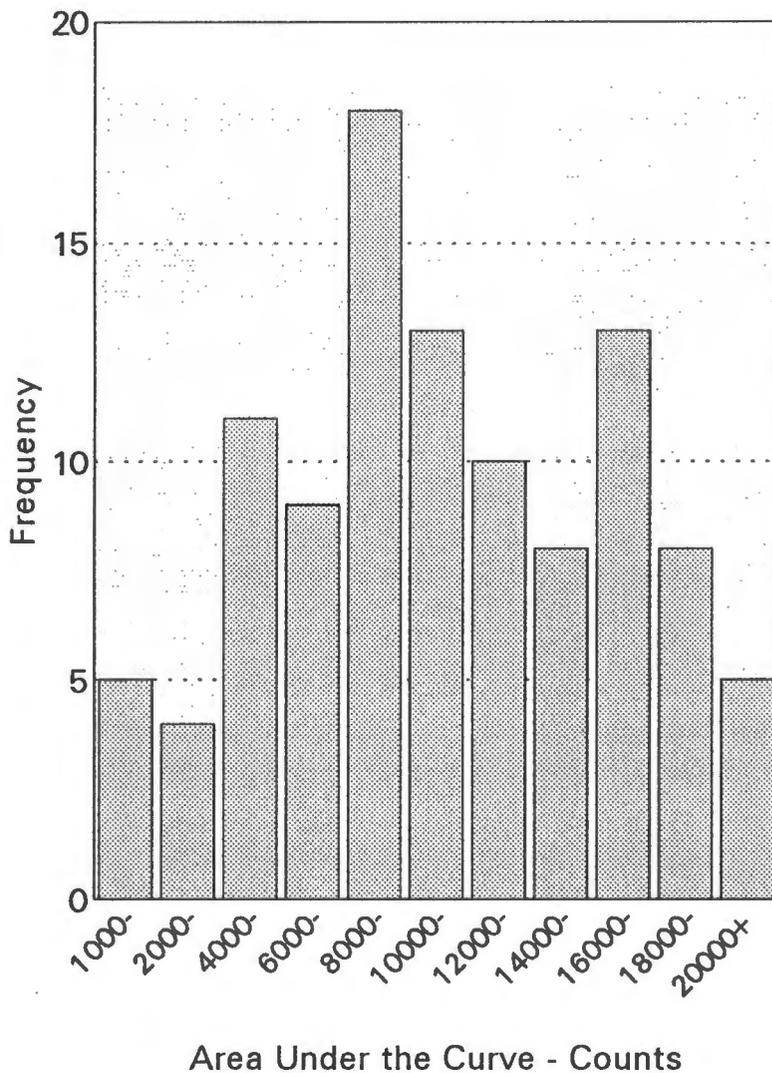
INTEGRATION - AREA UNDER THE TIME-ACTIVITY CURVE (AUC)

When measuring the gastric emptying half-times using the time-activity curve as described in the "Patients and Methods" section I encountered a problem in those patients in whom the imaging was completed before half of the activity had left the stomach. This occurred, for example, in the 12 patients in whom the gastric emptying half-times were greater than 300 minutes. Simple extrapolation was used to calculate the half-times in these patients. I decided to use integration - measuring the area under the time-activity curves as a confirmatory measure of gastric emptying.

AUC AFTER OVERDOSE

The frequency distribution of the areas under the curve of the studies following overdose are presented in **Figure 20**. A normal distribution was noted.

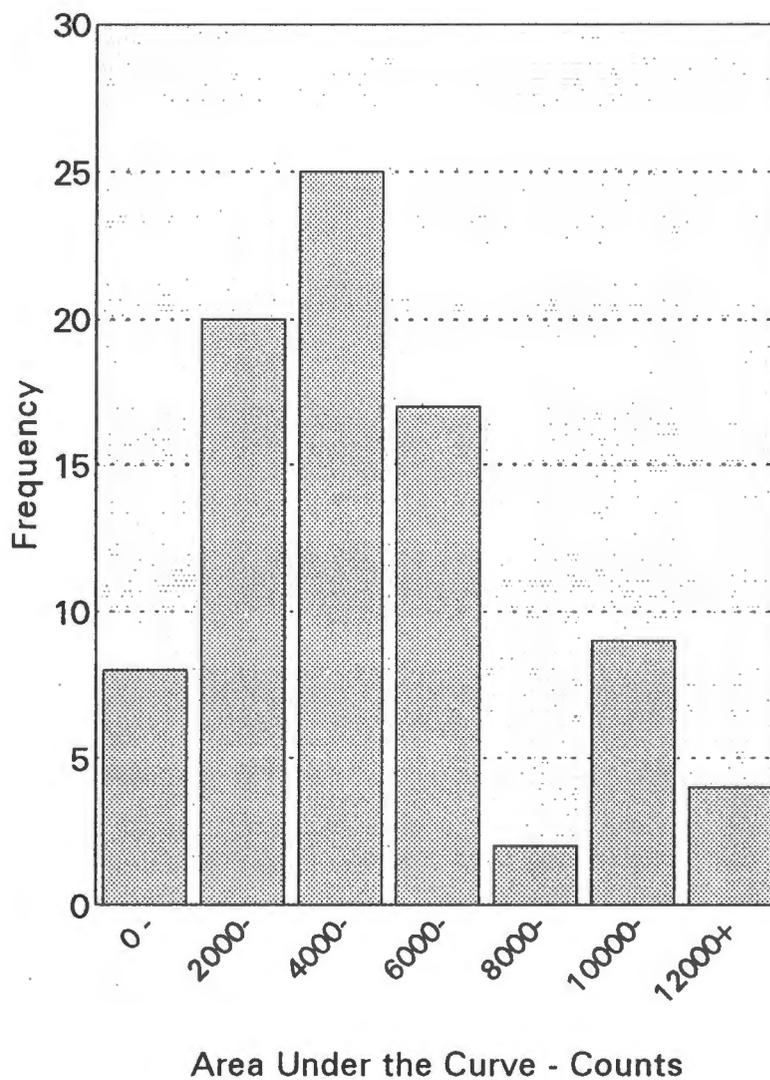
Figure 20. Histogram presenting the frequency distribution of areas under the gastric emptying curve in all the studies done at initial presentation (overdose).



AUC AT CONTROL

Figure 21 presents the frequency distribution of the areas under the curve of the control studies. The distribution appears approximately normal except for the discontinuity - the 8 000-10 000 group in which there are only two studies.

Figure 21. Histogram presenting the frequency distribution of the areas under the gastric emptying curve in all the studies at follow-up.



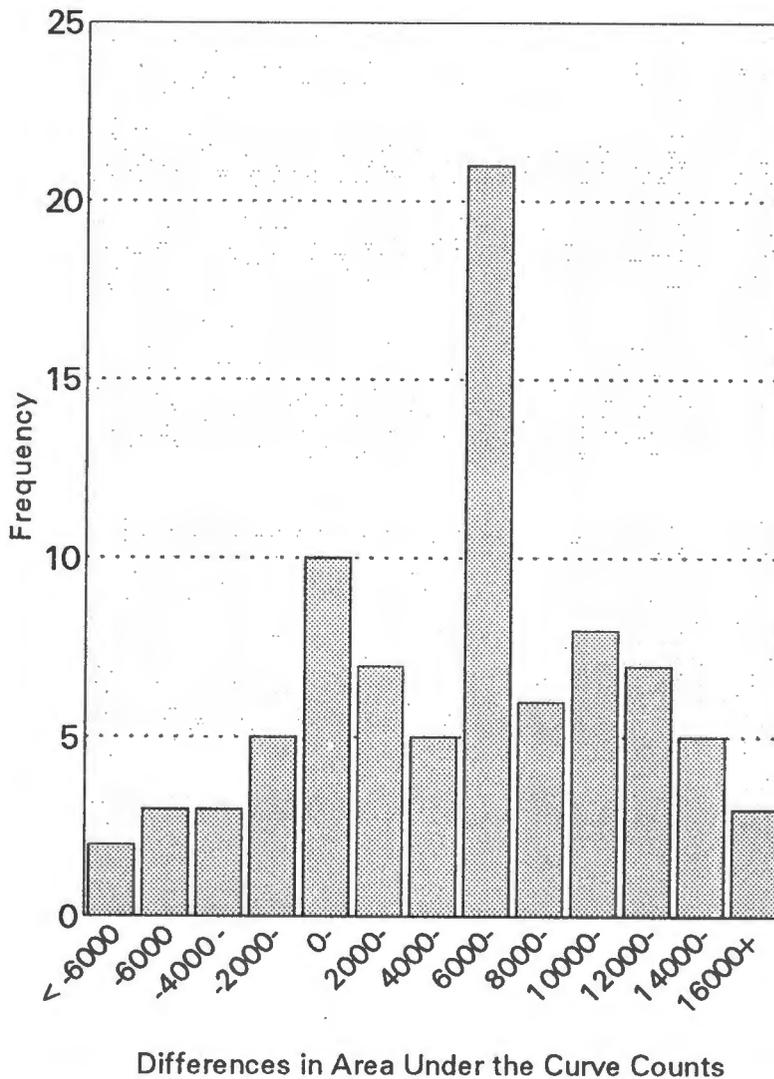
No significant differences were shown between those control studies where the drug levels > 0 and those where levels = 0 ($P = 0.36$; Kruskal-Wallis).

AUC DIFFERENCES (OVERDOSE - CONTROL AREAS)

1. Frequency Distribution

The frequency distribution of the differences in the areas under the curve between the studies at overdose and the respective controls are shown in **Figure 22**. The distribution appears to be normal.

Figure 22. Histogram demonstrating the frequency distribution of the differences in areas under the gastric emptying curves between initial and follow-up studies.



2. Differences between AUC after Overdose and those at Control

AUC differences between the studies after overdose and those at control are very significant. The simple t-test found a p value < 0.0001 . The mean AUC for studies after overdose = 11458.4 ± 5453.4 and for controls = 5621 ± 3192.7 .

Integration confirmed the markedly significant differences between the gastric emptying half-times measured after overdose with those determined at control.

GASTRIC MOTILITY

GASTRIC MOTILITY SCORES

An assessment of gastric motility was done based on the scoring system described in the "Patients and Methods" section. The author scored all of the studies. Table 9 shows significantly lower motility scores after overdose compared with control studies.

TABLE : 9

GASTRIC MOTILITY SCORES: OVERDOSE VS CONTROL

	Overdose	Control
Mean	3.2	10.95
Std Dev	4.2	8.2
P Value	= 0.0008	

Simple analysis on the gastric motility scores for the overdose group of studies versus the control group showed $p = 0.0008$. Gastric motility was therefore significantly diminished in the studies after overdose when compared with those at control. **The null hypothesis that gastric motility is not diminished by poisoning is rejected.** (See Figures 23 - 27).

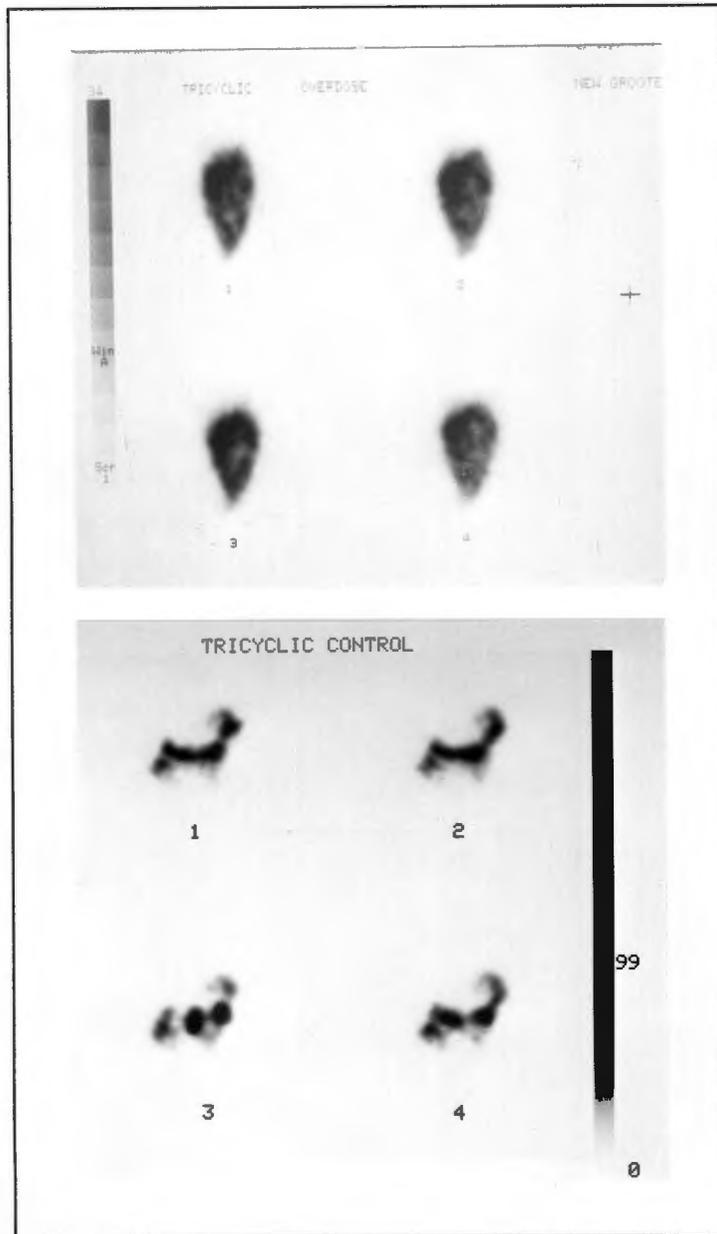


Figure 23. Selected dynamic frames showing gastric hypomotility after tricyclic overdose (upper 4 frames) and good contractility at follow-up in the same patient.

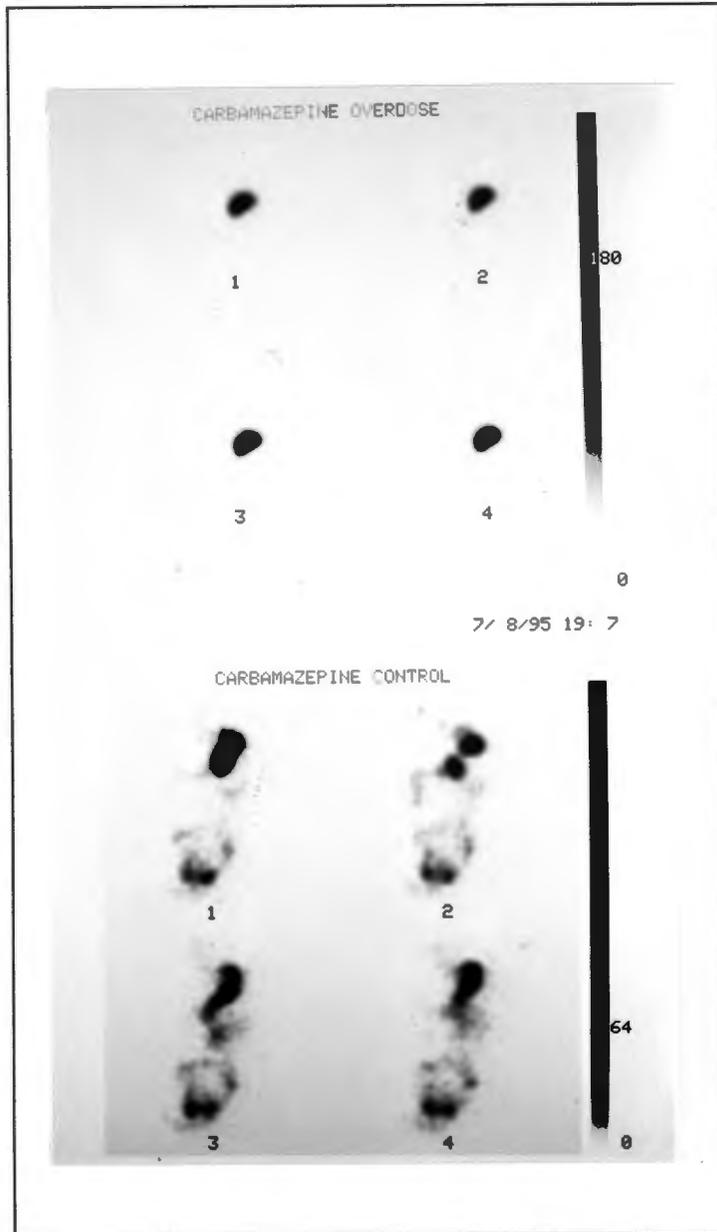


Figure 24. Selected Dynamic Frames Demonstrating An Absence Of Contractility After Carbamazepine Overdose (Upper 4 Frames) And Normal Motility At Control In The Same Patient.

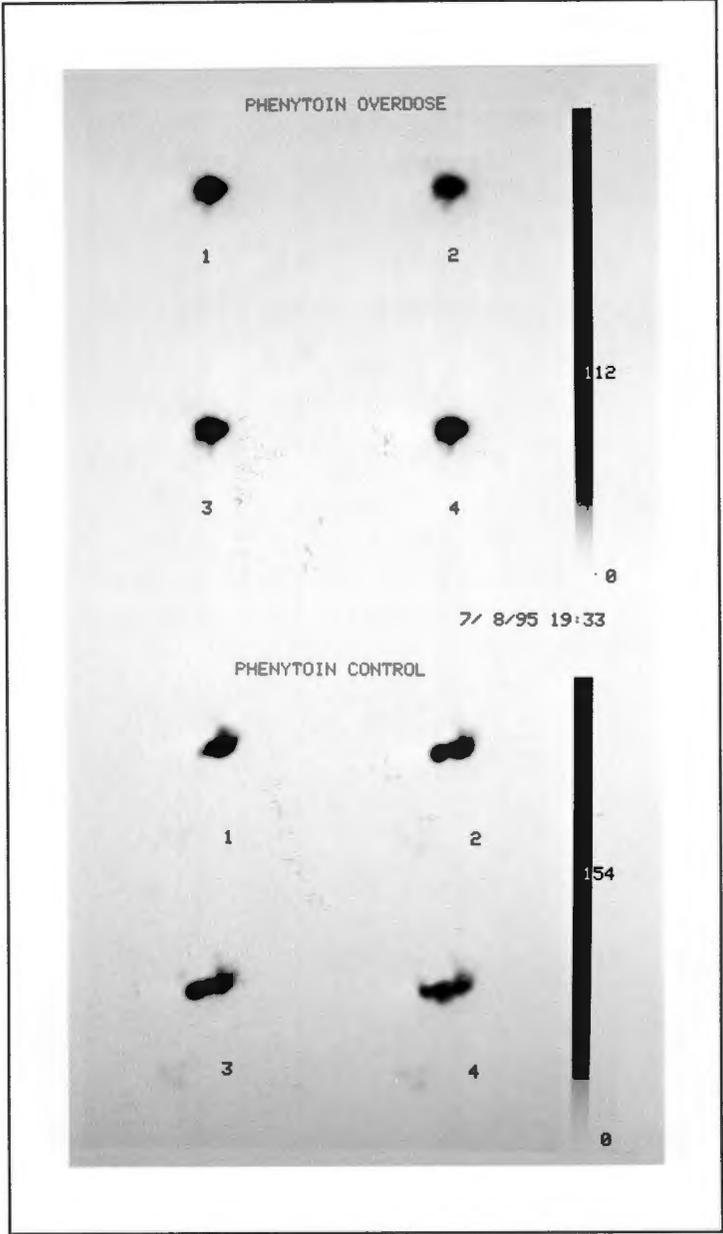


Figure 25. Selected Dynamic Frames Show A Lack Of Gastric Motility Following Phenytoin Overdose (Upper 4 Frames) And Normal Contractility At Control In The Same Patient.

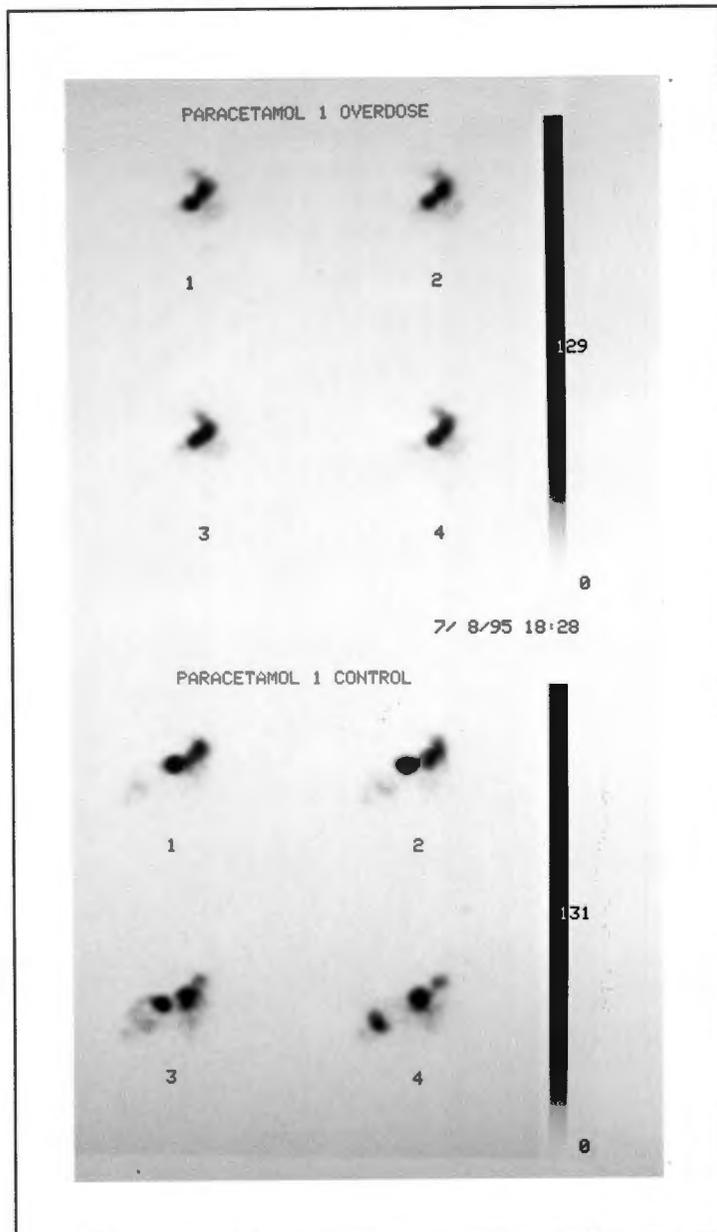


Figure 26. Gastric hypomotility on representative dynamic frames (upper 4 frames) after paracetamol overdose returns to normal at follow-up in the same patient.

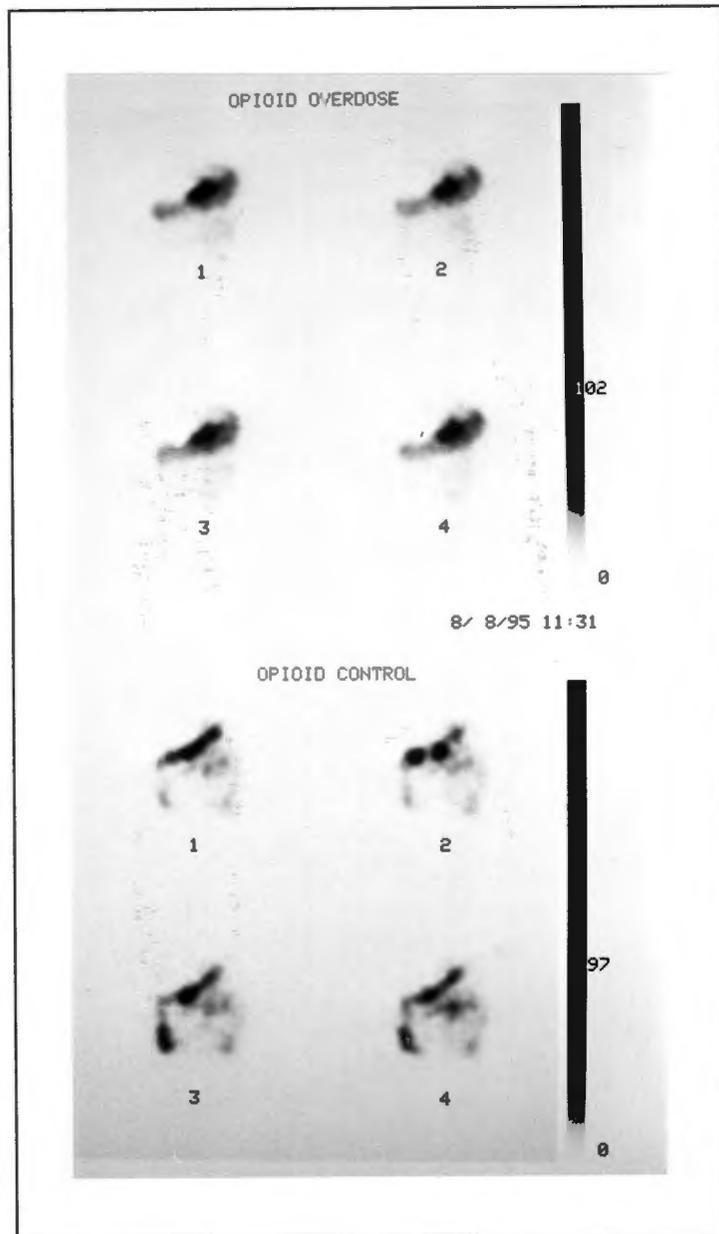


Figure 27. Absent gastric contractility (upper 4 dynamic frames) following opioid overdose is replaced by normal motility at control in the same patient.

The effects of a number of different variables on gastric motility scores were analysed.

THE DIFFERENT DRUG GROUPS ON MOTILITY SCORES

The Kruskal-Wallis test failed to show any inter-drug differences in either the overdose or control groups (P values = 0.47 and 0.1 respectively).

GASTRIC EMPTYING HALF-TIMES VERSUS GASTRIC MOTILITY SCORES.

A significant inverse relationship was shown: correlation coefficient = -0.51 (P value <0.001).

DIFFERENCES IN GASTRIC MOTILITY SCORES (OVERDOSE - CONTROL SCORES)

The average difference in motility score was 7.3 +/- 9.5. (P value <0.00001).

NUMBER OF CONTRACTIONS: OVERDOSE VERSUS CONTROLS

There was a marked difference in the number of contractions per dynamic study with the overdose group having far fewer contractions than the control group. See Table 10.

TABLE: 10**NUMBER OF CONTRACTIONS: OVERDOSE VS CONTROLS**

	Overdose	Control
Median	1	4
Mean	1.56	4.1
Coeff Var	130.3	70.1

The paired t-test showed a significant difference between the two groups (P <0.00001)

SUMMARY:

1. Significant differences were found between the gastric motility scores for the overdose and control groups.
2. Significant inverse relationships were found between gastric motility scores and gastric emptying half-times.
3. The number of gastric contractions were significantly fewer in the overdose studies.

DISTRIBUTION OF THE RADIOLABELED MEAL IN THE STOMACH

Activity Distribution Categories were coded as follows:

1 = Proximal half of stomach

2 = Fundus and Corpus

3 = Entire Stomach

OVERDOSE

Table 11 demonstrates longer gastric emptying half-times in patients with predominantly proximal distribution.

TABLE: 11

DISTRIBUTION OF ACTIVITY AND GASTRIC EMPTYING HALF-TIMES

Distribution	1	2	3
n	61	21	20
MEAN GE T _{1/2}	164.2	105.6	65.6
Std Dev	101.4	80.7	46.3

GE T_{1/2} = Gastric emptying half-times

The disks on which two of the studies were stored were technically defective and therefore not included.

The analysis of variance demonstrates significant differences ($p = 0.0036$) between gastric emptying half-times in the 3 different distribution groups. Gastric emptying

half-times (**Table 11**) for those with proximal distribution were longer than the other 2 groups ($P = 0.06$ - proximal vs fundus and corpus; and $p = 0.02$ - proximal vs entire stomach).

The activity remained in the proximal stomach [1] significantly longer than it did in the other two regions [2] and [3]. P value = 0.0018 (Kruskal-Wallis test). See Table 12.

TABLE: 12

ACTIVITY DISTRIBUTION AND THE TIME THAT THE ACTIVITY REMAINED IN THAT PART OF THE STOMACH

Distribution	n	Mean Time (min)	SD
1	61	139.6	87.4
2	21	99.3	77.7
3	20	66.0	38.4

DISTRIBUTION PATTERN AND DRUG GROUPS

No differences were demonstrated between the patterns of distribution and the various drug groups tested at overdose. Chi square = 3.60, DF (degrees of freedom) = 4; p value = 0.8909. For all the drug groups a higher proportion had distributions in the proximal half of the stomach when compared with the other two regions. Proximal half distribution patterns were noted in:

- | | | |
|----|----------------|-------|
| 1. | Tricyclics: | 53.3% |
| 2. | Carbamazepine: | 67% |
| 3. | Phenytoin: | 54.5% |
| 4. | Paracetamol: | 65.5% |
| 5. | Opioids: | 58.8% |

CONTROLS

Although the gastric emptying half-times are slightly longer when the radioactivity is proximally distributed (see Table 13) analysis of variance showed no significant differences in gastric emptying half-times among the three groups. $P = 0.345$.

TABLE: 13

DISTRIBUTION OF ACTIVITY AND GASTRIC EMPTYING HALF-TIMES

Distribution	Mean GE T½	SD
1	62.7	50.9
2	41.9	26.4
3	43.6	25.8

Table 14 demonstrates no significant difference when comparing the times that the radioactivity remained distributed in the different parts of the stomach.

P value = 0.1550 (Kruskal-Wallis test).

TABLE: 14**ACTIVITY DISTRIBUTION AND THE TIME THAT THE ACTIVITY REMAINED IN THAT PART OF THE STOMACH**

Distribution	Mean time (min)	SD
1	58.0	49.1
2	34.4	21.1
3	41.6	17.1

ACTIVITY DISTRIBUTION: OVERDOSE VERSUS CONTROL GROUP

Significant differences are shown when comparing the distribution of activity in the overdose group with that in the control group. Chi square = 14.09, DF = 1; p value = 0.0070. **The patterns of distribution are significantly different for the two groups. (See Figures 28 - 32).**

Figure 28a. Static images show prolonged retention of the radioactive meal mainly in the proximal stomach in a patient who ingested a tricyclic overdose.

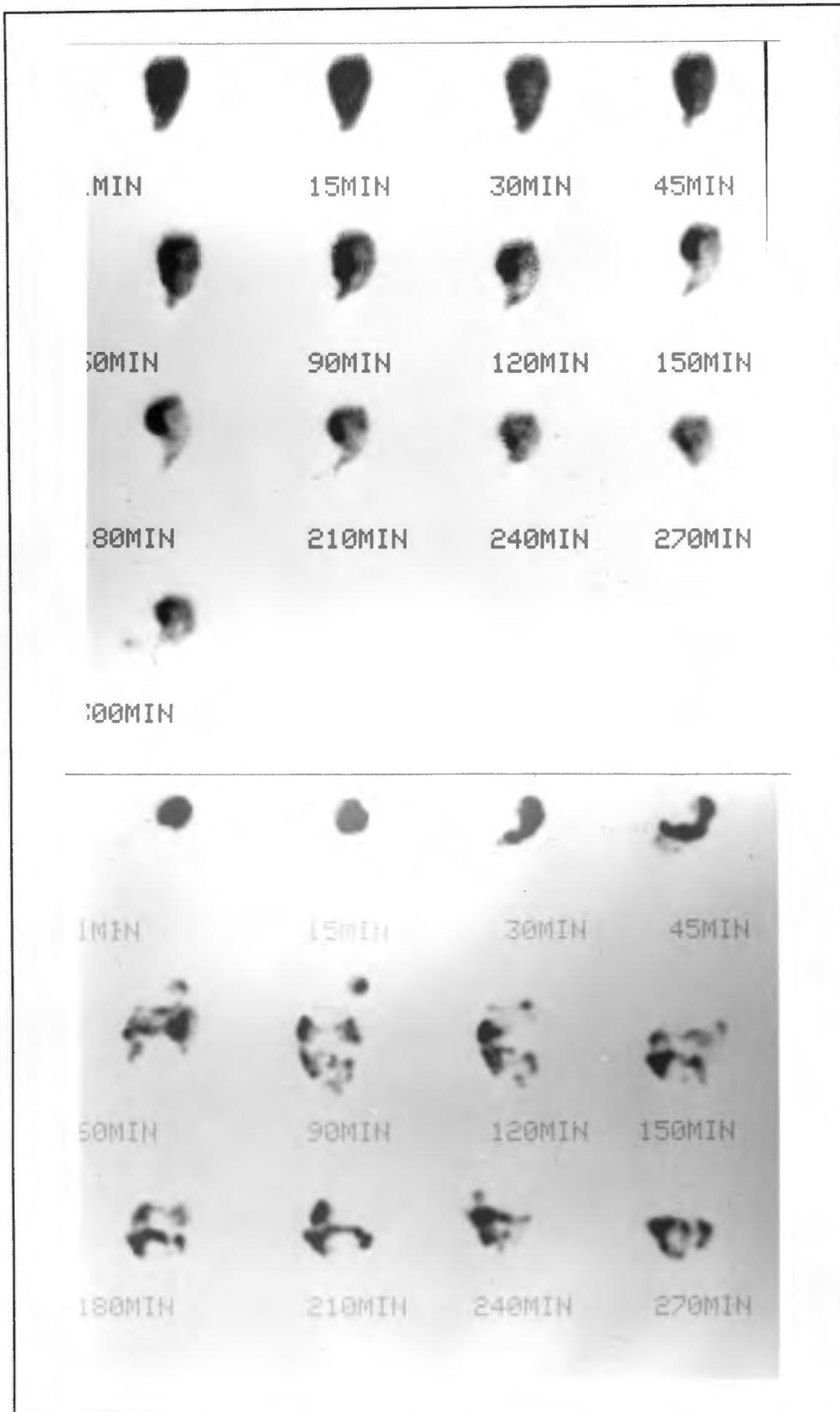


Figure 28b. A normal gastric emptying rate and distribution of radioactivity are seen on the static images at follow-up in the same patient.

Figure 29a. Static images demonstrate hold-up of the radioactive meal in the proximal stomach in a patient following carbamazepine overdose.

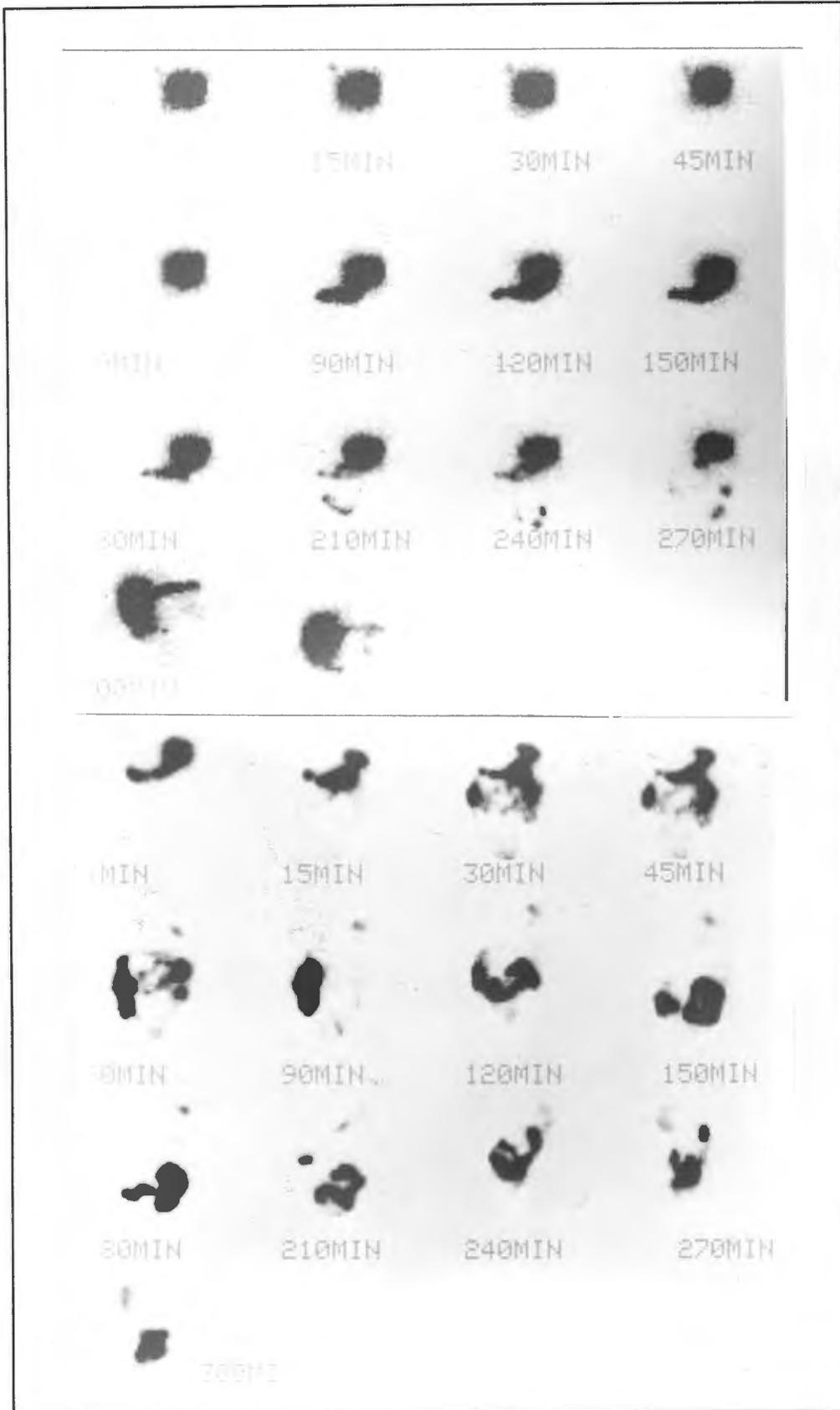


Figure 29b. Static images show a much quicker passage of radioactivity through the stomach in the same patient.

Figure 30a. Static images demonstrate prolonged proximal gastric retention of the radioactive meal in a patient following phenytoin overdose.

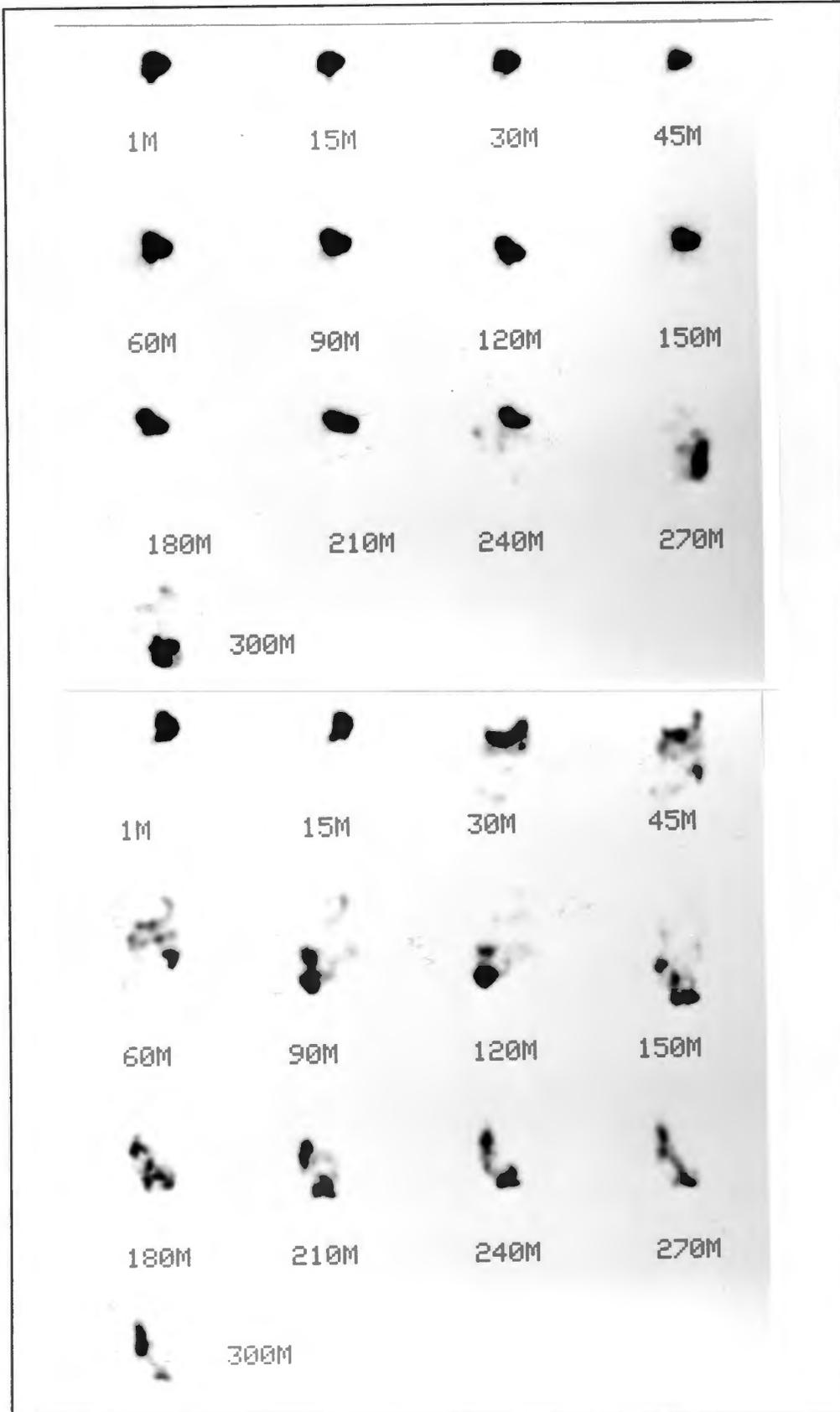


Figure 30b. A much more rapid gastric emptying pattern is noted on the static images at control in the same patient.

Figure 31a. Marked hold-up of radioactivity is seen in the proximal stomach in a patient after paracetamol overdose.

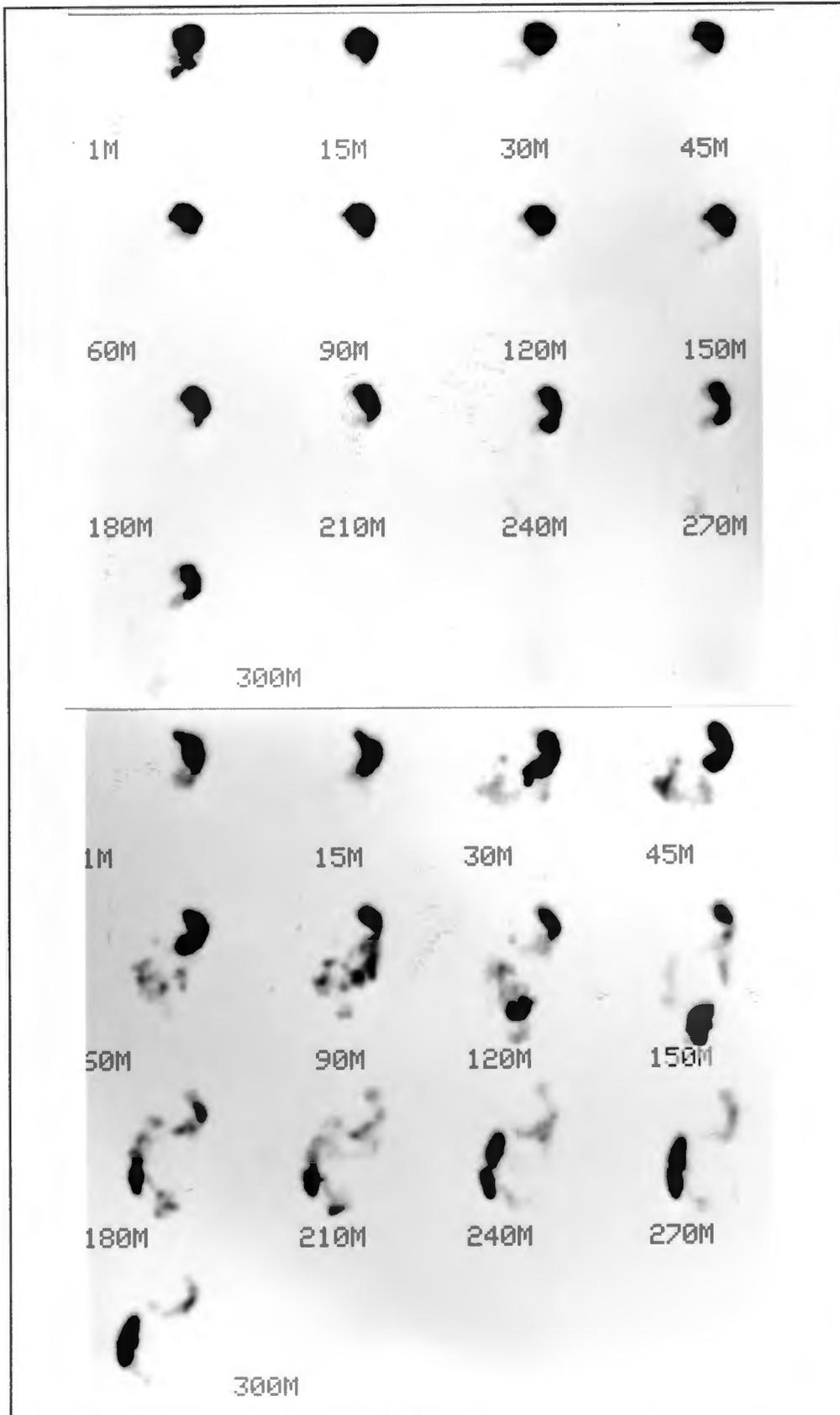
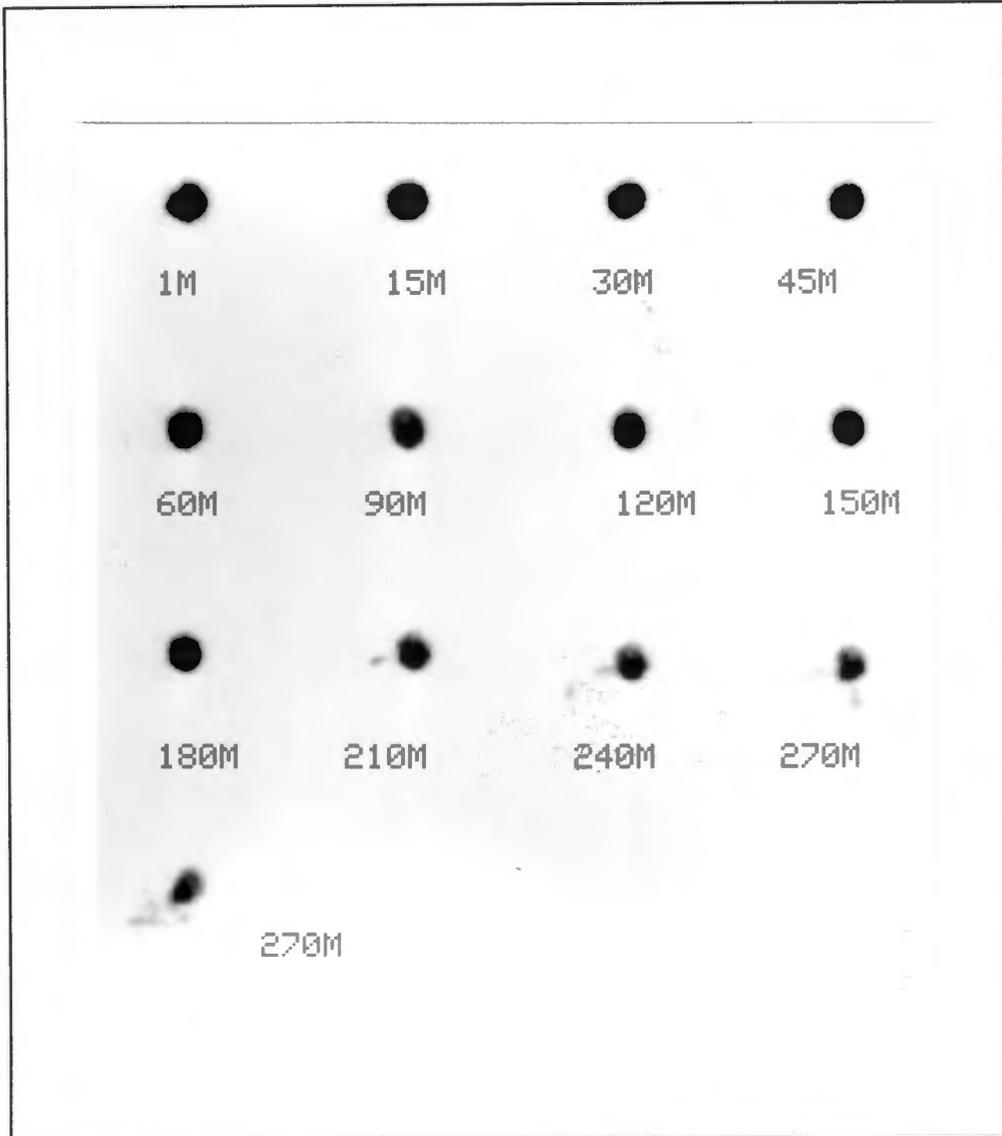


Figure 31b. Far more rapid emptying with the radioactivity being distributed throughout the stomach are features noted on the static images at follow-up in the same patient.

Figure 32. The static images show prolonged proximal stomach retention of the radioactive meal in a patient with opioid overdose. The patient did not return for a control study.



SUMMARY:

1. A mainly proximal pattern of distribution of the radioactivity in the stomach is associated with longer gastric emptying half-times than distribution in other areas of the stomach in overdose studies.
2. No significant differences were found in gastric emptying half-times for the different distribution patterns among the controls.
3. The distribution patterns were significantly different for overdose and control studies.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT

As indicated in the Methods section oro-caecal and small intestinal transit times were calculated from the time of ingestion of the radiopharmaceutical and the time that the leading edge of activity passed into the duodenum respectively. The time it took to reach the terminal ileum - caecal region was taken as the transit time. In those patients in whom it took longer than the imaging time to reach the small intestine the final imaging time was regarded as the end time. The most distal level reached by the radioactivity was identified and placed into one of 3 main regional categories: stomach to and including jejunum; ileum; and terminal ileum - caecum.

Oro-caecal and small intestinal transit times are discussed separately for each drug group in turn. Because of technical difficulties with the stored data, 1 tricyclic overdose and 2 control tests could not be processed. This made the total sample size 103 after overdose and 83 at control.

TRICYCLIC ANTIDEPRESSANTS

The transit times in minutes were:

ORO-CAECAL

AFTER OVERDOSE: 240 (median) 180 - 300 (IQR) n = 30

AT CONTROL: 180 (median) 120 - 210 (IQR) n = 25

The oro-caecal transit times after overdose were significantly longer than those at control ($p = 0.0003$; Mann-Whitney U test).

SMALL INTESTINAL TRANSIT TIME:

AFTER OVERDOSE: 217 (median) 135 - 266 (IQR) n = 30

AT CONTROL: 135 (median) 90 - 209 (IQR) n = 25

The small intestinal transit times were significantly longer after overdose than at control ($p = 0.006$; Mann-Whitney U test).

In 15 patients radioactivity did not reach the terminal ileum-caecal region (see Table 15).

TABLE: 15

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	11	4	15
Control	0	1	23

CARBAMAZEPINE

The transit time in minutes were:

ORO-CAECAL TRANSIT

AFTER OVERDOSE: 300 (median) 240 - 300 (IQR) n = 15

AT CONTROL: 150 (median) 90 - 180 (IQR) n = 11

The oro-caecal transit times after overdose were significantly longer than those at control ($p = 0.0002$; Mann-Whitney U test).

SMALL INTESTINAL TRANSIT TIME:

AFTER OVERDOSE: 225 (median) 150 - 255 (IQR) n = 15

AT CONTROL: 105 (median) 75 - 135 (IQR) n = 11

The small intestinal transit times were significantly longer after overdose than at control ($p = 0.021$; Mann-Whitney U test).

In thirteen out of 15 patients the radioactivity failed to reach the ileo-caecal region (see Table 16).

TABLE: 16

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	5	8	2
Control	0	0	11

PHENYTOIN

The transit times in minutes were:

ORO-CAECAL TRANSIT

AFTER OVERDOSE: 300 (median) 245 - 300 (IQR) n = 12

AT CONTROL: 150 (median) 60 - 210 (IQR) n = 7

The oro-caecal transit times after overdose were significantly longer than those at control ($p = 0.007$; Mann-Whitney U test).

SMALL INTESTINAL TRANSIT TIME:

AFTER OVERDOSE: 252 (median) 197.5 - 270 (IQR) n = 12

AT CONTROL: 135 (median) 30 - 180 (IQR) n = 7

The small intestinal transit times were significantly longer after overdose than at control ($p = 0.012$; Mann-Whitney U test).

In 6 patients the radioactivity did not reach the ileo-caecal region (see Table 17).

TABLE: 17

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	2	4	6
Control	0	0	7

PARACETAMOL

The transit times in minutes were:

ORO-CAECAL TRANSIT

AFTER OVERDOSE: 240 (median) 180 - 270 (IQR) n = 29

AT CONTROL: 150 (median) 90 - 210 (IQR) n = 27

The oro-caecal transit times after overdose were significantly longer than those at control ($p = 0.002$; Mann-Whitney U test).

SMALL INTESTINAL TRANSIT TIME:

AFTER OVERDOSE: 180 (median) 150-255 (IQR) n = 29

AT CONTROL: 120 (median) 89-209 (IQR) n = 27

The small intestinal transit times were significantly longer after overdose than at control ($p = 0.016$; Mann-Whitney U test).

The leading edge of radioactivity failed to reach the ileo-caecal region in 13 out of 29 patients after overdose (see Table 18).

TABLE: 18

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	9	4	16
Control	0	1	26

OPIOIDS

The transit times in minutes were:

ORO-CAECAL TRANSIT

AFTER OVERDOSE: 270 (median) 210 - 270 (IQR) n = 17

AT CONTROL: 120 (median) 120 - 150 (IQR) n = 13

The oro-caecal transit times after overdose were significantly longer than those at control ($p = 0.0006$; Mann-Whitney U test).

SMALL INTESTINAL TRANSIT TIME:

AFTER OVERDOSE: 180 (median) 150 - 225 (IQR) n = 17

AT CONTROL: 119 (median) 75 - 149 (IQR) n = 13

The small intestinal transit times were significantly longer after overdose than at control ($p = 0.004$; Mann-Whitney U test).

The head of the radioactive meal did not reach the ileo-caecal region in 9 out of 17 patients (see Table 19).

TABLE: 19

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	8	1	8
Control	0	1	12

THE ENTIRE GROUP

The transit times for the entire group of patients in minutes were:

ORO-CAECAL TRANSIT

AFTER OVERDOSE: 270 (median) 210 - 300 (IQR) n = 103

AT CONTROL: 150 (median) 90 - 210 (IQR) n = 83

The oro-caecal transit times after overdose were significantly longer than those at control ($p < 0.00001$; Mann-Whitney U test).

SMALL INTESTINAL TRANSIT TIME:

AFTER OVERDOSE: 209 (median) 150 - 255 (IQR) n = 103

AT CONTROL: 120 (median) 89 - 180 (IQR) n = 83

The small intestinal transit times were significantly longer after overdose than at control ($p < 0.00001$; Mann-Whitney U test).

Table 20 demonstrates a hold-up of radioactivity in the stomach and proximal small intestine in 35 out of 103 patients with activity in a further 21 patients being retained in the ileum.

TABLE: 20

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	35	21	47
Control	0	4	79

The radioactive meal fails to traverse the small intestine in 54% of all the patients at overdose as compared with less than 5% at control. In a third of patients at overdose the radioactivity is retained in the stomach or proximal part of the small intestine. This emphasises the marked delay in oro-caecal and small intestinal transit that occurs with overdose with all the drugs tested. The null hypothesis that intestinal transit is not retarded by poisoning is rejected.

THE RELATIONSHIP BETWEEN INTESTINAL TRANSIT TIMES, DRUG LEVELS AND THE DIFFERENT DRUG GROUPS

ORO-CAECAL TRANSIT TIMES

Multiple regression analyses show that standardised drug levels ($p = 0.82$) and the different drug groups ($p = 0.09$) had no significant relationship with oro-caecal transit times. Gender ($p = 0.21$) and age ($p = 0.06$) also had no influence on oro-caecal transit times. The analysis of variance for the full regression showed an R-squared (coefficient of determination) of 0.057 (5.7%).

No difference in the influence of the various drugs were found at control ($p = 0.73$).

SMALL INTESTINAL TRANSIT

Drug levels ($p = 0.10$) and the different drug groups ($p = 0.36$) did not correlate significantly with small intestinal transit times (multiple regression analysis). Age and gender also made no significant contribution to either oro-caecal or small intestinal transit times.

R-squared for the full multiple regression analysis on small intestinal transit times was 0.054 (5.4%).

THE RELATIONSHIP BETWEEN ORO-CAECAL, SMALL INTESTINAL TRANSIT AND GASTRIC EMPTYING

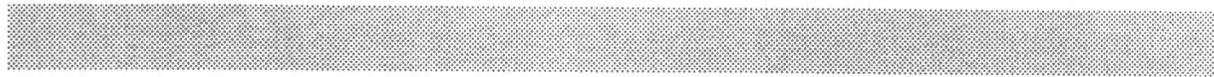
Multiple regression analyses using gastric emptying as the independent variable show a significant correlation between gastric emptying half-times and oro-caecal ($p = 0.0091$) and small intestinal ($p = 0.0125$) transit times.

R-squared = 0.073 (7.3%).

The same analysis found less significant correlation for the oro-caecal ($p = 0.052$) and small intestinal ($p = 0.091$) transit times at control. R-squared = 0.05 (5%).

SUMMARY:

1. Both oro-caecal and small intestinal transit times were significantly prolonged at overdose when compared with the times determined at control.
2. The radioactive meal was delayed at various levels in the small intestine and stomach, and in the majority (54%) of patients failed to reach the terminal ileum at overdose.
3. Drug levels, the different drug groups, age and gender had no significant correlation with oro-caecal or small intestinal transit times.



DISCUSSION

VALIDITY AND RELIABILITY OF THE GASTRIC MOTILITY SCORING SYSTEM

Gastric motility was evaluated using the scoring system described in "Patients and Methods" section on the basis of the intra-observer reliability determined before the studies were read. After the author examined all the studies an inter-observer reliability assessment was performed. Although the intra-observer reliability was very good, the inter-observer readings were significantly different between the author and the consultant, and the consultant and the technologist. These were the three most experienced observers (in terms of general nuclear medicine experience though not with the method itself). This suggests that the method of scoring is somewhat unreliable as the two most qualified nuclear medicine physicians differed significantly. The consultant gave higher scores and scored more contractions per study than the author. The fact that the technologist was given a longer practical demonstration may account for his scores not being significantly different from those of the author.

However, the motility scores awarded by the author, consultant and technologist were significantly higher when measured after overdose compared to those determined for controls (See **Figure 2**). This lends support to the validity of the method as this trend is expected. The registrar, the least experienced observer, obtained only a small increase in control over overdose scores. The consultant recorded greater differences between the overdose and control groups than the author although the overdose-control slopes were similar for the three experienced observers. This suggests that if the author erred his assessment was probably conservative.

Despite subjective factors influencing the outcome, the test provides some evidence for the scoring system's validity and reliability. But the registrar's readings detract from its validity and the consultant's scores from its reliability as the former failed to demonstrate the expected increase in the scores for the controls and the latter awarded scores that were significantly higher than the author and technologist. The observers' lack of experience with the method, except for the author, and the short "training" period (except for the technologist) could have contributed to the lack of inter-observer reliability and the validity of the scoring method.

METHODOLOGICAL CONSIDERATIONS AND PROBLEMS

A number of factors might bias the results of my study. I shall discuss each of these in turn.

1. PATIENT SELECTION AND TERMINATION OF STUDIES

1. Patients were selected on the basis of the type of drug they ingested. I felt that a randomisation process was unnecessary as poisoning and the presentation of patients to the Emergency Unit could themselves be regarded as random processes. Therefore, this factor was unlikely to bias the results.

2. Patients who took anticonvulsants were selected as part of a single group. Out of thirty patients selected only three had ingested phenobarbitone. This is probably due to fewer patients being treated with phenobarbitone than with carbamazepine and phenytoin. The decrease in barbiturate poisoning was also noted by Nogue et al (1992) who reported a decline from 54% in 1980 to 2% in 1990. The omission of patients in the phenobarbitone group was unlikely to affect significantly the outcome of the study as the number of patients in this group was too small to draw meaningful conclusions.

3. Although most patients were imaged over a period of five hours ($n = 67$), studies were terminated before this time if the patient's condition deteriorated. In all of these patients except one who had the study terminated at 90 minutes, the studies were stopped at between 2.5 and 4.5 hours - well after the gastric emptying half-times for liquids and solids recorded in healthy volunteers, and those recorded for control studies in my patients. Thus the results could not have been biased by this problem.

2. FASTING

Patients in my study received 100 to 200 ml of activated charcoal slurry followed by a radiopharmaceutical with 20 ml of water. The vast majority of patients had nothing to eat for at least 3 to 4 hours prior to drinking the radiopharmaceutical. A number of them had gastric lavages done at least 1 hour before imaging was commenced. Each patient fasted for a minimum of 4 hours before the control study. I had no way of determining, however, what part of the interdigestive myoelectric complex patients were in at the time of performing gastric scintigraphy. The varying rates of gastric emptying of bland liquids ingested after a period of fasting appear to depend, at least in part, on the phase of the interdigestive myoelectric complex during which they were ingested (Oberle et al 1990).

3. CONTROL STUDIES

All but 19 of the total group of patients ($n = 104$) who were recruited to the first part of the study returned for a second study. Therefore, virtually each patient acted as his/her own control. Those patients who were taking therapeutic doses of tricyclic antidepressants and anticonvulsants failed to reveal a significant difference in gastric emptying half-times when compared with patients who were not taking any drugs at the time of the control study. This suggests that the therapeutic doses did not significantly alter gastric emptying half-times which were considerably shorter than those obtained in the same patients when they presented after ingesting overdoses. Therefore, this factor was not likely to bias the results.

During the control studies certain of the patients wanted to sit up or walk a short distance to the television after the first hour was completed. Although Moore et al (1989 and 1990) reported increases in gastric emptying rates in sitting, standing and walking when compared with the supine position, the median gastric emptying half-

times for controls of 40 (IQR = 24 - 70) minutes falls in large part within the first hour during which patients were requested to lie quietly. Therefore, the results were unlikely to be affected significantly by this factor.

4. ACTIVATED CHARCOAL

In certain patients it was difficult to administer the same amount of activated charcoal before the control study as the they received following the overdose. Although attempts were made to keep the quantity given constant for both studies, vomiting of ingested charcoal as well as refusal by a minority of patients to drink all of the charcoal, made this difficult. I have not been able to find any evidence to suggest that activated charcoal influences gastric emptying rates. Moreover, the relatively small differences in quantity of activated charcoal ingested are unlikely to affect gastric emptying rates sufficiently to bias the results. However, the effects, if any, of activated charcoal on gastric emptying in healthy subjects should be ascertained in a future study.

5. BLOOD LEVELS

I measured drug levels in the blood and urine in all my patients. These levels were done only once, usually at the beginning of each study. This meant that I had no way of telling whether the levels in the blood were rising, had peaked or were falling during the 5 hour scanning period. Although this made it difficult to relate gastric emptying half-times to the blood levels, increased blood levels had no statistically significant relation to gastric emptying rates.

6. STRESS

During the initial study patients were often under a great deal of stress due to acute depression, anxiety or remorse that accompanied the act of self-poisoning, or that followed in its wake. By the time the control studies were done the majority of patients had improved and their moods had lifted. I had no way of controlling for the different mental states and the impact that these had on the respective gastric emptying rates. Stress, anxiety, fear and pain are thought to delay gastric emptying and inhibit gastrointestinal motility. Therefore, stress might well have influenced the gastric emptying rates and intestinal transit times of patients after overdose. This requires further study.

7. IMAGING

1. TIME BETWEEN INGESTION AND SCINTIGRAPHY

The times of drug ingestion volunteered by the patients or those who accompany them are notoriously unreliable. The times between drug ingestion and the commencement of the scan was approximately 13 hours on average. There was usually a delay of approximately 1 to 2.5 hours from the time the patient presented to the Emergency Unit to the time of scintigraphy. However, in a small number of patients this delay lasted for up to 5 hours. This usually occurred in the seriously ill patient who had to be clinically stabilised before the scintigraphy could be started.

Despite these delays the presentation time appears to be considerably longer in my patients than in certain other studies. Kulig et al (1985) reported a mean time from ingestion to hospital presentation of 3.3 hours while Soslow (1981) found a mean time of over 2 hours. These are considerably shorter periods than in my study.

Socio-economic levels, modes of transport, the accessibility of the hospital and other referral centres are all factors that could influence the ingestion to presentation time and thereby the time at which scintigraphy begins. A retrospective study on patients with paracetamol poisoning done at Groote Schuur Hospital found a median time of 5 hours (0.5 - 12 hours) between the time of drug ingestion and assessment by the doctor (Monteagudo and Folb 1987).

The majority of my patients came from the lower socio-economic levels and lived several kilometres away from the hospital. Transport is costly and finding transport at night is difficult when there is no motor vehicle available. Using public transport in these areas is not only expensive but also dangerous, especially at night. The ambulance service is erratic in these areas and this compounds the problem. All these factors prolong the time that it takes for the patient to present to hospital.

2. ^{99m}Tc TIN COLLOID

The radiopharmaceutical and method of imaging were standard for liquid gastric emptying and intestinal transit studies. The ^{99m}Tc tin colloid was administered orally or through a nasogastric tube in comatose patients in a small volume of water. The volume was kept small (20 ml in all) so as not to influence gastric emptying rates.

However, the possibility exists that some of the tin colloid might adhere to areas of mucosal trauma caused by the gastric lavage. This could falsely prolong gastric emptying times. Saetta and Quinton (1991) found bruising at the cardia at endoscopy in four out of seventeen patients following gastric lavage. Fixed areas of radiocolloid may also remain in the stomach after most has cleared. I had no way of distinguishing between activity in the lumen and that stuck to the mucosa. But the

fact that no significant differences in gastric emptying half-times were found when comparing the patients who had gastric lavages with those who did not suggests that colloidal adherence to the mucosa was not a significant factor in delaying gastric emptying. The use of another marker such as ^{99m}Tc -DTPA may be considered for future studies of this kind.

3. TWO DIFFERENT CAMERA SYSTEMS

It was decided to image those patients who were well enough in the department of nuclear medicine and consent was obtained for mobile imaging of moribund patients in the respiratory intensive care unit. Patients were imaged on an Elscint gamma camera in the nuclear medicine department and those in the intensive care unit were scanned on a General Electric mobile camera. All the control studies were done in the nuclear medicine department on the Elscint system. This meant that certain patients had their initial and control studies done on different cameras. Although this is not ideal the nuclear medicine department has only one mobile camera. The service demands of the department during the day made this camera unavailable for control studies. Therefore these studies had to be done on the Elscint cameras. However, quality control of the cameras done on a daily and weekly basis showed the different cameras to be equally reliable. This factor was thus unlikely to have a significant impact on the estimation of gastric emptying and small intestinal transit times. Ideally, the same camera should be used for all the studies.

4. THE GEOMETRIC MEAN METHOD VERSUS ANTERIOR COUNTS

Studies done in the nuclear medicine department included both anterior and posterior projections permitting geometric mean corrections of gastric emptying

data. Those done in the intensive care unit consisted of anterior projections only making only anterior data available for determining gastric emptying half-times. I dealt with this problem by determining the relation between gastric emptying half-times derived from anterior data and the geometric mean corrected ones. The correlation was better than expected permitting the use of the gastric emptying half-times calculated on anterior counts alone for all the analyses.

As I have already noted depth correction is important because the stomach lies anteroposteriorly in the abdomen. Tothill et al (1978) performed phantom studies which showed that the geometric mean of the counts were dependent only on overall phantom thickness and independent of the depth of the radioactive source. Tothill et al (1978) demonstrated an increase in detection efficiency by the anterior detector on average of 26% for solids and 16% for liquids in healthy volunteers. This resulted in a commensurate underestimation of the gastric emptying rate. The regression lines for anterior versus geometric corrected gastric emptying times were $R = 0.89$ for solids and 0.96 for liquids (Tothill et al 1978). These results were confirmed by a study which showed that gastric emptying rates were underestimated by 10.3 to 34.2% for solids, and 7.9 to 15% for liquids (varying with meal size) when anterior counts are used to calculate them (Christian et al 1980).

However, more recent studies have shown only slight differences between anterior and geometric mean corrected gastric emptying rates for liquids (Moore et al 1985; Fahey et al 1989). Moore et al (1985) and Fahey et al (1989) while confirming the underestimation of gastric emptying rates for solid phase gastric emptying using anterior data alone, demonstrated only slight differences between the anterior and geometric mean corrected emptying rates for liquids. The very close correlation between gastric emptying rates derived from anterior data and the geometric mean method in my study confirms these findings.

5. ANTRAL MOTILITY

In many instances there was so little antral activity that contractility in this area could not be assessed. Stacher et al (1987; 1992) use a semi-solid meal to overcome this problem. In studies of my patients with prolonged gastric emptying times, the bulk of activity remained in the proximal half of the stomach for considerable periods of time. In those who emptied within the normal time limits, activity passed through the pylorus rapidly without sufficient retention in the antrum to examine the area properly.

6. DECAY CORRECTION

It has been stated that corrections for decay are required for short half-life radionuclides like ^{99m}Tc (6 hour half-life) to preclude an underestimation of gastric emptying times, particularly in patients with prolonged gastric emptying (Christian et al 1983). I did not correct for radioactive decay in my study. This was not deemed necessary as I did not base gastric emptying rate calculations on the counts in the initial gastric image. I used the counts inside and outside of the stomach in each individual image to determine the percentage of activity remaining in the stomach at that time. Therefore, each image was analysed independently of the other images in the study. It was thus critical that all the activity in the stomach and intestines was in the field-of-view. This at times necessitated two images, particularly when using the mobile camera.

7. POSITION OF RADIOACTIVITY IN THE SMALL INTESTINAL

Despite careful observation and constant review of the preceding images in sequence in certain patients it was difficult to determine what level the radioactivity had reached in the small bowel. This evaluation was more difficult in patients in whom the radioactivity had not passed into the large bowel or ileo-caecal region where progressive accumulation invariably occurred prior to passage into the caecum.

8. THE RELIABILITY TEST FOR GASTRIC MOTILITY

The reliability test for the gastric motility scores became more complex than I initially expected. If the study is repeated more time should be spent on training the different observers. Before and after demonstration scores and a third score, subsequently, might have demonstrated the benefits of the extra training and experience on reliability and validity.

DEMOGRAPHIC FEATURES

AGE AND GENDER

The age and gender patterns in my group of patients is, in the main, similar to demographic studies on patients with self-poisoning noted elsewhere. The average age in my patients was 29.3 +/- 10.9 years. Young females predominated. Patients who took tricyclic antidepressants were significantly older than the rest of the patients with an average age of 35.7 +/- 11.9 years. This was probably due to the fact that a number of these patients were on longterm treatment for depression. By contrast patients with paracetamol poisoning were significantly younger (mean age 24.2 +/- 8 years) than the rest. The vast majority of them were young females. Paracetamol is a cheap drug to which patients have easy access. The ready availability makes it a drug of choice. Patients on tricyclic antidepressants or anticonvulsants tend to use these drugs because they are readily available.

Although there were also a greater number of females in a Danish study done between 1979 and 1985 the age pattern was slightly different (Worm and Steentoft 1990). Most patients fell into the 30-39 and 40-49 year groups each of which included twice as many women. Men dominated only in the 20-29 year group. The average age of patients in a Spanish study done over a ten year period remained constant at 36 years. In a study of 592 patients with poisoning Kulig et al (1985) found the mean age to be 29.3 years. Therefore, my study appears representative of patients with self-poisoning. The age and gender profiles are typical (with minor variations) of those found in other studies.

Whether the ageing process affects gastric emptying has also been a question that has spawned different answers (Gainsborough et al 1993; Moore et al 1983).

In the present study age and gender played no role in influencing gastric emptying. Regression analysis shows no correlation between age and gastric emptying at the time of the overdose and at the control study. No correlation was found between gender and gastric emptying times after overdose, although a significant correlation was found at control. A wider variation was noted among female patients.

GASTRIC EMPTYING AND SMALL INTESTINAL TRANSIT

The results show a marked delay in gastric emptying following overdose of all the drugs studied. This was demonstrated by the conventional method of using the time-activity curves to determine gastric emptying half-times which were then compared with those in the control group. This method is simple and provides relatively accurate results. However, it is based on those measurements taken before and up to the time that half of the gastric activity has passed into the intestine. In patients who did not empty half of the gastric activity by the time the scanning was completed ($n = 14$) simple extrapolation was used to determine half-emptying times. This proved a problem in patients in whom the time-activity curves showed only a very slight decline. Gastric emptying half-times could have been overestimated in these cases. Interpolation was used in 2 patients who had a repeat image at 10 hours.

I attempted to confirm the results by integrating the curves as an additional measure of gastric emptying. The marked difference between the overdose and control studies was replicated using the integration method to measure the areas under the curves of overdose and control studies and comparing them. As this method uses all the points on the curve it therefore utilises a greater amount of data than that used for the time-activity curve derived half-times. It therefore reduces the uncertainties of the measure. Moreover, this method does away with the need for extrapolation. However, integration had the limitation of using the same time endpoint for all the studies. A number of patients had not emptied their stomachs by this time and varying amounts of intragastric radioactivity remained.

There are significant and often gross differences between gastric emptying times obtained following overdose and those from control studies. These findings have

profound implications for our understanding of the pathophysiology of poisoning and the clinical management of the patients.

THE EXTENT OF THE DELAY IN GASTRIC EMPTYING

Radioscintigraphic methods for measuring gastric emptying half-times have proven to be both physiological and accurate. Gastric emptying half-times for liquids in healthy volunteers have mean values of between 15 and 55 minutes with the radionuclide imaging techniques (Malmud et al 1982; Collins 1983; Brophy et al 1986; Datz et al 1987; Christian et al 1990; Caner et al 1991; Datz et al 1991; Dapoigny et al 1991). Considerable intra- and inter-individual differences have been found in gastric emptying rates (Petring and Flachs 1990). Liquid emptying usually follows an exponential pattern (Collins et al 1983). In scintigraphic studies reported over the last decade mean gastric emptying half-times for solids in healthy subjects have varied between 58 and 97 minutes (Brophy et al 1986; Datz et al 1987; Collins et al 1988; Datz et al 1990; Christian et al 1990; Mones et al 1993). Both the liquid and solid mean times include studies with male and female subjects.

My patients were given a liquid meal. The mean values for the control studies fell within the range obtained in the above-mentioned studies for liquid emptying. However, the median values obtained for the study following ingestion of the drugs were 99.5 (IQR 54.5 - 208.25) minutes. **A number of the patients in my study were found to have grossly increased gastric emptying half-times: 12 patients had half-times greater than 300 minutes; 14 greater than 200 minutes and 21 greater than 120 minutes. Therefore 47 patients had markedly prolonged gastric emptying half-times.** This was far in excess of the half-times obtained in all the studies on normal subjects for liquid emptying. If residual solid matter including pieces of tablets were present at the time that I administered the

radiocolloid liquid to my patients then I would expect emptying half-times to approximate those obtained with solid meals. Nevertheless, half-times in many patients in my study were far greater than those demonstrated in the studies mentioned above. This I believe is principally due to the effect of the poisoning.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT

There was a marked delay in oro-caecal and small intestinal transit in patients after overdose when compared with the control tests. A visual evaluation was made of the passage of the radioactive meal into and through the small intestine as described in the "Patients and Methods" section. An outstanding feature of this assessment was the fact that in over half (54%) of patients the radioactivity did not reach the terminal ileum at the end of the 5 hour scanning period. The majority of these patients (34% of the total scanned) demonstrated very slow movement with retention of radioactivity in the proximal half of the small intestine or stomach for this entire period. Despite the fact that the differences between the scans after overdose and those at control were reduced by using the end of the scanning period as the "caecal" time in tests in which the radioactivity did not reach the caecum, they remained considerable. The oro-caecal and small intestinal transit times were significantly longer after overdose than at control for all the drug groups studied.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT DELAY

Scintigraphy is proving to be a simple and reliable method of measuring small intestinal transit times. Mean values for small intestinal transit times for liquids were measured at 73 to 81 minutes (SD +/- 6.5 and +/- 11) (Prokop et al 1988; Caride et al 1984). Using twice the concentration of lactulose, Sciarretta et al 1994 found a mean oro-caecal values of 45 minutes (range 10-75). Mean and median values for

oro-caecal transit times measured by the lactulose hydrogen breath studies range between 66 and 105 minutes (Harris and Martin 1994; Soffer and Launspach 1993; Basilisco et al 1989; Keeling and Martin 1987). Intra- and inter-subject variations have been reported (Caride et al 1984; McCallum 1984).

Patients in my study were given a liquid meal of ^{99m}Tc -colloid in water. Oro-caecal and small intestinal transit times were markedly prolonged when compared with the studies quoted above. Median oro-caecal and small intestinal transit times were 270 minutes (IQR 210-300) and 209 minutes (150-255) respectively. The medians for the individual drug groups ranged between 240 and 300 minutes for oro-caecal transit and 180 and 252 minutes for small intestinal transit. All of these were significantly longer than their respective control values. This suggests that the poisoning and/or related factors inhibited gastrointestinal motility.

The intestinal transit times were longer in the tests done at control than in the studies mentioned above. The medians and interquartile ranges at control were 150 minutes (90-210) for oro-caecal transit and 120 minutes (89-180) for small intestinal transit. The use of lactulose for the hydrogen breath test and in the liquid radioactive meals (Sciarretta et al 1994; Prokop et al 1988; Caride et al 1984) may well have reduced intestinal transit times. In addition, the activated charcoal administered to my patients immediately prior to the control study may have retarded intestinal transit. Krenzelok et al (1985) reported a mean total gastrointestinal transit time of 23.5 hours in healthy subjects who ingested activated charcoal.

CLINICAL SIGNIFICANCE OF THE DELAY IN GASTRIC EMPTYING AND SMALL INTESTINAL TRANSIT

As the small intestine is the chief site of drug absorption the rate of absorption depends principally on the rate of gastric emptying which determines the time for passage into the small intestine (Rowland 1978), the contact time with the intestinal mucosa and the rate of drug dissolution. Rosenberg et al (1981) maintain that the delay in absorption due to drug overdose delays the onset or peak intensity of the drug's action. Delayed drug absorption may be due to gastrointestinal hypomotility and/or the formation of a poorly soluble mass of drug (Rosenberg et al 1981). Delayed gastric emptying was almost invariably associated with both gastric hypomotility and retarded intestinal transit in patients in my study. The gastroparesis would have delayed entry into the small intestine of whatever proportion of the poison was present in the stomach at the time of its onset. This would inhibit absorption of this fraction. However, the portion of poison that entered the small intestine prior to gastroparesis could remain there for considerable periods of time exposed to the absorptive mucosal surface. But absorption may be diminished by the intestinal hypomotility.

Whether and to what extent these factors could affect the clinical presentation was beyond the scope of my study. However, Rosenberg et al 1981 argue that retarding gastrointestinal motility may lead to a decrease in the rate but an increase in the amount of drug absorbed. It could also result in prolonged, erratic and delayed absorption. This theoretically would affect the clinical presentation and course of poisoned patients.

A significant correlation was found between gastric emptying half-times and oro-caecal ($p = 0.009$) and small intestinal times ($p = 0.012$). Therefore, patients with the greatest gastric emptying delay also had the longest intestinal transit times. This

suggests that poisoning (and/or related factors) caused a paresis of both stomach and small intestine. Whether and to what extent the absorptive capacity of the small intestine is affected under these conditions is not known and was beyond the scope of this study.

The marked gastric emptying delay experienced by many patients in my study following poisoning with tricyclic antidepressants, carbamazepine, phenytoin, paracetamol and paracetamol-opioid compounds means that measures for removing or neutralising these drugs can be instituted several hours after ingestion if they are still present in the stomach. Saetta and Quinton (1991) found endoscopic evidence of residual solids including tablet fragments in 15 out of 17 patients after gastric lavages performed 1 to 4.5 hours after drug ingestion. On the other hand, if a considerable quantity of the poison has already passed into the small intestine before treatment is instituted then gastric decontamination will be less or ineffective. Activated charcoal will neutralise the intragastric poison but it will be denied access to the poison already present in the small intestine.

MANAGEMENT OF POISONING BY GASTRIC DECONTAMINATION

Patients in my study demonstrated significant gastric emptying delay following overdose. My findings indicate that gastric contents take a considerable time to pass into the small intestine. This implies that after an initial amount of the drug has been absorbed a proportion remains in the stomach unavailable for absorption by the small intestine for up to several hours. Alternatively, gastric emptying is delayed from the outset, possibly due to stress, with comparatively small amounts of the drug passing into the small intestine at a relatively slow rate. My study has shown that the delay in gastric emptying occurs in self-poisoning in patients who have taken any of the five different groups of drugs tested. Surprisingly, patients who

took paracetamol also had prolonged gastric emptying times. The delay in gastric emptying therefore prolongs the time in which to eliminate the drug from the body or to render it unabsorbable by the small intestine. But as I have already pointed out, the gastric emptying delay will limit access to that fraction of poison that has passed into the small intestine prior to decontamination measures being instituted.

1. GASTRIC LAVAGE

The question of whether to carry out gastric lavage on patients who present several hours after poisoning remains controversial. I shall summarise the different points of view. Some suggest that it is an important part of management when :

1. patients present soon (within 1 to 2 hours) after drug ingestion (Comstock 1981; Kuling et al 1985; Lovejoy and Linden 1991);
2. patients have ingested large quantities of paracetamol which may overwhelm the adsorptive capacity of activated charcoal (Neuvonen and Olkkola 1988);
3. patients have ingested overdoses of drugs that delay gastric emptying (Dziukas and Vohra 1991).

Others discourage the use of gastric lavage pointing out that there has been no measurable clinical benefit, that it has resulted in a number of serious complications (Sullivan et al 1990; Merigian et al 1990; Linden and Lovejoy 1991). It has been found to be inefficient in removing gastric contents including tablets and has been associated with an increase in blood concentrations of the drugs (Comstock 1981; Watson et al 1989; Seatta and Quinton 1991; Serena et al 1994).

The delay in gastric emptying that was found in my patients might support the contention that decontamination is necessary. However, the problems outlined above make it difficult to justify the use of gastric lavage even in patients with prolonged gastric emptying. Possibly the only circumstance in which gastric lavage is useful is the obtunded patient who presents within an hour after ingestion. Such early presentation occurred rarely in my study. If gastric lavage is indicated, a sensible precaution would be to administer activated charcoal before the lavage. This could be done through a nasogastric tube in the obtunded. The activated charcoal would adsorb the poison including that portion that may pass into the small intestine as a result of the lavage. A second dose of charcoal could be given after the gastric lavage if this was deemed necessary.

2. EMESIS

Although induced emesis reduces the toxic load it has been shown to be inefficient (Saetta et al 1991; Seatta Quinton 1991), and there have been a number of reports of complications with the use of both apomorphine and syrup of ipecacuanha (Wheeler-Usher et al 1986; Czajka and Russel 1985). Moreover, they have not been effective in altering the clinical course of poisoned patients (Kulig et al 1985; Sullivan et al 1990). In addition, Saetta et al (1991) demonstrated an increase in aboral emptying of the stomach following the use of ipecacuanha making more poison available for absorption by the small intestine.

My findings suggest that a large proportion of poison and gastric contents could remain in the stomach for several hours. This makes patients who are treated with emetics susceptible to aspiration and pulmonary complications. The use of emetics in outlying clinics, and other primary health centres therefore cannot be supported especially since a dose of activated charcoal should adsorb the intragastric poison

giving sufficient time for the patient to reach a poison centre for thorough assessment.

3. ACTIVATED CHARCOAL

Despite reservations being expressed by certain clinicians as to whether activated charcoal is of real clinical benefit (Vale and Proudfoot 1993; Palatnick and Tenenbein 1992; Tenenbein 1991; Merigian 1990;), it is generally accepted that either multiple or single dose therapy is the mainstay in the treatment of poisoning (Jawary et al 1992; Palatnick and Tenenbein 1992; Smolinske 1990; McNamara RM 1989; Neuvonen and Olkkola 1988; Olkkola and Neuvonen 1984; Levy 1982; Berlinger et al 1983; Berg et al 1982; Goldberg and Berlinger 1982). However, there have been an increasing number of reports of complications with the use of multiple dose activated charcoal including several of fatal pulmonary aspiration (Benson et al 1989; Harsch 1986; Pollack et al 1981), and charcoal induced bowel obstructions (Ray et al 1988; Anderson and Ware 1987; Watson et al 1986).

The delayed gastric emptying in my patients means that the rate of absorption of the residual intragastric poison is reduced. Activated charcoal could therefore be given up to several hours after ingestion of any of the poisons that I tested. A considerable proportion of the drug might be accessible for binding to the activated charcoal in the stomach thereby reducing its absorption. Although desorption of the drug from the activated charcoal may occur during the prolonged period in the stomach, the large activated charcoal-to-drug ratio would conceivably result in reabsorption of the drug to the charcoal.

A large single dose should be enough to adsorb the toxic gastric contents while at the same time minimising the risk of vomiting triggered by repeated doses of

activated charcoal. The risk of vomiting and aspiration is enhanced in patients who have diminished gastric motility or in whom the poison itself causes repeated vomiting. All of my patients were at risk because of the prolonged retention of gastric contents. Those with paracetamol and opioid poisoning were also prone to vomiting. Furthermore, the intestinal hypomotility in many of my patients put them at risk of developing intestinal obstruction. My patients were therefore particularly susceptible to the complications that could occur with repeated doses of charcoal. Although these complications are relatively rare they are a high price to pay when treating patients for mild to moderate poisoning with an agent the clinical efficacy of which is still in doubt. There were no complications of this nature reported in my group of patients.

Other than a single dose of activated charcoal and the use of gastric lavage in selected obtunded patients it would appear that supportive care and specific antidotes are sufficient. The body's response to overdose might contain the drugs within the stomach for considerable periods of time permitting only a slow release into the small intestine. This could result in slower absorption in smaller quantities with a longer time to peak and lower peak concentrations of the drug in the circulation. (This hypothesis will have to be tested by measuring serial blood levels of a drug that empties from the stomach at different rates in different groups of patients - possibly after the one group is given a prokinetic agent.) Gastric decontamination procedures especially gastric lavage and induced emesis tend to disrupt the body's response to poisoning. Some clinicians, however, persist with gastric lavage in potentially life-threatening situations claiming that removal of a proportion of the drug is better than removing none of it.

POSSIBLE CAUSES OF DELAYED GASTRIC EMPTYING AND PROLONGED SMALL INTESTINAL TRANSIT

1. THE DRUGS

Only 2.5% of the gastric emptying half-time was explained by all of the variables tested. The latter included the different drugs, gender, age and the drug level. Notwithstanding the fact that certain of the groups chosen - the tricyclic antidepressants and the opioids are reported to exhibit powerful inhibitory effects on gastric emptying and motility, none of the various drug groups had a significantly different effect on the delay in gastric emptying than any of the others at overdose levels.

Although the tricyclic antidepressant and opioid overdoses were expected to cause a greater delay in gastric emptying and small intestinal transit than the other drugs, this did not prove to be the case. Patients who ingested paracetamol and the anticonvulsants which are not considered to have a marked effect on gastrointestinal motility had gastric emptying half-times and intestinal transit times which were not significantly different from those who took the other drugs.

Oro-caecal and small intestinal transit times were also not significantly influenced by factors like the the different drug types, drug levels, age or gender. Together all the variables tested accounted for less than 6% of the variance in oro-caecal and small intestinal transit times.

In summary, therefore, the drugs themselves and the drug levels only accounted for a small proportion (<6%) of the variances in gastric emptying and small intestinal

transit times in my patients. There had to be other factors that played a more dominant role than the drugs themselves.

2. STRESS

The delay in gastric emptying and intestinal transit in self-poisoning might be the result of neuro-humoral mediated mechanisms that act to protect the body against massive overdosage. These might inhibit gastric motility and emptying of the poison and retard its passage through and absorption by the small intestine. These effects may be triggered by severe stress or excessive quantities of poison passing into the small intestine. Receptor mediated enterogastric reflexes and sympathetic activation may play a role. The central nervous system is known to regulate gastrointestinal motility via both the autonomic nervous system and hormonal pathways and probably plays a major role in stress-mediated hypomotility and inhibition of gastric emptying. This protective-regulatory response may be set off in response to both the excessive drug load and the stress associated with an attempted suicide.

A number of human studies using scintigraphy, radiotelemetry and paracetamol absorption tests have shown that anxiety, fear and pain inhibit gastric emptying and alter gastrointestinal motility (Thompson et al 1982; Simpson and Stakes 1986; Valori et al 1986). Datz et al (1990) showed a delay in both solid and liquid emptying in response to physical and mental stress. Camilleri et al (1986) noting that beta-endorphin levels rise during acute stress, found that physiological quantities of intravenously administered beta-endorphin increased pyloric pressure and reduced phasic pressure in the antrum in healthy humans. Sympathetic stimulation delays gastric emptying and inhibits antral motility (McIntyre et al 1988). Animal studies have confirmed the inhibitory effect of stress on gastric emptying and

motility (Gue et al 1988; Lenz et al 1988) and small intestinal transit (Williams et al 1988).

These studies have all been conducted under controlled conditions in which the degree of stress was regulated by the investigators. My patients were under no such control. Circumstances had driven them to commit an act which could be life-threatening. The stress, anxiety, fear and guilt inherent in these situations both as a result of the underlying causes and the act of committing self-poisoning must be tremendous. This is often compounded by the patient being rushed to hospital and having gastric lavage performed. The level of stress in these patients must be far in excess of anything that can be generated in a laboratory situation. What therefore appears as significantly increased delays in gastric emptying and intestinal transit (increases of 20-50%) under experimental conditions is converted to grossly elevated gastric emptying and small intestinal transit times in many of my patients.

3. DIURNAL VARIATION

Goo et al (1987) demonstrated that gastric emptying half-times of solids were significantly more rapid in the morning at 8h00 (64.8 +/- 6.4 minutes) compared with the evening times at 20h00 (97.1 +/- 11.5 minutes). Many of my patients were studied at night and in the early hours of the morning. The control studies were all performed during the morning and early afternoon. This time was the most appropriate and practical for both the patient and the nuclear medicine department. I could not justify asking the patient to return for a control study lasting 5 hours late at night. In the light of Goo's findings the overdose times in my patients appear far in excess of those that could be expected on the basis of circadian variation alone.

4. GASTRIC LAVAGE

Read et al (1983), found that gastrointestinal intubation significantly delayed gastric emptying in 12 healthy subjects when comparing them with 10 counterparts who were not intubated. Gastric emptying times after a solid test meal were 90 +/- 6 minutes for the intubated group and 72 +/- 6 minutes for the controls. They postulate that the delay may be due to stimulation of mucosal mechanoreceptors in the oesophagus, stomach and small intestine which inhibit contractions in the gastric body and antrum. Saetta and Quinton (1991) discovered bruising of the gastric cardia as a result of gastric lavage in four out of seventeen patients on whom they performed endoscopy after lavage.

Statistical testing comparing patients who had gastric lavages and those who were not treated in this way showed no difference at the 5% significance level between the two groups in my study. However, the Mann-Whitney U test demonstrated a tendency to differ between the group that had gastric lavage and those who did not ($p = 0.077$). (The median for the first group was higher (131, IQR 69 - 211.75 minutes) than the second (87.5, IQR 41.5 - 178.25). There could be a number of reasons for this. Gastric lavages were done more readily on patients who had taken higher doses of drugs. Intubation could traumatise the stomach causing a further disturbance of the normal gastrointestinal regulatory mechanisms and inhibition of gastric emptying. Furthermore, intubation with a large bore tube instils fear into patients that might inhibit gastric motility.

5. N-ACETYL-CYSTEINE AND PARACETAMOL TOXICITY

N-acetylcysteine is used to protect patients with paracetamol poisoning from liver necrosis. Several patients who presented with paracetamol overdose were treated

with intravenous N-acetylcysteine at the Emergency Unit. Patients received N-acetylcysteine once their paracetamol levels had been shown to be within the toxic range as determined on the nomogram (Rumack and Matthew 1975), or before plasma levels were available, if the estimated ingestion was over 10 grams. As imaging was often started before the drug levels were available certain patients received N-acetylcysteine up to 2 hours (n=2) into the study and 4 others who did not receive N-acetylcysteine until after scintigraphy was completed.

Whitehouse et al (1981) suggest that the delay in gastric emptying could be a major mechanism for the protective action of N-acetylcysteine in mice. It is argued that prolonged gastric emptying reduces the amounts of paracetamol absorbed by the intestine thus allowing the liver to cope (Müller et al 1983). The paracetamol antidote is known to cause nausea, vomiting and diarrhoea (Flanagan and Meredith 1991; Holdiness 1991). Whether and to what extent N-acetylcysteine inhibits gastric emptying and intestinal transit in humans, however, is a question which requires further study.

When comparing those patients who fell within the toxic range (n=13) with those who did not (n=16), there was a significant difference noted ($P = 0.002$) between the gastric emptying half-times. A number of factors might account for this observation. Firstly, patients with blood levels in the toxic range are more likely to have ingested larger quantities of paracetamol. Secondly, the majority of these patients (9 out of 13) received N-acetylcysteine during the course of the imaging. This might have had an inhibitory effect. Finally, those driven to take larger amounts of the poison might have been under greater stress.

6. ALTERED LEVEL OF CONSCIOUSNESS

Thirty-one patients were obtunded or confused. Gastric emptying half-times were found to be significantly greater in this group than in the rest of the patients. Patients with coma due to cerebro-vascular accidents (Inoue et al 1993) and those with severe head injury (Ryo et al 1990; Ott et al 1991) have delayed or altered patterns of gastric emptying. Patients under general anaesthesia induced by different agents all had delayed gastric emptying (Mushambi et al 1992). These studies suggest a central nervous system mechanism for altering gastric emptying.

Patients in my study with altered levels of consciousness might have been under greater stress and taken larger doses of drugs to begin with. Patient position can be excluded as a possible factor as all the patients remained relatively still throughout the scanning period after overdose. Alternatively or additionally, the action of the drugs on the central nervous system in causing an alteration in level of consciousness might result in inhibition of gastrointestinal motility.

7. INTRA- AND INTERSUBJECT VARIABILITY

Marked inter- and intra-subject variability have been reported in healthy subjects. However, the variations of gastric emptying half-times for both the liquid (12-37 minutes) and solid (29-92 minutes) ranges fall well within the normal ranges (Brophy et al 1986). These factors are therefore unlikely to have accounted for the significant differences between the gastric emptying half-times in my patients following overdosage and at control.

8. PRIMARY ANOREXIA NERVOSA AND BULIMIA NERVOSA

Marked delays in gastric emptying and intestinal transit have been found with both anorexia nervosa (Dubois et al 1979; Holt et al 1981; McCallum et al 1985; Stacher et al 1986,1987,1991; Hirakawa et al 1990), and bulimia (Kiss et al 1990). Although the majority of my patients were young women who fitted the demographic profile for these disorders only one of them was diagnosed as bulimic and was receiving psychotherapy at the time of her self-poisoning. It is unlikely that gastric emptying and intestinal transit were influenced by these disorders in a significant number of patients.

GASTRIC MOTILITY

METHOD OF EVALUATING GASTRIC MOTILITY

Gastric motility has been examined in a number of different ways (Akkermans et al 1984; Stacher et al 1987, 1992; Urbain et al 1993; Hausmann et al 1993; Bergmann and Stacher 1994). However, many of these methods are complex and require sophisticated, expensive equipment. For these reasons these studies cannot be performed routinely in many nuclear medicine departments. I used a visual analysis of the dynamic studies at different frame rates and a scoring system to quantify and therefore compare the studies after overdose with those at control.

MOTILITY PATTERNS

1. GASTRIC EMPTYING : NORMAL MOTILITY

Large peristaltic waves were invariably the cause of emptying in patients with normal gastric emptying rates. The majority of these contractions had their origins in the proximal stomach in the region of the fundal-corporis junction along the greater curvature. They swept the activity aborally from the proximal stomach through the distal stomach and pylorus into the duodenum. Bergmann and Stacher (1994) have described a similar contractile pattern. Intermittent, smaller distal corpus and antral contractions assisted the emptying process. The results indicate a significantly greater gastric motility score in control studies when compared with studies after overdose. This suggests that the overdose process suppressed gastric motility. Contractions were also more numerous in control studies than studies done after overdose.

2. DELAYED GASTRIC EMPTYING : HYPOMOTILITY

Stasis in the proximal part of the stomach was the main feature in patients who had marked decreases in gastric emptying rates. No contractions were seen in the majority of these patients. Some had weak contractility. The results show a significant correlation between prolonged gastric emptying half-times and distribution of the bulk of the activity in the proximal stomach. The distal stomach and especially the antrum were rarely visualised because of the lack of activity in these areas. Gastric motility scores were lowest in those studies that had the longest gastric emptying times. The results show a very significant inverse relationship between gastric emptying half-times and gastric motility scores. Studies after overdose had significantly lower scores (3.2 +/- 4.2) when compared with studies at control (10.95 +/- 8.2). The results therefore indicate a significant hypomotility after drug overdose. No single drug group has a greater effect on the gastric motility scores than any other.

These patterns indicate a virtual paralysis of the stomach following overdose. The proximal half of the stomach fulfills its role as a reservoir but appears to have lost its contractile functions. Activity therefore pools in the fundus and upper corpus. The large peristaltic waves seen in those with normal gastric emptying rates are absent. The weak contractions noted in some are unable to carry the bulk of activity into the distal stomach. The force of gravity does not seem sufficient to pull the gastric contents aborally in these cases. Stacher and Bergmann (1992) note that delayed gastric emptying could be due to decreased tonic activity of the reservoir part of the stomach. The cause(s) of this lack of contractility is unknown. Inhibition of the pace-maker which is situated in the proximal stomach is a possible additional cause of the gastroparesis.

It may be speculated that neurohumoral factors are at work. It is not inconceivable that the central nervous system may play a prominent role in inhibiting gastric motility. Stress has been shown to be a powerful inhibitor of gastric motility (Camilleri and Neri 1989). Although antral hypomotility are associated with gastric stasis (Camilleri et al 1986), I were unable to assess its role in many patients with prolonged gastric emptying because of the absence of activity in these regions. Intestinal dysmotility is also implicated in gastric stasis (Lin 1994; Camilleri and Neri 1989). Prolonged gastric emptying was associated with intestinal hypomotility in my patients. Enterogastric reflexes and other feedback mechanisms may have exerted an inhibitory effect on gastric motility.

DISTRIBUTION OF THE RADIOLABELED MEAL IN THE STOMACH

DISTRIBUTION PATTERNS, GASTRIC EMPTYING RATES AND DISTRIBUTION TIMES IN STUDIES FOLLOWING OVERDOSE

Significant differences were found in gastric emptying half-times when comparing the three distribution patterns. The proximal distribution group displayed longer times than the other 2 groups. The radioactivity was retained in the proximal stomach for significantly longer times than in the other two regions. These figures confirm findings by Van den Maegdenbergh et al (1993) and Hausmann et al (1993) that retention of activity in the proximal stomach is associated with prolonged gastric emptying.

DISTRIBUTION PATTERNS IN CONTROL STUDIES

In contrast, the control group showed no significant differences between gastric emptying half-times for the different patterns. Moreover, the time of distribution was not significantly different for any of the distribution groups.

COMPARISON BETWEEN THE DISTRIBUTIONS OF OVERDOSE AND CONTROL STUDIES

Significant differences were found between the distribution patterns in the overdose and control groups. Patterns were therefore different in the same patient at overdose when compared with the control study.

These findings tend to support the hypothesis that the prolonged gastric emptying found following overdose is due to paralysis of the proximal stomach. The latter might be part of a general paralysis of the stomach but this is difficult to ascertain with the information at hand.

PART 1: PRINCIPAL FINDINGS

GASTRIC EMPTYING AND MOTILITY

1. Gastric emptying half-times were significantly prolonged for patients ingesting overdoses of all the drugs tested.
2. Gastric emptying half-times were within the normal range for liquid emptying in the same patients at control.
3. Gastric motility was significantly diminished after overdose when compared with control studies.
4. No significant differences were observed between the effects of the different drugs after overdose and at control.
5. The bulk of the radioactive meal remained in the proximal half of the stomach in patients with prolonged gastric emptying.
6. Patients who had gastric lavage had a tendency to have longer gastric emptying half-times than those who were not lavaged.
7. No significant correlation was shown between gastric emptying half-times and drug levels.
8. Patients with blood levels in the toxic range had significantly longer gastric emptying half-times than the other patients who ingested overdoses of paracetamol.
9. Obtunded and confused patients had significantly greater gastric emptying half-times than the rest.

ORO-CAECAL AND INTESTINAL TRANSIT

1. Oro-caecal transit times were significantly longer after overdose than at control.
2. Small intestinal (duodeno-caecal) transit times were significantly prolonged after overdose when compared with control studies.
3. In the majority of patients the radioactive meal was retained in the proximal half of the small intestine after overdose.
4. A significant correlation was found between gastric emptying half-times and small intestinal transit times.
5. No differences were found in the effects of the different drug groups tested on small intestinal transit times.
6. Drug levels did not correlate significantly with small intestinal transit times.

IN CONCLUSION THEREFORE:

1. Poisoning and/or associated factors resulted in gastroparesis with prolonged gastric emptying times and hypomotility of the stomach.
2. Poisoning and/or associated factors caused prolonged small intestinal transit times.
3. Patients with gastric stasis also had intestinal stasis. Therefore, both gastric and small intestinal motility were inhibited in poisoning.

4. All the variables tested for explained less than 6% of the variances of both gastric emptying half-times and small intestinal transit times suggesting other, untested for causes of the above-mentioned findings.



PART TWO

RATIONALE

It has been argued that the sorbitol-charcoal mixture adsorbs the poison, neutralising it and then hastens its elimination by shortening the intestinal transit time. Results in Part 1 revealed a marked inhibition of gastric emptying in patients following poisoning with all of the drugs tested. Therefore, either unknown proportions of the drug passes into the small intestine and is absorbed and paralyses the gut, or/and another factor like stress retards gastrointestinal motility allowing only small portions of the drug to seep into the small intestine.

In the event of the former, the bulk of the activity might have passed into the small intestine. The sorbitol-charcoal mixture cannot therefore exert any influence if it is held up in the stomach and has no contact with the poison in the small intestine. For it to be effective, therefore, the mixture would have to enhance gastric emptying in these patients.

On the other hand, if the gut was paralysed by some factor like stress, then considerable quantities of the poison might still be inside of the stomach at the time of administering the charcoal-sorbitol mixture. This would serve to neutralise the poison left in the stomach and prevent or reduce further absorption as the poison that passes into the the intestine will be adsorbed to charcoal. But in the absence of increasing the rate of gastric emptying the charcoal-sorbitol mixture would have no effect on the poison that has passed into the intestine prior to its (the sorbitol's) administration.

It was also necessary to test the hypothesis that sorbitol increases the rate of small intestinal transit in patients poisoned by the 5 drugs ingested by patients in my study.

Sixty-one patients were part of the second study to assess the effects of a mixture of the osmotic laxative, sorbitol (70%) and activated charcoal on gastric emptying and small intestinal transit. All of the patients were imaged in precisely the same manner as for Part 1 after receiving a similar regime of treatment save for the addition of sorbitol. These patients were not asked to return for a second (control) study.

The aims of this study were to investigate whether adding sorbitol to the treatment regime would:

1. reduce gastric emptying times in patients who had ingested overdoses of the same drugs tested in Part 1, and
2. increase the small intestinal transit rate in these patients.

PATIENTS AND METHODS

The methods used were precisely the same as those described in the "Methods" section for Part 1 other than for certain omissions detailed below. In the interests of brevity a summary of this method is provided below.

PATIENT SELECTION

Patients were selected on exactly the same basis as for Part 1. Patients who had taken overdoses of the same four groups of poisons were selected for the study :

- 1 tricyclic antidepressants;
- 2 anticonvulsants;
- 3 paracetamol;
- 4 opioid-paracetamol mixtures.

Patients who had ingested combinations of these or additional drugs were also selected. The type of drug ingested was determined in the same manner as in Part 1.

PATIENT MANAGEMENT AND REFERRAL

When the patients arrived at the Emergency Unit (EU) they received standard clinical management which included:

1. A history was taken which included attempts to determine the type and quantity of poison taken and the time of ingestion.

2. Gastric lavage was performed in all cases in whom the clinician deemed it necessary.
3. The administration of activated charcoal in 200 - 300ml of water mixed with sorbitol. This mixture was administered to the patient orally.
4. N-acetylcysteine for paracetamol toxicity was the only antidote used in my patients.
5. Drug levels were measured in blood and urine.
6. The investigator was informed of the patient by the nursing sister or attending doctor.
7. Patients who were severely ill were transferred to the ICU after the initial management was carried out in the EU.
8. Patients were transferred to the nuclear medicine department (NMD) where the scintigraphy was commenced in the shortest possible time. Patients admitted to the ICU were imaged there with a mobile camera.
9. Informed consent was obtained for the study from every patient or from a close relative where this was not possible because of confusion or coma.

PERFORMANCE OF THE GASTROINTESTINAL SCINTIGRAPHY

1. PREPARATION OF THE LIQUID TRACER

The liquid tracer consisted of 18-22 MBq of $^{99m}\text{Tc-Sn}$ colloid mixed in 10ml of water prepared in the same manner as for Part 1.

2. ACTIVATED CHARCOAL

Patients were given to drink a slurry consisting of 25 or 50g of activated charcoal (AC) and 200 to 300ml of a water and **sorbitol (70%)** respectively.

3. Each patient was given the liquid tracer containing approximately 20 MBq of $^{99m}\text{Tc-Sn}$ colloid in water which was "washed down" by 10ml of water. This was administered orally to conscious patients in the sitting position, and through a nasogastric tube in the obtunded.

4. The study was performed as for Part 1.

5. The exact time that the patient drank the radiopharmaceutical was recorded, and data collection was started 1 minute afterwards and continued for up to 5 hours. The exact time period depended on the patient's clinical condition.

6. No additional fluids or meals were taken until the study was complete. Smoking was not permitted.

DATA ACQUISITION

Data was acquired in precisely the same manner as for Part 1. The same camera systems were used - Elscint Apex 415 and 410 for patients in the nuclear medicine department, and patients in the ICU were imaged on a General Electric 300a mobile camera fitted with the same collimators used in Part 1.

Static 60 second images were taken at: 1, 15, 30, 45 and 60 minutes in the first hour. Subsequent images were taken at 30 minute intervals for 60 seconds each for the next four hours. Marker pictures were recorded prior to each anterior image in the same way as described in Part 1.

Two - 10 minute dynamic studies were performed - the first between the 15 and 30 minute and the second between the 45 and 60 minute images.

DATA ANALYSIS

Data was processed and analysed in precisely the same manner as described in Part 1. Gastric emptying rates were calculated from the same 2 data sets: anterior counts only and anterior and posterior counts.

A histogram/time-activity curve was generated for each study expressed as the proportion of activity retained in the stomach (i.e. as a percentage of the total activity as derived from the above formulae) versus time. The main parameter derived from these curves was the time it took for 50% of the activity to empty from the stomach - $T_{1/2}$.

Oro-caecal and small intestinal transit times were calculated in exactly the same way as for Part 1.

OMISSIONS

1. There were no control studies done as I could not justify giving sorbitol to well patients at control.

2. Integration

The areas under the time-activity curves were not determined for Part 2 as this method had confirmed the great discrepancy in gastric emptying half-times after overdose and at control in Part 1 and was not considered necessary.

3. Assessments were not made of gastric motility and of the distribution of the radioactive meal in the stomach.

IN SUMMARY:

The data was collected and processed in the manner described for Part 1 (other than for the omissions mentioned). Care was taken that every step of the method including patient selection, scintigraphy and processing was performed in precisely the same manner for the two studies.

RESULTS

OVERALL DESCRIPTION OF THE SAMPLE

The analysis will give:

1. a general description
2. detail regarding the gastric emptying and small intestinal transit times
3. a comparison between the results obtained in Part 2 with those from Part 1.

Table 21 provides a summary of all the patients by drug group and gender.

TABLE: 21
PATIENTS BY DRUG GROUP AND GENDER

DRUG	TOTAL PAT. NO.	MALES	FEMALES
TCA	15	4	11
CBZ	7	5	2
PHE	8	6	2
PAR	13	4	9
OPI	18	5	13
TOTAL	61	24	37

TCA = Tricyclic antidepressants

CBZ = Carbamazepine

PHE = Phenytoin

PAR = Paracetamol

OPI = Opioid

AGE AND GENDER IN PATIENTS TREATED WITH SORBITOL

A total of 61 patients were investigated of whom

37 were female and 24 male. The mean age for the entire group was 26.9 +/- 10.7 years. The mean age for females = 25.1 +/- 11.1 compared with males = 29.7 +/- 9.6 years. Age ranges were: females 13-53, males 19-46 years. There was no significant difference between females and males regarding age: the two-sample test produced a p value = 0.10

The majority of patients are under 40 years of age with the the biggest single category being the 20 - 30 year group. Young females predominate.

AGE AND GENDER BY DRUG GROUP

TRICYCLIC ANTIDEPRESSANTS

There were 11 females and 4 males in this group. The mean age was 30.3 +/- 13.0 years. The mean age for females was 30.4 +/- 14.0 and males 30.3 +/- 11.6 years. Patients who ingested tricyclic antidepressants were not significantly different in age than patients in the entire group ($p = 0.29$; two-sample analysis).

There was no significant gender difference between the group of patients that ingested tricyclic antidepressants and the whole group of the patients ($p = 0.37$ two-sample analysis).

CARBAMAZEPINE

There were 2 females and 5 males in this group. The mean age for the group was 29.3 +/- 9.9 years. The mean age for females was 23.0 +/- 2.8 and males 31.8 +/- 10.8 years. There was no significant age difference between patients

who ingested carbamazepine and all the patients ($p = 0.57$; two-sample analysis).

PHENYTOIN

There were 2 females and 6 males in this group. The mean age was 31.3 ± 9.6 years. The average age of the females 19.5 ± 4.9 and males 35.2 ± 7.1 years. There no significant age difference between this group and the entire group of patients ($p = 0.27$; two-sample analysis).

PARACETAMOL

There were 9 females and 4 males in this group. The mean age was 21.9 ± 8.8 years. The average age for the females was 21.4 ± 11.3 and males 23.0 ± 3.9 years. The age of this group was significantly lower than the whole group of patients ($p = 0.02$; two-sample analysis).

No significant gender difference was found between the group that ingested paracetamol and the entire group of patients ($p = 0.57$; two-sample analysis).

OPIOIDS

There were 13 females and 5 males in this group. The mean age was 25.1 ± 9.5 years. The mean age of the females was 24.3 ± 8.6 and males 25.8 ± 10.8 years. There was no significant age difference between this group and all of the patients ($p = 0.44$; two-sample analysis).

There was no significant gender difference between the patients in this group and the entire group ($p = 0.38$; two-sample test).

DRUG INGESTION TO SCANNING TIME

The mean time between drug ingestion and the commencement of gastric scintigraphy was 11.4 +/- 5.45 hours (range = 1.25 to 21.5 hours).

DURATION OF GASTRIC SCINTIGRAPHY

Patients were scanned for the times shown in Table 22.

TABLE : 22

DURATION OF SCAN

Number	Scan Duration (minutes)
43	300
13	240 - 299
2	210 - 239
3	<210

Range: 2.5 to 5 hours.

GASTRIC EMPTYING HALF-TIMES

On the basis of the excellent correlation between gastric emptying half-times derived from anterior data and those determined by geometric means found in Part One, gastric emptying half-times generated from anterior data alone were used throughout.

GASTRIC EMPTYING HALF-TIMES BY DRUG GROUP

TRICYCLIC ANTIDEPRESSANTS

AFTER OVERDOSE: 180 (median), 45 - 300 (IQR) minutes.

Nine patients had gastric emptying half-times greater than 120 minutes. Of these 3 gastric emptying half-times were longer than 300 minutes and 2 longer than 240 minutes.

Multiple regression analysis found no significant association between age and gender and gastric emptying half-times following tricyclic overdose (age: $p = 0.43$; gender $p = 0.53$). But drug level correlated significantly ($p = 0.01$) indicating that patients with higher drug levels had longer gastric emptying half-times (r value = 0.694, simple regression analysis). The R-squared = 0.476 (47.6%).

CARBAMAZEPINE

AFTER OVERDOSE: 75 (median), 27 - 104 (IQR) minutes.

Two patients in this group had gastric emptying half-times longer than 100 minutes.

Drug level, age and gender had no significant influence on gastric emptying half-times: drug level ($p = 0.38$), age ($p = 0.59$), gender ($p = 0.51$) (multiple regression analyses).

PHENYTOIN

AFTER OVERDOSE: 131 (median), 31.5 - 172.5 (IQR) minutes.

Four patients in this group had gastric emptying half-times of over 120 minutes. One of these had a half-time of over 240 minutes.

The following variables were analysed by multiple regression analysis and showed no significant relationship to gastric emptying half-times: drug level (0.62), age ($p = 0.99$) and gender ($p = 0.51$).

PARACETAMOL

AFTER OVERDOSE: 82 (median), 67-110 (IQR) minutes.

Four patients who ingested overdoses of paracetamol had gastric emptying half-times of over 100 minutes. One of them had a gastric emptying half-time of longer than 300 minutes.

Age ($p = 0.79$) and gender ($p = 0.58$) had no significant relation to gastric emptying half-times. Simple regression analysis found a non-significant correlation, r value = 0.447 ($p = 0.125$) between gastric emptying half-times and drug levels.

The Mann-Whitney U test shows a tendency for gastric emptying half-times to be longer in patients with toxic drug levels of paracetamol ($p = 0.075$).

OPIOIDS

AFTER OVERDOSE: 71.75 (median), 30 - 126(IQR) minutes.

Five patients in this group had gastric emptying half-times of over 120 minutes. Two of the five had half-times longer than 270 minutes.

Drug level correlated significantly with gastric emptying half-times ($p = 0.0032$, $r = 0.65$, simple regression analysis). R -squared = 0.4225 (42.25%). Other variables entered into the multiple regression analysis had no significant influence: age ($p = 0.82$), gender ($p = 0.16$).

THE ENTIRE GROUP OF PATIENTS

GASTRIC EMPTYING HALF-TIMES:

AFTER OVERDOSE: 82 minutes (median), 43 - 180 (IQR) minutes.

Multiple Regression Analysis

The following variables were entered into multiple regression analysis to assess their respective correlations with gastric emptying half-times: standardised drug levels, drug group, age and gender. Standardised drug level was found to correlate significantly with gastric emptying half-times ($p = 0.0005$). Different drug groups also had significantly different effects on gastric emptying half-times ($p = 0.03$). None of the other variables correlated significantly with gastric emptying half-times: age ($p = 0.29$), gender ($p = 0.45$).

R-squared for the full regression was 0.283 (28.3%).

IN SUMMARY:

1. The different drug groups were found to have a significantly different effects on gastric emptying half-times.
2. Tricyclic antidepressant and opioid levels correlated significantly with gastric emptying half-times. An increase in drug level was therefore paralleled by an increase in gastric emptying half-times in these patients. Drug level did not contribute significantly in patients who ingested the other drugs.
3. Age and gender made no significant contribution.
4. The small numbers of patients who ingested carbamazepine and phenytoin might have caused some statistical error.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT

TRICYCLIC ANTIDEPRESSANTS

The oro-caecal transit time

After overdose: 270 (median) 210 - 300 (IQR) minutes.

Drug level had no significant effect on oro-caecal transit time (regression analysis).

Small intestinal transit time:

After overdose: 235 (median) 150 - 285 (IQR) minutes.

Drug level had no significant influence on small intestinal transit.

In 9 of the 15 patients the leading edge of radioactivity failed to reach the ileo-caecal region (see Table 23).

TABLE: 23

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	5	4	6

CARBAMAZEPINE

The oro-caecal transit time

After overdose: 90 (median) 90 - 210 (IQR) minutes.

Drug level correlated significantly with oro-caecal transit times ($p = 0.013$).

Small intestinal transit time:

After overdose: 75 (median) 75 - 180 (IQR)

A significant relation was found between drug level and small intestinal transit times ($p = 0.012$).

The radioactive meal reached the ileo-caecal region in all the patients (see Table 24).

TABLE: 24

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	0	0	7

PHENYTOIN

The oro-caecal transit time

After overdose: 195 (median) 92.5 - 255 (IQR) minutes.

There was no significant relation between oro-caecal transit times and drug levels.

Small intestinal transit time:

After overdose: 125 (median) 39.5 - 225 (IQR) minutes.

Drug level had no influence on small intestinal transit times.

In 6 out of 8 patients the head of the radioactivity reached the ileo-caecal region (see Table 25).

TABLE: 25

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	1	1	6

PARACETAMOL

The oro-caecal transit time

After overdose: 180 (median) 90 - 210 (IQR) minutes.

No significant correlation was found between oro-caecal transit times and drug levels.

Small intestinal transit time:

After overdose: 135 (median) 75 - 255 (IQR).

There was no significant correlation between small intestinal transit and drug level.

The leading edge of radioactivity reached the ileo-caecal region in 11 of 13 patients who ingested paracetamol.

TABLE: 26

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	1	1	11

OPIOIDS

The oro-caecal transit time

After overdose: 240 (median) 180 - 300 (IQR) minutes.

Drug level had no significant influence on oro-caecal transit time.

Small intestinal transit time:

After overdose: 225 (median) 135 - 240 (IQR).

There was no significant correlation between drug level and small intestinal transit.

Table 27 shows that in 14 out of 18 patients the leading edge of the radioactive meal reached the ileo-caecal region.

TABLE: 27

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	2	2	14

THE ENTIRE GROUP

The oro-caecal transit time

After overdose: 210 (median) 120 - 270 (IQR) minutes.

Small intestinal transit time:

After overdose: 165 (median) 83 - 235 (IQR) minutes.

In 44 out of 61 patients the leading edge of the radioactive meal reached the ileo-caecal region (see Table 28f).

TABLE: 28

THE MOST DISTAL REGION IN WHICH THE LEADING EDGE OF RADIOACTIVITY WAS OBSERVED AT THE END OF THE SCANNING PERIOD.

	STOMACH-JEJUNUM	ILEUM	ILEO-CAECAL
Overdose	9	8	44

The delay in oro-caecal and small intestinal transit is most marked following tricyclic antidepressant ingestion. In 60% of patients who ingested tricyclics the radioactive meal failed to reach the ileo-caecal region during the scanning period; in a third of them the meal was retained in the proximal half of the small intestine.

THE RELATIONSHIP BETWEEN ORO-CAECAL AND SMALL INTESTINAL TRANSIT TIMES, DRUG LEVELS AND THE DIFFERENT DRUG GROUPS

ORO-CAECAL TRANSIT TIMES

Multiple regression analyses failed to show significant correlations with standardised drug levels ($p = 0.65$), drug group ($p = 0.34$), age ($p = 0.63$) and gender ($p = 0.097$). R-squared for the full regression = 0.065 (6.5%).

SMALL INTESTINAL TRANSIT

No significant contribution was made to small intestinal transit times by the following variables: standardised drug levels ($p = 0.30$), drug groups ($p = 0.81$), age ($p = 0.56$) and gender ($p = 0.14$). R-squared for the full regression analysis was 0.054 (5.4%).

THE RELATIONSHIP BETWEEN ORO-CAECAL AND SMALL INTESTINAL TRANSIT AND GASTRIC EMPTYING

Multiple regression analyses show a highly significant correlation between gastric emptying half-times and oro-caecal ($p < 0.0001$) and small intestinal ($p < 0.0001$) transit times .

IN SUMMARY:

1. Both oro-caecal and small intestinal transit times were significantly prolonged in patients who ingested tricyclic antidepressants, opioids and, to a lesser extent, paracetamol and phenytoin.
2. Other than in the case of patients who ingested carbamazepine no significant contribution to oro-caecal and small intestinal transit times was made by drug levels, age or gender.
3. A significant relationship was found between gastric emptying half-times and oro-caecal and small intestinal transit times.

DISCUSSION

DEMOGRAPHY

The age and gender of the whole group of patients recruited to Part 2 of the study corresponds with patterns observed in patients with poisoning. Young females in the 20 to 30 year age group predominated. However, males predominated among those who took anticonvulsants. This is probably due to the fact that many of these were epileptics who took overdoses of the drug at hand, or who ingested excessive quantities of the drugs unintentionally.

GASTRIC EMPTYING HALF-TIMES

Gastric emptying half-times were prolonged in patients for all the drug groups tested being especially marked in patients who ingested tricyclic antidepressants and phenytoin. The median of 82 minutes (IQR 43 - 180) was considerably than the 15 to 55 minutes found in normals in other studies mentioned in Part 1 for liquid gastric emptying. Both tricyclic antidepressant blood levels and opioid urine levels correlated significantly with gastric emptying half-times in those respective groups of patients. Therefore, higher drug levels were associated with longer gastric emptying half-times in these groups of patients.

SMALL INTESTINAL TRANSIT TIMES

Oro-caecal transit (median 210, IQR 120 - 270) minutes and small intestinal transit (median 165, IQR 83 - 235) minutes were markedly prolonged when compared with figures quoted for normals in Part 1 which ranged between 45 and 105 minutes. No significant correlation was found between oro-caecal and small intestinal transit times and drug levels, drug groups, age and gender.

A significant correlation was found between gastric emptying half-times and small intestinal transit times. Therefore, the greater the delay in gastric emptying the longer the time for the radioactive meal to traverse not only the oro-caecal tract which was expected because of the long gastric emptying times but also the duodeno-caecal region. This implied that there was a significant association between poisoning and both gastric stasis and intestinal hypomotility.

A COMPARISON OF PART ONE AND PART TWO

In order to make a proper evaluation of the role played by sorbitol in gastric emptying and intestinal transit in the patients studied, a comparison between the relevant data from Part 2 and Part 1 was necessary.

AGE AND GENDER

AGE:

There was no significant difference in age between patients in Part 2 and those in Part 1 ($p = 0.11$, Mann-Whitney U).

GENDER:

No significant difference existed between the two groups of patients ($p = 0.07$, Mann-Whitney U).

DRUG LEVELS:

No significant difference was found between the drug levels in the two groups.

The Mann-Whitney U test found the following:

Tricyclics	(0.073);
Carbamazepine	(0.052);
Phenytoin	(0.91),
Paracetamol	(0.69)
Opioids	(0.32).

GASTRIC EMPTYING HALF-TIMES

	Part One	Part Two
Sample Size	104	61
Median	99.5	82
Lower Quartile	54.5	43
Upper Quartile	208.25	180

There was no significant difference between the gastric emptying half-times in patients in Part 1 after overdose and those in Part 2 ($p = 0.31$, Mann-Whitney U).

The addition of sorbitol to the treatment regime made no difference to the gastric emptying half-times. Sorbitol had no effect on gastric emptying in my patients. **The null hypothesis that sorbitol does not reduce gastric emptying times is thus accepted.**

Given that no significant differences were found in regard to demographic features, drug levels and gastric emptying half-times after overdose, a comparison was made between the gastric emptying half-times of patients in Part 2 and the gastric emptying half-times **at control (follow-up)** of the patients in Part 1.

The Mann-Whitney U analysis found a highly significant difference ($p < 0.000001$). The gastric emptying half-times of the patients in Part 2 were therefore considerably longer than the control half-times in Part 1.

ORO-CAECAL AND SMALL INTESTINAL TRANSIT TIMES

ORO-CAECAL TRANSIT TIMES:

	Part One	Part Two
Sample Size	103	61
Median	270	210
Lower Quartile	210	120
Upper Quartile	300	270

A comparison between oro-caecal transit times in Part 1 and Part 2 revealed a significant difference between the patients in the 2 groups ($p = 0.0007$, Mann-Whitney U). Oro-caecal times in Part 2 were therefore considerably shorter than those in Part 1.

Comparisons made for patients in each drug group in Part 1 with their counterparts in Part 2 showed:

Tricyclic antidepressants:	$p = 0.53$;
Carbamazepine:	$p = 0.00074$;
Phenytoin:	$p = 0.028$;
Paracetamol:	$p = 0.0059$;
Opioids:	$p = 0.57$.

Oro-caecal transit times were therefore significantly reduced in patients who took overdoses of carbamazepine, phenytoin and paracetamol in Part 2 when compared with those who took the corresponding drugs in Part 1. Oro-caecal transit times were not significantly different in patients who took tricyclic antidepressants and opioids in Part 1 and Part 2.

When comparing oro-caecal transit times between Part 2 with Part 1 patients at **control**, the times in Part 2 were significantly longer ($p = 0.001$, Mann-Whitney U).

SMALL INTESTINAL TRANSIT TIMES:

	Part One	Part Two
Sample Size	103	61
Median	209	165
Lower Quartile	150	83
Upper Quartile	255	235

A comparison between small intestinal transit times determined in Part 1 with those in Part 2 showed that the latter were significantly shorter ($p = 0.0056$, Mann-Whitney U).

Comparisons for patients in the individual drug groups revealed:

Tricyclic antidepressants	$p = 0.82$;
Carbamazepine	$p = 0.03$;
Phenytoin	$p = 0.069$;
Paracetamol	$p = 0.0017$;
Opioids	$p = 0.69$.

Small intestinal transit times were therefore significantly reduced in patients in Part 2 who ingested carbamazepine and paracetamol. Those who took tricyclic antidepressants and opioids in Part 2 had similar transit times to patients who ingested the same drugs in Part 1.

Although they tended to be longer in Part 2, the Mann-Whitney U analysis showed no significant difference between small intestinal transit times in Part 2 and those **at control** in Part 1 ($p = 0.073$).

IN SUMMARY:

1. There were no significant differences regarding age, gender and drug levels between patients in Part 1 and those in Part 2.
2. There was no significant difference in gastric emptying half-times when comparing patients in Part 1 after overdose with those in Part 2.
3. There was a significant difference in gastric emptying half-times when comparing patients in Part 2 with patients **at control** in Part 1.
4. Oro-caecal transit times were significantly shorter in patients in Part 2 who ingested paracetamol, carbamazepine and phenytoin when compared with their counterparts in Part 1, but were not significantly different for those who took tricyclic antidepressants and opioids.
5. Oro-caecal transit times in Part 2 were significantly longer than those of patients **at control** in Part 1.
6. Small intestinal transit times were significantly reduced in patients who took overdoses of paracetamol and carbamazepine in Part 2 but not in those who took tricyclic antidepressants and opioids.
7. Small intestinal transit times in patients in Part 2 were not significantly different from patients in Part 1 **at control**.



DISCUSSION

THE EFFECT OF SORBITOL ON GASTRIC EMPTYING AND INTESTINAL TRANSIT

Activated charcoal-sorbitol (70%) mixtures are used commonly in the management of poisoning. The rationale for the use of purgatives is that it is supposed to increase the passage of the poison-charcoal complex through the intestine thereby increasing the rate of drug elimination. There is some evidence to suggest that the activated charcoal-sorbitol complex may work in certain cases of salicylate poisoning (Keller and his co-workers 1990) and in healthy volunteers who had taken salicylates (Curtis et al 1984), and that it reduced absorption of theophylline and phenobarbitone (Goldberg et al 1987; Berg et al 1987). A study demonstrated improved survival rates in mice with paraquat toxicity following charcoal and magnesium citrate administration when compared with activated charcoal alone (Gaudreault et al 1985). In the absence of any drug ingestion Krenzelok et al (1985) found that the osmotic saccharide, sorbitol (70%), caused stooling in 0.9 hours in normal volunteers as compared with the mean gastrointestinal transit time for charcoal alone of 23.5 hours.

As I have stated, markedly reduced gastric emptying rates were demonstrated in patients with tricyclic antidepressant, carbamazepine, phenytoin, paracetamol and opioid poisoning. Krenzelok et al (1985) had shown that the activated charcoal-sorbitol complex reduced the gastrointestinal transit time in volunteers. Furthermore, it has been shown to reduce the plasma theophylline concentration while shortening the time for the maximum level to be reached in healthy volunteers (al-Shareef et al 1990). Given the profound delay in gastric emptying demonstrated in Part 1 it became clear that for the sorbitol to be effective it would have to increase the rate of gastric emptying as well as reduce intestinal transit times. If it did not act in this way the sorbitol-charcoal mixture would neutralise the drug in the stomach but have little effect on the drug that had

already passed into the small intestine. The results showed no significant difference in gastric emptying half-times when comparing patients in Part 1 (without sorbitol) with those in Part 2 (on sorbitol treatment). Therefore, the activated charcoal-sorbitol mixture had no effect on the rate of gastric emptying in patients in Part 2. Accordingly, the gastric emptying half-times in these patients were significantly longer than those in Part 1 at control.

The fact that sorbitol fails to increase the rate of gastric emptying means that it exerts little influence on drug absorption in patients in whom the bulk of the poison has passed into the small intestine prior to the administration of the charcoal-sorbitol mixture. It would neutralise whatever portion of the drug is still present in the stomach at the time of treatment.

Sorbitol is not, therefore, an appropriate agent for increasing the rate of gastric emptying in patients with poisoning. Prokinetic agents such as metoclopramide or cisapride might have increased gastric motility and shortened emptying times in these patients. However, the stomach paralysis induced by the poisoning may have been difficult to overcome. Moreover, the rapid passage of poison into the duodenum could enhance absorption and result in increased blood levels and earlier peaking. Treating the patient with activated charcoal before administering the prokinetic agent could reduce absorption of the poison if the increased motility of the intestinal tract does not somehow enhance desorption of the poison from the charcoal.

Oro-caecal transit times were significantly shorter in patients who had ingested paracetamol, carbamazepine and phenytoin in Part 2 compared with their counterparts in Part 1. On the other hand, those who ingested tricyclic antidepressants and opioids had oro-caecal transit times that were not significantly different in Part 1 and Part 2 despite the fact that no significant

difference was found between the gastric emptying times in Parts 1 and 2. This suggested that the sorbitol enhanced oro-caecal transit in patients who took paracetamol, carbamazepine and opioids but had no effect on the oro-caecal transit times in patients who ingested tricyclic antidepressants and opioids.

Small intestinal transit times were significantly reduced in patients who ingested paracetamol and carbamazepine in Part 2 compared with those in Part 1, but transit times were no different in those who took tricyclics and opioids. Sorbitol appeared to nullify or at least reduce the effects of poisoning on intestinal transit in patients who ingested paracetamol, carbamazepine and phenytoin but had little influence on those who took overdoses of tricyclic antidepressants and opioids. This suggests that different or additional mechanisms could be involved in paralysing the gut. Although the sorbitol reduced the elimination time of paracetamol, carbamazepine and phenytoin, this time was still markedly prolonged for all of them except carbamazepine (medians of 90 and 75 minutes for oro-caecal and small intestinal transit respectively) when compared with the normal range of 45 to 105 minutes. Given the adverse effects of sorbitol this partial effect on gastrointestinal transit does not justify its routine use in patients with poisoning.



PART THREE

PARACETAMOL CONTROL STUDY

RATIONALE

At the end of the Part 1 it was observed that patients who had taken overdoses of paracetamol had markedly prolonged gastric emptying. Control studies in these patients showed normal gastric emptying rates suggesting that the abnormal gastric emptying times were related in some way to the paracetamol overdose or the treatment thereof. As there is little in the literature to suggest that paracetamol influences gastric emptying, these findings were unexpected. Therefore, it was decided to do a study on a small group of healthy volunteers who were given therapeutic doses of paracetamol to ingest. This study would act as a test of my method and give an indication as to whether therapeutic doses of paracetamol were likely to affect gastric emptying. Permission was obtained from the Ethics and Research Committee of the University of Cape Town to do the study on five volunteers.

The study was done in the following manner:

1. Each volunteer was kept entirely drug-free for a minimum of 48 hours prior to the study.
2. Each volunteer was kept nil per mouth for at least 4 hours before taking the radiopharmaceutical and throughout the period of the study.

3. Each subject received 1g of paracetamol orally approximately 90 minutes prior to taking the liquid tracer. They received no activated charcoal nor sorbitol.
4. Blood and urine samples were taken at 4 hours after ingestion of the paracetamol to measure paracetamol levels.
5. Each volunteer was given 20 MBq of $^{99m}\text{Tc-Sn}$ colloid in 10ml of water followed by 10ml of water to rinse.
6. The subjects were scanned on the Elscint Apex 415 over a 5 hour period in precisely the same way that the patients were imaged in the study described above. They were made to lie down quietly for the entire imaging time.
7. Care was taken to acquire and analyse the data in exactly the same way as in the patient study described above.
8. Results were compared with those obtained in the studies above.

RESULTS

TABLE 4

Subject No.	Para (mg/L) (4 hour)	T _{1/2} (Geom)	T _{1/2} (Ant)	Control T _{1/2} (Ant)
1	8	8	12	6.5
2	5	8	10	5.0
3	7	4.5	6.5	na
4	9	60	60	21
5	5	8	10	8

A repeat study was not done on subject 3 as she fell pregnant soon after the first study was done.

DISCUSSION

Of the five volunteers who had each ingested one gram of paracetamol 90 minutes prior to gastric scintigraphy four emptied the radiocolloid rapidly. These volunteers had geometric mean corrected gastric emptying half-times ranging between 4.5 and 8 minutes and half-times of 6.5 to 12 minutes calculated from anterior data. The other volunteer had a gastric emptying time of 60 minutes for both geometric means and anterior data methods. Despite the fact that this emptying half-time falls well within the range of my control studies, it is considerably longer than the half-times of the other volunteers. The gastric emptying half-time measured after a repeat study done on this volunteer in the absence of any paracetamol ingestion was 21 minutes.

Was this marked difference in gastric emptying time in the one subject following paracetamol ingestion due to an abnormal individual response to the paracetamol or were there other unidentified factors involved? Schurizek et al (1989) studied 11 healthy volunteers on therapeutic doses of paracetamol (20mg/Kg). In this study the paracetamol absorption test and manometric measurements of motility identified two who were slow absorbers, t_{max} was not reached during the investigation period of three hours, no antral contractions were seen and the motility index was very low. This volunteer in my group could fit into the same category. Do therapeutic doses of paracetamol indeed alter the gastric emptying rates in certain individuals? If this is so then the paracetamol absorption test would give a false index of gastric emptying in these individuals. This topic requires more study. Larger groups of individuals need to be studied before any conclusions can be drawn regarding sensitivity of the stomach to paracetamol.

Markedly prolonged gastric emptying times were found in patients who had ingested overdoses of paracetamol. Although it is possible that some of the

patients might display a similar sensitivity to paracetamol as found in one of my volunteers and two of Schurizek et al's (1989) subjects, it is unlikely that they made up a significant number of cases.

Although gastric emptying was far more rapid in the other four volunteers, two of these had half-times on control studies that were shorter by half when compared with the study on paracetamol. The only other volunteer who had a control study done showed a 20% decline in half-emptying time compared with the initial study. However, caution should be exercised when comparing half-times that are so short - 5 to 8 minutes for the controls - as the instrumental and operational error built into the imaging and processing techniques could account for this. Furthermore, interpolation error might have affected the gastric emptying half-times. Due to the very short half-times only two measurements were used for interpolation - the one and fifteen minute readings. The margin for error is greater therefore, than when there are more points to derive the half-time from. The reason for the shorter gastric emptying times in the other four volunteers is difficult to explain. They are shorter than the normal range quoted for liquid emptying half-times of approximately 12 - 60 minutes.

At the control study patients demonstrated longer gastric emptying half-times (46.3 +/- 36.4 minutes) than the four volunteers. Patients were given activated charcoal prior to their control studies. Volunteers were not given activated charcoal. Furthermore, patients were attending the nuclear medicine department for the first or second time depending on whether they had their initial scans done in the department or in the intensive care unit. This meant that they were unfamiliar with the imaging environment. By way of contrast the volunteers worked in the nuclear medicine department and were familiar with the environment and the apparatus. This meant that they were under far less pressure than the patients. Stress is known to delay gastric emptying.

Finally, the fact that the paracetamol itself might have altered gastric emptying in the volunteers has profound implications for those using the paracetamol absorption test as an index of gastric emptying rates. A fundamental premise of the test is that paracetamol does not alter gastric emptying. As I have indicated there is a need for more and larger studies to elucidate the effects of therapeutic doses of paracetamol on gastric emptying.



CONCLUSION AND RECOMMENDATIONS

At the beginning of this study a number of questions were posed. Each of these can now be answered.

- 1. Do overdoses of certain commonly used drugs alter the time it takes for the stomach to empty? If so, is this time shortened or prolonged - that is, to what extent is the rate of gastric emptying altered? And do overdoses of the aforementioned drugs alter small intestinal transit times? If so, to what extent?**

In answer to the first question the reply is an unequivocal yes for both parts. Poisoning with all of the drugs tested, retards gastric emptying and inhibits small intestinal transit. Indeed, gastric emptying and small intestinal transit times were markedly increased in a considerable number of patients. This has profound implications in our understanding of the pathological changes induced by overdose and for clinical management.

Gastric emptying and small intestinal transit were significantly prolonged in patients with paracetamol overdose, especially in those whose levels fell within the toxic range. This finding is unexpected as paracetamol is not known to alter gastric emptying or inhibit small intestinal transit. Taken together with the findings in the small group of volunteers studied in Part 3 (Paracetamol Control Study) the results in Part 1 indicate that paracetamol might well play a role in gastric emptying delay and small intestinal hypomotility. This is of great pharmacological, pathophysiological and clinical significance. In addition, the finding that paracetamol might prolong gastric emptying calls into question the fundamental premise upon which the acetaminophen absorption test is based. Further research is required into the effects of paracetamol on gastrointestinal motility.

Although it would be tempting to invoke a direct causal relationship between drug overdose and gastric emptying delay and small intestinal hypomotility, the statistical tests suggest that the matter is more complex. No significant correlation was found between drug levels and prolonged gastric emptying and small intestinal transit in Part 1. The results of statistical analyses indicated that the various drugs might have a subordinate role in reducing gastric emptying rates and small intestinal transit times. Furthermore, the type of drug appears to have little influence. In Part 2, however, tricyclic antidepressant and opioid levels correlated significantly with gastric emptying half-times. Further research is needed to determine the cause and mechanism of the inhibition of gastrointestinal motility and gastric emptying in patients with poisoning.

I have postulated that stress might play a significant role in delaying gastric emptying in my patients. I did not attempt to quantify the level of stress but I feel that the combination of psychological and emotional factors that lead to self-poisoning must have been considerable; considerably greater than could have been artificially created in an experimental situation. Further studies should be carried out to determine the influence of different forms and levels of stress on gastric emptying. The fact that patients who were obtunded and/or confused had significantly longer gastric emptying half-times might support the theory of a central mechanism inhibiting gastrointestinal motility.

Another possibility is a reflex response of the gastrointestinal tract to excessive amounts of drug. This might saturate certain receptors in the small intestine (and possibly the stomach) and set off inhibitory responses via neural and humoral pathways. The virtual paralysis of the stomach prevents further passage of poison into the intestine from where it could be absorbed. The extremely slow seepage of poison into the small intestine retards its absorption

thereby reducing the maximum plasma levels. Theoretically, this should temper the clinical condition and ultimately improve the patient's outcome. More studies are needed to test this assumption. Controlled studies with and without a prokinetic agent to enhance gastric emptying of certain drugs might provide an answer.

2. Does management with sorbitol, an osmotic laxative, have an effect on the changes caused by the drugs?

I found that sorbitol had no effect on gastric emptying in patients with poisoning in my study. Gastric emptying rates were the same in the sorbitol group of patients as in the group without sorbitol. Patients who ingested overdoses of paracetamol, carbamazepine and phenytoin had significantly shorter small intestinal transit times than their counterparts who did not receive sorbitol. It appears, therefore, that sorbitol enhanced small intestinal transit in these patients. In contrast, sorbitol was found to have no significant effect on small intestinal transit of patients who ingested overdoses of tricyclic antidepressants and opioids.

3. Are there problems with the use of nuclear medicine techniques in gastric emptying, motility and small intestinal transit in patients with poisoning?

Gastric scintigraphy has proven to be a very valuable tool in patients with poisoning. It has the advantage of using radiopharmaceuticals which are not

absorbed by the gut and do not influence gastric emptying rates. The study can be carried out at the patient's bedside without any interference with clinical management. It has the advantage of being simple, non-invasive and safe.

However, certain problems arose. Firstly, although dynamic scintigraphy proved useful for recording gastric hypomotility, it became clear that expertise is necessary for reading and interpreting these dynamic gastric studies. With more experience this technique could become an important part of the nuclear physician's armamentarium. Secondly, it was difficult to identify accurately the region of small intestine occupied by the radioactive meal. The ileocaecal region proved difficult to identify in a minority of patients. However, this remains a useful method for evaluating small intestinal transit.

Scintigraphy is therefore an excellent instrument for measuring alterations in normal physiological functions like gastric emptying and gastrointestinal motility.

IMPLICATIONS FOR MANAGEMENT

The implications for management depend on when the marked inhibition of gastrointestinal motility occurs. If this happens before the bulk of poison has passed into the small intestine then the drug would remain in the stomach for several hours following its ingestion. This makes it accessible to activated charcoal and/or other gastric decontamination measures even when the patient presents many hours after poisoning. On the other hand, if the gastrointestinal paresis occurs after a considerable proportion of poison has passed into the small intestine then gastric decontamination would prove less or ineffective.

Small intestinal transit was enhanced by sorbitol after poisoning with paracetamol, carbamazepine and phenytoin. Given the adverse side effects, careful consideration should be given to using sorbitol in patients poisoned with these drugs. Sorbitol did not increase the rate of small intestinal transit in patients with tricyclic antidepressant and opioid poisoning and is unlikely to prove effective in eliminating the poison in these patients.

RECOMMENDATIONS FOR FURTHER INVESTIGATIONS

1. THE EFFECT OF PARACETAMOL ON GASTRIC EMPTYING

Patients with paracetamol poisoning had gastric emptying times similar to those who had ingested overdoses of the other drugs tested. This is surprising as paracetamol is not known to inhibit gastric emptying. One of the healthy volunteers in my paracetamol control study showed a marked delay in gastric emptying half-time following a therapeutic dose of paracetamol (60 minutes) when compared with the gastric emptying half-time measured when he did not take paracetamol (21 minutes). In three other volunteers the initial gastric emptying half-times determined after paracetamol ingestion were also longer than when paracetamol was not ingested.

This response of gastric emptying to therapeutic doses of paracetamol warrants further study. A larger study of healthy volunteers before and after ingesting one to two grams of paracetamol is required to confirm or dispel the doubts regarding the effects of paracetamol on gastric emptying. In addition, a dose response study could be set up with gastric emptying half-times being measured after volunteers are given a placebo, 0.5 g, 1.5 g and 2.5 g of paracetamol.

2. THE EFFECT OF ACTIVATED CHARCOAL ON GASTRIC EMPTYING

Further study will be necessary to determine whether, and to what extent activated charcoal affects gastric emptying rates and motility. A number of healthy volunteers could have their gastric emptying half-times and motility measured scintigraphically. Different doses of activated charcoal

can be administered at different times and these parameters can be determined on each occasion. This should answer the question as to whether the activated charcoal influences gastric emptying.

3. THE INFLUENCE OF N-ACETYLCYSTEINE ON GASTRIC EMPTYING

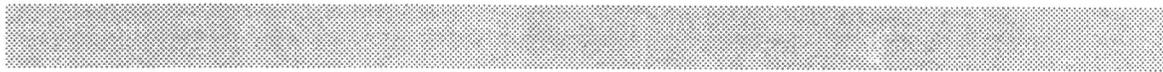
A study is required in which the role of N-acetylcysteine in gastric emptying and motility is evaluated. However, this might be difficult to perform on volunteers because there are a number of side-effects associated with its use. I have shown that gastric emptying half-times of patients who had toxic levels of paracetamol differed significantly with those who did not. Most of these patients received intravenous N-acetylcysteine either before or at some point during the study. A study could be done using oral N-acetylcysteine - a less invasive and potentially less noxious route.

4. Patients who have ingested overdoses of other drugs need to be studied to confirm whether gastric emptying and small intestinal rates are reduced. This would support the hypothesis that the drug type has little influence and that other factors play a more important role in delaying gastric emptying in self-poisoning.
5. Gastric emptying and intestinal transit should be studied in patients who have ingested drugs which have no known effect on the central nervous system. All the drugs that I tested have some central effect.
6. Gastric emptying rates and intestinal motility should be measured on patients with coma and confusion not related to overdosage to determine

the effects of the altered mental state on gastric emptying without interference from the drugs.

7. Gastric emptying studies should be done on patients who have attempted suicide by other means. This would support the hypothesis that stress plays a major role.

8. The assumption that with delayed gastric emptying the slow passage of the poison from the stomach into the small intestine leads to lower maximum plasma levels and, therefore, less toxicity and improved clinical status, should be tested.



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APPENDIX 1

EXCLUSIONS

Four patients were excluded from the Part 1 study. Three of these were the only patients to have ingested overdoses of phenobarbitone. The other patient ingested an overdose of paracetamol and was being treated with a powerful anticholinergic drug, clozapine at the time of the control study.

GASTRIC EMPTYING HALF-TIMES:

	Overdose	Control
Phenobarbitone:		
Patient 1	9	7
Patient 2	137	32
Patient 3	23	27
Paracetamol:		
Patient 1	55	113



APPENDIX 2

1 COLLIMATOR TESTS

It was anticipated that a number of ill patients would be imaged in the intensive care unit on a mobile gamma camera. A suitable collimator had to be chosen for the camera. The diverging collimator permitted visualisation of the entire abdomen on a single image. Use of the parallel-hole collimator of the type used on the bigger cameras in the nuclear medicine department to scan the rest of the patients meant doing two sets of images on certain patients so as to see all of the radioactive meal. I performed uniformity tests on both collimators so as to ensure that the collimator that was used was reliable.

EVALUATION OF COLLIMATORS FOR MOBILE STUDIES ON THE GENERAL ELECTRIC 300a MOBILE GAMMA CAMERA.

Studies were done to determine whether the mobile camera equipped with a low energy diverging collimator (ledc) was appropriate for scanning patients in the intensive care unit. Because of the known distortion of images produced with the diverging collimator it was decided to measure the uniformity of response over the entire field of view (fov) of this collimator and to compare this with the lepc.

1.1 UNIFORMITY

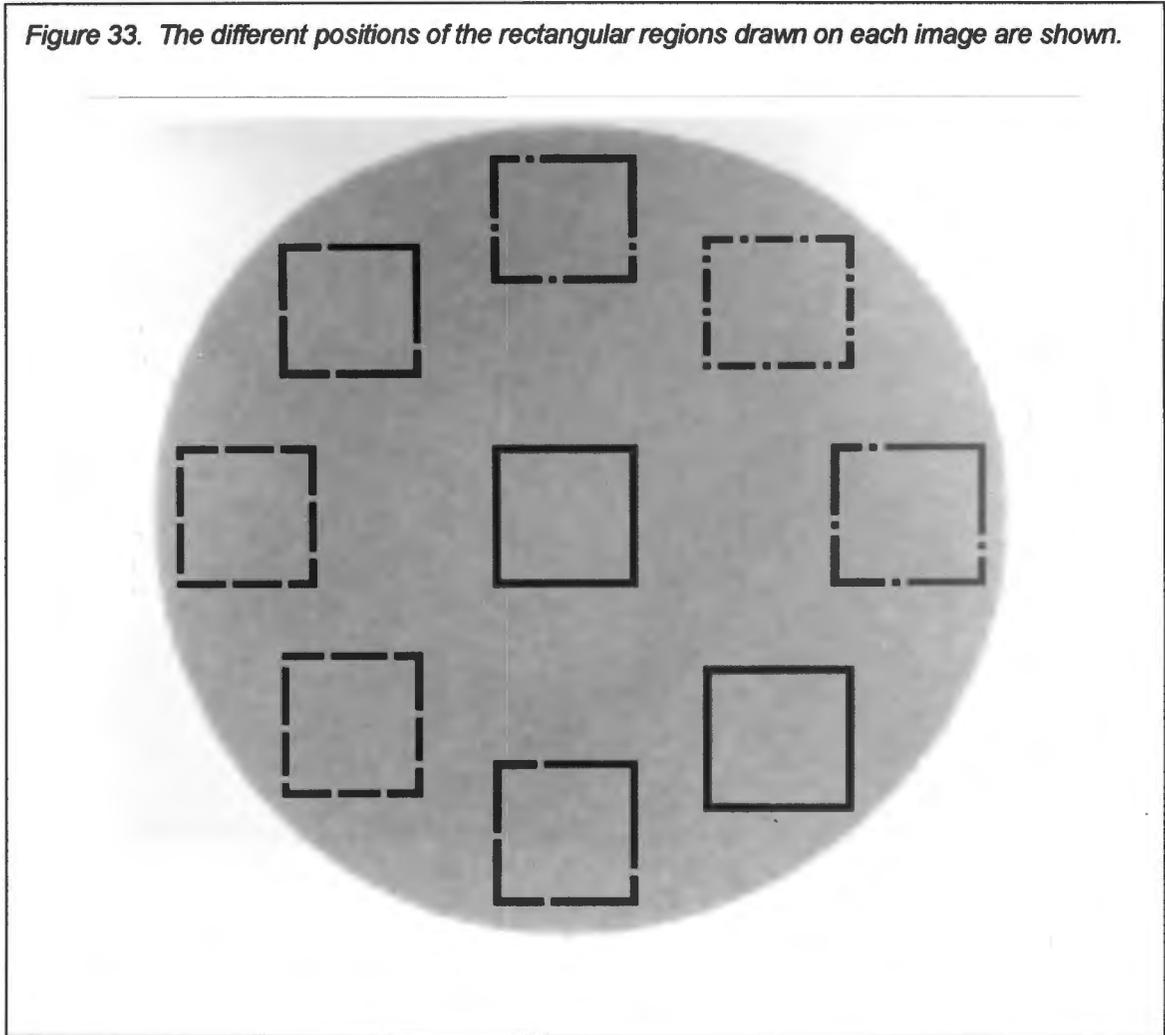
Integral and differential uniformity measurements were made for both the ledc and the lepc. A refillable flood source was uniformly filled with 150MBq of ^{99m}Tc pertechnetate. The detector fitted with the ledc was placed at the following distances from the flat-field source: 2.5, 5, 10, 15, 20, 30 and 35cm, and it was positioned at 2.5, 15 and 30cm from the source when fitted with the lepc. Uniformity was calculated for the full field of view (ffov) and the central field of

view (cfov) for each collimator at the different distances from the source. Software used for the uniformity measurements is supplied with the camera and is based on the National Electrical Manufacturers' Association (NEMA) standards.

1.2 DIVERGING AND PARALLEL-HOLE COLLIMATORS: A COMPARISON

The detector fitted with the ledc was placed at the same distances from the radioactive source as in 1.1. Images were taken for 10 minutes at each distance. Rectangular regions of equal size were drawn in the following positions on the images: in the centre and at 12, 1.30, 3.0, 4.30, 6.0, 7.30, 9.00 and 10.30 o'clock (**Figure 33**). The counts were measured in each of these regions and the percentage difference was calculated between counts at the centre and counts at the other sites.

Figure 33. The different positions of the rectangular regions drawn on each image are shown.



1.2.2 The study was repeated after fitting the detector with a lepc. Images were obtained at distances of 5, 15 and 35cm with this collimator. Percentage differences were calculated in the same way as for the ledc.

RESULTS

The diverging and parallel-hole collimators on the mobile camera were tested for uniformity and variation in response over different distances from a radioactive source in order to select the most suitable collimator for the mobile studies.

1.1 UNIFORMITY EVALUATION

TABLE 1 DIVERGING COLLIMATOR

Dist (cm)	Integral Uniformity		Differential Uniformity	
	FFOV	CFOV	FFOV	CFOV
2.5	8.16	5.26	3.63	3.05
5	8.07	5.12	4.65	2.79
10	8.45	5.46	4.11	3.29
15	8.81	5.33	4.03	3.63
20	7.92	5.28	4.64	3.35
30	8.56	5.95	4.72	3.47
35	8.49	6.11	3.55	3.57
Mean	8.35	5.50	4.20	3.31
SD	0.31	0.38	0.5	0.3
COEF VAR	3.7	6.9	11.9	9.1

TABLE 2 PARALLEL-HOLE COLLIMATOR

Dist (cm)	Integral Uniformity		Differential Uniformity	
	FFOV	CFOV	FFOV	CFOV
2.5	7.77	5.35	4.12	3.28
15	8.31	6.48	4.29	3.28
30	7.49	5.39	3.95	3.73
Mean	7.86	5.74	4.12	3.43
SD	0.42	0.64	0.17	0.26
COEF VAR	5.3	11.1	4.13	7.6

1.1.1 Integral Uniformity - FFOV

The t-test showed no statistical difference between the diverging and parallel-hole collimators. P = 0.09.

1.1.2 Integral Uniformity - CFOV

No significant difference was shown between the two collimators. T-test p value = 0.3.

1.1.3 Differential Uniformity - FFOV

No significant difference was demonstrated between the two collimators. P = 0.9.

1.1.4 Differential Uniformity - CFOV

Differences in the collimators were not significant. $P = 0.9$.

There are therefore no significant differences between the diverging and parallel-hole collimators regarding both integral and differential uniformity.

1.2 TABLE 2: COMPARISON BETWEEN DIVERGING AND PARALLEL-HOLE COLLIMATORS FOR USE ON THE MOBILE GAMMA CAMERA.

Test of variation in collimator response over full field of view.

DIVERGING COLLIMATOR: PERCENTAGE DIFFERENCE FROM THE CENTRE

Distance (cm)	Percent difference
2.5	-4.7
5	-4.5
10	-5.2
15	-5.6
20	-6.1
30	-7.4
35	-7.9
Mean	-5.9
SD	1.3
COEF VAR	22.0

PARALLEL-HOLE COLLIMATOR

Distance (cm)	Percent difference
5	-4.7
15	-4.3
35	-3.9
Mean	-4.3
SD	0.4
COEF VAR	9.3

There is a significant difference in deviation from the centre when comparing the diverging with the parallel-hole collimator. P value = 0.039. The diverging collimator demonstrates a more significant variation in response from the centre to the periphery than the parallel-hole collimator. Therefore, I selected the parallel-hole collimator for imaging patients on the mobile camera even though this meant having to do two images instead of one on several patients.

DISCUSSION

1.1 UNIFORMITY MEASUREMENTS

The comparison of uniformity measurements between the diverging and parallel-hole collimators demonstrated that both the collimators fell well within the manufacturer's specifications for central field of view (CFOV) uniformity (General Electric User Manual Rev 04-90). The manufacturer's test determined the uniformity with a point source and with no collimator. Despite using a flood-field source and the collimators (which make for a tendency to greater non-uniformity), both collimators were well within the specifications of less than 8% for integral uniformity (CFOV) and less than 5% for differential uniformity (CFOV). There was no significant difference between the two collimators for uniformity measurements of FFOV and CFOV.

1.2 COMPARISON BETWEEN DIVERGING AND PARALLEL-HOLE COLLIMATORS FOR THE MOBILE CAMERA

As the diverging collimator showed a greater variation in response across the crystal face, the parallel-hole collimator was selected for imaging patients on the mobile camera in the intensive care unit.

