GASTRO-OESOPHAGEAL REFLUX

AND

THE SUDDEN INFANT DEATH SYNDROME

Observations on gastro-oesophageal reflux in infants at increased risk for the Sudden Infant Death Syndrome

By

JAMES Y PATON

Thesis presented for the Degree of Doctor of Medicine

University of Leicester

1987

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

To Ann

TABLE OF CONTENTS

DECLARATION

I declare that this thesis is my own composition and that I carried out the work described.

The thesis has not been submitted for a degree of another University.

James Y. Paton

ACKNOWLEDGEMENTS

The work described in this thesis was undertaken while holding the post of Research Assistant to Professor Hamish Simpson in the department of Child Health at the University of Leicester. Professor Simpson initiated and supervised the research undertaken and his friendship, understanding and support throughout the project has been unfailing and unstinting. I should like to thank the Foundation for the Study of Sudden Infant Death for financial support throughout.

It is a pleasure to record my sincere gratitude to the people who directly and indirectly helped in this research.

I am indebted to Dr Peter Swift who contacted parents and informed me of the birth of siblings of SIDS victims and to the other consultants and medical staff in the paediatric units in Leicester who referred cases for study.

I owe a special debt to my research colleagues Dr U Macfadyen, Dr C Beardsmore and Dr CS Nanayakkara who provided advice, assistance and discussion in these and related studies. Dr Macfadyen particularly helped by using her expertise in sleep physiology to score all the sleep studies.

The technical staff in the department of Child Health were always enormously helpful. I am particularly grateful to Mrs Ann Williams for her painstaking assistance in the analysis of polygraphic traces, to Mr Paul Goodenough for his technical wizardry and to Mr Goff Sargent for his help and advice.

Mr PS Cosgriff and the staff of the radioisotope department at The Leicester Royal Infirmary willingly carried out nearly one hundred radionuclide scan studies in small, and not always peaceful, children.

I would especially wish to ackowledge the generous support of all the many parents who allowed me to study their babies.

Finally, a special personal thanks is due to Professor and Mrs Simpson for frequently welcoming a visitor into their home. Did I say finally? One person remains - my wife Ann. She has cheerfully endured an absent husband, and then long hours spent over a hated computer screen. The time should have been hers. My thanks.

LIST OF TABLES

LIST OF FIGURES

CHAPTER 6

CHAPTER 7

CHAPTER 8

LIST OF ABBREVIATIONS

AS	Active sleep
bpm	beats per minute
CA	Central apnea
ECG	Electrocardiogram
EMG	Electromyogram
EOG	Electrooculogram
GI	gastro-intestinal
GOR	Gastro-oesophageal reflux
Hg	Mercury
hr	hour
IS	Indeterminate sleep
LOS	Lower oesophageal sphincter
min	minute
mths	month
OA	Obstructive apnea
PtcO2	Transcutaneous oxygen tension
QS	Quiet sleep
RDS	respiratory distress syndrome
REM	Rapid eye movement
sd	standard deviation
sec	seconds
sem	standard error of mean
SIDS	Sudden infant death syndrome
UK	United Kingdom
UOS	Upper oesophageal sphincter
URTI	upper respiratory infection
yr	year

ABSTRACT

TITLE: GASTRO-OESOPHAGEAL REFLUX AND THE SUDDEN INFANT DEATH SYNDROME

AUTHOR: JAMES Y PATON

Gastro-oesophageal reflux (GOR) has been reported in infants presenting as 'near miss' for the sudden infant death syndrome (SIDS). This study investigated the occurrence of GOR in infants at increased risk for SIDS and examined the relation between GOR and cardio-respiratory abnormalities, particularly during sleep.

82 infants were studied by radionuclide scan: suspected tracheo-bronchial aspiration (7), sibs of SIDS victims (12), persistent possetters (8), mentally retarded (4), minor cardio-respiratory 'events' eg choking (29) and 'near miss' for SIDS (22). In 22 children respiration and heart rate were recorded simultaneously. To assess the relationship between GOR and cardio-respiratory events during sleep 24 infants, including 17 with significant GOR on scan, were monitored polygraphically during sleep at night with simultaneous lower oesophageal pH monitoring to detect acid GOR.

Radionuclide scan images were collected for two hours following a labelled milk feed. Severe GOR (to the upper oesophageal/pharyngeal level) was observed in 58 (70%), from each of the groups studied. 7/22 infants had both severe GOR and respiratory pauses >6sec but no clear relation between GOR and such pauses was observed.

The night studies confirmed that GOR was frequent in all 'at risk' groups. Cardio-respiratory abnormalities were also frequent but only 5 central apneas lasted longer than 10sec and no significant bradycardia (<80 bpm for >=10sec) was observed. A pathological finding was the presence of 56 mixed and obstructive apneas. No direct temporal relation was observed between the occurrence of GOR and cardio-respiratory abnormalities. An association between gross body movements and pH drops was noted with movement often preceding a pH drop.

These studies confirm that GOR is common in 'near miss' SIDS infants but demonstrate that it is also found frequently in other 'at risk' groups. Despite its frequent occurrence, GOR did not precipitate respiratory pauses or bradycardia.

CHAPTER 1

INTRODUCTION

CHAPTER 1

INTRODUCTION

Sudden Infant death syndrome (SIDS) is now the major post neonatal cause of infant death in the UK. It accounts for two deaths per thousand live births in the UK and has a peak occurrence between two and four months of age. Most SIDS deaths occur during the winter months and in the majority of SIDS victims there is a history of apparently minor symptoms within days of death.

The current belief is that SIDS victims die an asphyxial death. Any interruption of airflow to an infant's lungs would rapidly lead to hypoxaemia, hypercapnia, tissue hypoxia and acidaemia followed by circulatory failure and death. But what triggers the interruption of airflow to start this fatal sequence in infants who have otherwise not appeared unwell? Absence of airflow is the central feature of both central apnea (cessation of airflow at the nose and mouth with absent chest and abdominal movement) and obstructive apnea (cessation of airflow and continuing respiratory movements). Both types of apnea have been observed in infants and it has been suggested that either might initiate the sequence which culminates in SIDS. The question might then be reformulated; what triggers apnea, central or obstructive, in infants? This question has been the subject of considerable research.

One view is that infants who die of SIDS are in some way vulnerable from birth, or earlier, to "stresses" eg infections which the majority of infants shrug off. In such infants these "stresses" might trigger apnea and start a sequence of events, perhaps at a critical age or stage in post-natal development, culminating in SIDS. This idea of subtle pre-existing "defects" predisposing to cardio-respiratory abnormalities in response to stresses has led to investigation of many potential areas of vulnerability.

An alternative view is that all infants are potential SIDS victims, and share a common vulnerability at around three months of age. Then a particular stress or coincidence of stresses might be all that is required to precipitate death. With this view, the nature and severity of the various stresses and the particular environmental aspects of the death become of primary importance.

To date the idea of stresses acting on an infant has been studied from either an epidemiological (Stanton et al 1978) or a pathological (Werne 1942, Williams 1980) standpoint. For example, 59% of 145 victims of SIDS studied by Stanton et al (1978) had recent symptoms, predominantly respiratory, compared with only 16% of 154 controls. The nature and severity of naturally occurring stresses has received little attention (Abreu e Silva 1986). How such stresses might conspire to precipitate cardio-respiratory abnormalities such as apnea is not known and has been little studied.

Gastro-oesophageal reflux (GOR) is one possible precipitating stress that has attracted considerable interest following reports in the late 70's suggesting a link between GOR in infants and cardio-respiratory abnormalities. These reports described infants presenting with asphyxial episodes apparently directly precipitated by GOR, where, but for cardio-pulmonary resuscitation performed by the parent or attendant, it was believed the infant would have died.

Asphyxial episodes, for which cardiopulmonary resuscitation was performed and death supposedly averted, have been labelled 'near-miss' episodes. Such 'near-miss' infants have been studied frequently as a human model for understanding the physiological events that might lead to sudden unexpected death. A number of reports have described the finding of frequent GOR in 'near-miss' infants. The precise relationship between GOR and 'near-miss' episodes has been the subject of subsequent research but the results of these studies have been conflicting and the relation, if any, between GOR and cardio-respiratory abnormalities remains controversial.

The uncertain nature of the relation between GOR and asphyxial episodes allied with the exciting and plausible nature of the hypothesis and its potential importance as a "cause" of SIDS stimulated the present studies. This thesis describes studies designed to examine and evaluate the interrelation of GOR with cardio-respiratory abnormalities in infants considered to be at increased risk for SIDS.

The material in this thesis is presented in 9 chapters. In chapter 2 the literature is reviewed. The developing medical understanding of GOR in infants and children is traced from the initial awakening of interest through the increasing appreciation of the potentially serious pulmonary consequences of GOR to the current interest in the role of GOR in SIDS and 'near-miss' for SIDS. The areas of knowledge and uncertainty which form the background to this study are reviewed in detail. In chapter 3 the aims of the study, the questions posed and the hypotheses being tested are laid out in detail. In chapter 4 the selection of the index and control infants are described and the methods (and their limitations) outlined. The results relating to each question posed and a discussion of their interpretation, significance and relation to previous studies are presented in the next four chapters. In the final chapter, the main conclusions are summarised and their implications for further research are considered.

CHAPTER 2 page

BACKGROUND TO THE STUDIES

CHAPTER 2

BACKGROUND TO THE STUDIES

1 Gastro-oesophageal reflux (GOR)

"All the world's a stage,
and all the men and women merely players;
They have their exits and their entrances;
And one man in his time plays many parts,
His acts being seven ages. At first the infant,
Mewling and puking in the nurse's arms;
...."

As You Like It, Act II Scene 7
Shakespeare

That infants have a tendency to vomit has been known for centuries. Shakespeare recognised this in Elizabethan times; anatomical markers often present in vomiting infants such as hiatus hernia and shortened oesophagi, have been found in Egyptian mummies. Such persistent or recurrent vomiting in infancy has been given many different names eg "puking", "possetting", "wet burps" or "windy vomits", and is frequently regarded as entirely normal. However, in the last 40 years the medical complications of persistent vomiting in infants have attracted increasing attention.

Neuhauser and Berenberg (1949) described 24 infants with persistent unexplained vomiting in whom retrograde filling of the oesophagus through the oesophageal hiatus was detected during a barium swallow examination. This phenomenon was noted particularly during inspiration, or with increased intra-abdominal pressure. The vomiting could be alleviated by keeping the infants upright. These authors labelled this condition "chalasia" to emphasise the "apparently persistent relaxation of the hiatal portion of the oesophagus with failure of the gastric cardia to perform its usual 'sphincter' action". This was one of the first descriptions of gastro-oesophageal reflux (GOR) as a cause of vomiting in infants.

In the British literature, Astley and Carré (1954) described a similar group of infants with persistent vomiting and no other detectable cause. They concluded that the commonest cause of vomiting in such infants was not the persistent cardio-oesophageal relaxation described by Neuhauser and Berenberg but the protrusion of a small loculus of stomach through the oesophageal hiatus, demonstrable on barium studies. In this situation, the gastro-oesophageal junction lies within the chest. Astley and Carré called this condition "hiatus hernia" or "partial thoracic stomach", their preferred term. Subsequent reports by these authors of vomiting in childhood were confined to children with this abnormality.

Carré's studies (1959) showed that in 60-65% of untreated children the condition was benign and resolved by two years of age. Improvement occurred commonly around the time of weaning. Recognised medical complications included failure to thrive,

haematemesis secondary to oesophagitis and ulceration, and oesophageal stricture formation. In 35% vomiting and its complications did not improve with weaning to mixed feeding; in these children troublesome symptoms continued up to four years of age. Some 5% of the group on follow up had developed oesophageal strictures. Of the untreated children without oesophageal stricture formation around 5% died, usually of inanition and pneumonia. Hence, persistent, untreated vomiting in infancy was not always benign.

1.2 GOR and hiatus hernia

In these and other early studies, radiological techniques were used to investigate vomiting infants. The presence of a hiatus hernia (or partial thoracic stomach) came to be regarded as the anatomical marker of gastro-oesophageal incompetence and it was believed that the presence of a hiatus hernia played a central role in the development of vomiting by compromising the functioning of the lower oesophageal sphincter.

In adults, a high percentage of patients with symptoms related to GOR have a hiatus hernia, and for many years the relation between hiatus hernia and GOR was assumed to be one of cause and effect, similar to the situation described for children. However, in 1971 Cohen and Harris compared adult patients with chronic persistent reflux symptoms and asymptomatic persons, and found that the incidence of hiatal hernia was equal in both groups. In that report, measurements of lower oesophageal sphincter pressure showed a strong association between low sphincter pressures and reflux

symptoms, irrespective of the presence or absence of a hiatus hernia. The symptoms previously ascribed to hiatus hernia were in fact due to the reflux of gastric contents through the lower oesophageal sphincter.

Similarly, the use of sensitive techniques for detecting GOR in children, particularly prolonged lower oesophageal pH monitoring, has led to the realisation that in children too, GOR is the fundamental abnormality. Many studies have shown that significant GOR is frequently present with no evidence of hiatus hernia on barium studies. Astley and Carré (1954) had themselves acknowledged that in some children with a typical history the radiological examination was equivocal or negative. They attributed this to the transient nature of the abnormality but it can now be more easily explained as reflecting GOR without hiatus hernia.

It has therefore become clearer that the pathophysiological basis of this syndrome of vomiting in infants is GOR. The term, GOR, has been variously defined (Table 1) but the essential feature is included in a simple definition from Astley and Carré: "the reflux of gastric contents into the oesophagus". Some definitions restrict the term GOR to reflux into the lower oesophagus. However, it is often difficult to determine the extent of GOR as the situation is dynamic and varies from minute to minute and episode to episode. Hence, such a restriction does not seem useful. It has also become clear that GOR can occur without associated vomiting. Thus, while vomiting was an essential part of the original syndrome the emphasis is now on GOR as the important abnormality. It describes the primary event of which vomiting

is not a constant marker. Recent reports have recognised this change of emphasis and distinguish GOR from regurgitation; a symposium in 1985 recommended a more precise terminology (Platzker, 1985) (Table 2).

Clinical studies over the last 30 years have led to the recognition of a wide variety of complications attributable to GOR (Table 3).

Table 1: Definitions of GOR

1. Dysfunction of the distal oesophagus causing frequent return of stomach contents into the oesophagus (Herbst 1981).

2. Reflux of gastric contents into the oesophagus. (Astley and Carré 1953).

3. Any passage of stomach contents in a retrograde fashion through the LOS into the lower oesophagus. (Allen and Newhouse 1984).

4. Return of gastric contents to the lower oesophagus (Reid 1985).

5. The spontaneous passage of acidic gastric contents from the stomach into the oesophagus (Balistreri and Farrel 1983)

Table 2: Terminology and definitions

Term	Definition
Aspiration	Entry to the larynx/trachea during air breathing
Penetration	Entry to the larynx/trachea during swallowing
Reflux	Return of gastric contents to lower oesophagus
Regurgitation	Return of oesophageal or gastric contents to pharynx
Emesis	Expulsion of gastric contents out of the mouth

Reid LM Am Rev Respir Dis 1985; 131: Suppl; S60-S61

Table 3: Clinical manifestations of GOR

1. Growth: Failure to thrive

2. Gastrointestinal:
   a. Heartburn / irritability / abdominal pain
   b. Oesophagitis and oesophageal stricture
   c. Oesophageal spasm
   d. Haematemesis / melaena. Iron deficiency anaemia
   e. Finger clubbing / protein losing enteropathy

3. Pulmonary:
   a. Aspiration pneumonia
   b. Asthma or recurrent wheeze
   c. Chronic respiratory disease
   d. ? SIDS or 'near-miss' for SIDS

4. Others (rare):
   a. Rumination
   b. Sandifer syndrome
   c. Neuropsychiatric syndromes

1.3 The lower oesophageal sphincter

1.3.1 Physiology

GOR occurs when there is a pressure gradient between stomach and oesophagus sufficient to overcome the intervening pressure barriers and cause retrograde flow of gastric contents into the oesophagus. Normally, there are physiological mechanisms which prevent GOR occurring (Diamant 1985). The lower (LOS) oesophageal sphincter bars entry to the lower oesophagus while the upper (UOS) oesophageal sphincter prevents reflux extending into the hypopharynx with the attendant risk of aspiration into the lungs. These sphincters act by maintaining a local pressure barrier with a pressure greater than that found at rest either in the stomach or oesophagus. Should any material breach the LOS then oesophageal peristalsis, voluntarily initiated by the act of swallowing or by oesophageal distension, clears the oesophagus of its contents and prevents refluxed material challenging the UOS.

The maintenance of closure of the LOS has traditionally been ascribed to a number of factors. These have included the H-shaped lumen of the oesophagus, the "pinchcock" effect of the muscular right crus of the diaphragm and the natural obliquity of insertion of the oesophagus into the stomach maintained by the oblique fibres of the stomach wall and the sling-like action of the right crus of the diaphgram. The final element is the sphincteric action inherent in the lower oesophageal muscle. Views of the importance of this physiological sphincter have changed with time and it is now regarded as the major barrier preventing GOR (Werlin et al 1980).

In adults, the LOS is a zone of high pressure 3-5cm long with the pressure normally between 15-30mmHg. It is not an anatomically distinct sphincter but has special physiological features. It has three main functional characteristics; resting tone, relaxation with a swallow and active contraction.

Resting tone serves to separate negative intrathoracic pressure from positive intra-abdominal pressure, and to prevent GOR. The LOS exhibits high resting pressure in vivo and high resting tonus in vitro. Pressure and tonus are largely myogenic in origin as they are scarcely affected by non-specific neural blockade. Circulating hormones may modulate resting LOS pressure but no known hormones have been demonstrated as essential for its maintenance. The LOS tonus is maintained in vitro in the absence of extrinsic hormonal and neural influences but these influences may have a modulating role in vivo (Hillemeier and Biancani 1985).

Relaxation of the LOS allows free passage of the swallowed bolus into the stomach. Active relaxation of the LOS is neurally mediated through postganglionic nonadrenergic noncholinergic inhibitory fibres with an input from vagal fibres. The neurotransmitter for these inhibitory fibres is probably vasoactive intestinal peptide (Biancani et al 1984).

The active contraction of the LOS occurs in sequence with the advancing oesophageal peristaltic waves, and on other occasions, in response to or in association with events that can predispose to GOR such as increased intra-abdominal pressure or gastric contractions.

Both LOS pressure and LOS length change with age (Diamant 1985). In infants at birth, there appears to be no relationship between the LOS pressure and the birth weight or gestation, at least between 32 and 40wks. There is the suggestion that LOS pressures are relatively low at birth and perhaps for the first week or two of life, but this is not a consistent finding (Strawcynski et al 1964, Vanderhoof et al 1978). Thereafter, the pressures tend to be higher than those usually seen in adults but settle to adult levels between 1 and 3yrs of age. In adults, complicated symptomatic GOR is usually associated with decreased LOS pressure. However, in infants the relation of GOR and low LOS pressure is less clear. In most infants with GOR, LOS pressures are not decreased, but are on average slightly lower than in control subjects. As the infants mature and regurgitation and GOR diminish sphincter pressures increase in some.

A second consistent feature of the LOS is a change in LOS length as infants mature. The sphincter varies between 0.5 - 1cm at birth depending on the measurement techniques employed and increases to about 1.5cm in length by 1yr. Infants and children with regurgitation and GOR tend to have shorter sphincters particularly after the age of 6mths. This suggests that the bulk of the sphincter muscle plays an important role,

even though this is not reflected in the measured LOS resting pressure (Moroz et al 1976).

1.3.2 Pathophysiology of reflux

The original studies of Neuhauser et al (1950) and Astley and Carré (1954) postulated an abnormality in function of the LOS due either to a temporary neuromuscular problem causing persistent relaxation or the anatomical abnormality of partial thoracic stomach which placed the LOS at a mechanical disadvantage. Subsequent research has not substantiated these suggestions. Some workers have suggested that GOR is likely in young children when basal pressure is low (Euler and Ament 1977) but there is usually no clear correlation between clinically significant GOR and low LOS pressure (Moroz et al 1976).

In adults, episodes of inappropriate LOS relaxation are the main cause of GOR in normal and symptomatic patients (Dodds et al 1980; Dodds et al 1982). LOS relaxation is considered inappropriate when it occurs in the absence of oesophageal peristalsis. The situation in children appears similar. Werlin et al (1980) reported combined LOS pressure and oesophageal pH measurements in 29 children with known or suspected GOR. They found that only a small percentage of GOR episodes were associated with a low basal LOS pressure. Most reflux episodes were associated with intervals of normal basal LOS pressure accompanied by either transient inappropriate relaxation of the LOS, transient increase in intra-abdominal pressure, or both. The inappropriate LOS relaxations were not related to

swallowing or to other triggering events detectable by manometry. GOR occurred during the brief intervals of LOS relaxation. The transient nature of LOS relaxation may explain why many children with GOR have sample values of LOS pressure within the normal range. The mechanism of inappropriate LOS relaxation has not yet been determined.

2 GOR in normal infants

The amount of information available on GOR in normal infants and children is surprisingly scanty largely because ethical constraints have precluded comprehensive studies of GOR in healthy asymptomatic infants. As recently as 1985, a major symposium stressed the need to assess normal values for GOR more definitively (Cohen, Am Rev Respir Dis 1985; 131: Suppl S61).

For obvious reasons information on normal infants is not obtainable from barium studies or radionuclide gastro-oesophageal scans. In adults prolonged lower oesophageal pH monitoring has been the most widely used method for investigating both the physiology and the pathophysiology of GOR. In the main, the information that is available in infants and children has also come from oesophageal pH studies. These studies were made possible by the development of small rugged pH probes, suitable for use in infants and young children, which allowed monitoring for GOR over an extended period.

In adults, lower oesophageal pH monitoring has shown that normal volunteers have GOR, without symptoms, in both the supine and upright positions (Johnson and Demeester 1973). Such "physiological" reflux rarely occurs during sleep but is the rule during and after eating. Patients with symptoms of GOR have proportionally more time with reflux, both overall and in particular positions eg upright or supine than do asymptomatic subjects. In addition, the number of single reflux episodes, of episodes lasting longer than 5 minutes and the duration of the single longest reflux episodes are all significantly greater in symptomatic patients than in asymptomatic controls (Johnson and Demeester 1973). In normal adult volunteers, the oesophageal mucosa is exposed to acid for approximately 2% of the time spent in the upright position and 0.3% of the time spent recumbent.

These observations establish that some GOR is physiological in adults. Almost all healthy individuals will have occasional episodes of GOR and there is no qualitative difference between normal and abnormal reflux; the distinction is quantitative and depends on the frequency and duration of reflux.

Adult studies have also shown that oesophageal pH varies from 5-7. A pH of 4 has usually been chosen as marking the occurrence of GOR. This follows a study by Tuttle et al (1961) which showed that, in adults, a pH of 4 marked the subjective onset of pyrosis when acid was perfused into the distal oesophagus. In addition, peptic activity is minimal at pH 4 (20%), and absent at pH 5 or above. Even though gastric acid may not account for all the clinical manifestations of GOR

(Johnson 1981), the acid pH of gastric secretion in the normally neutral distal oesophagus is an excellent indicator of the occurrence of GOR.

The application of lower oesophageal pH monitoring to infants and children depended on the development of a probe sufficiently small to pass through an infant's or child's nose into the oesophagus. Once such probes became available they were quickly applied to studying GOR in infants. Most such studies have also used an oesophageal pH below 4 as a marker of GOR. However, there are no studies in infants or young children to confirm that this pH level is a satisfactory and appropriate indicator of GOR in this age group. Indeed, there is some reason to suspect that a pH of 4 will result in some episodes of GOR being missed. In young infants gastric acidity is low especially in the newborn period. In addition, frequent feeds of milk with a pH around 6 may have a potentially important buffering capacity. Mason (1962) has shown that in breast fed infants in the first 2wks of life it can take over 2hrs for the mean stomach pH to fall below pH4 after a feed. Hence, using pH 4 as the marker for GOR may underestimate the number of episodes GOR which occur.

The following section is a resume of information on physiological GOR in infancy and childhood culled from published reports of lower oesophageal pH monitoring in normal infants and asymptomatic controls.

In 1978, Jolley and his associates published one of the first reports of extended lower oesophageal pH monitoring in children. 38 children ages from 16days - 12yrs were studied. Twenty four (24/38, 70%) had no history suggestive of GOR while 14 (39%) had well-documented histories of recurrent, effortless vomiting. Hiatus hernia was demonstrated in 8 of the latter children. The pH probe was positioned under radiological control approximately 2.5cm above the gastro-oesophageal junction. GOR was defined as a pH of less than 4 for greater than 15sec. Recordings were divided into periods less or greater than 2hrs post feed. The values calculated included: the number of GOR episodes per 12hr; number of GOR episodes greater than 5min; longest episode of GOR during the monitoring period in minutes and percent time with pH less than 4. These were derived from measurements when the subject was awake and sleep, upright or supine. These results were combined in a scoring system and normal values were calculated for the asymptomatic children. The calculated values are listed below for the twenty four control infants:

Oesophageal pH monitoring in 24 asymptomatic children - Jolley et al 1978

	<2hr postcibal mean +/- sd		>2hr postcibal mean +/- sd	
	Awake	Asleep	Awake	Asleep
Episode (no/12hr)	21.6+/-24.5	10.2+/-16.8	7.7+/-7.6	0.7+/-1.3
Longest episode (min)	8.8+/-14.9	5.2+/-9.4	1.5+/-1.7	0.4+/-0.9
%time pH <4.0	8.2+/-10.1	5.9+/-11.9	1.2+/-1.3	0.1+/-0.3

From this data, GOR is particularly frequent in the two hours following food. There is considerably less GOR during sleep, particularly after the 2hr post feed period. These children ranged in age from 1mth to 12yrs and were, therefore, not wholly representative of an infant population. However, it can be seen that GOR occurs in asymptomatic individuals. The pattern of GOR is similar to that in adults with GOR being frequent after feeds and least common during sleep. In this study the control patients were easily separated from the symptomatic patients by the >2hrs post-feed pH score.

In 1980 Sondheimer reported a study of continuous lower oesophageal monitoring in 17 infants <2yrs and 6 age matched controls. Of the latter, 5 had feeding problems and 1 was an asymptomatic twin of an infant with reflux. There were a number of differences from Jolley's study. The infants were kept in a fixed position - supine at a 30deg angle in an infant seat - and were handled as little as possible during the study. They were fed alternately apple juice (pH 3.5-4.0) and cow's milk formula (pH 6.5-7) rather than solely milk. The probe was sited 87% of the distance from nose to LOS (13% orad of the LOS) located by oesophageal manometry. GOR was judged to have occurred when the pH fell below pH 4 for at least 8sec preceded and followed by at least 4sec above pH 4. The state (awake or asleep) of the infants was not noted. The values for the 5 controls after milk feeds are summarised below:

Oesophageal pH in 6 control children - Sondheimer (1980)

After milk feed	<2hr postcibal	>2hr postcibal
Episodes/hr	0.3+/-0.2	1.2+/-0.8
%time pH <4.0	0.4+/-0.2	1.2+/-0.8

+/- sem

The percent time with pH <4 in the less than 2hr post-prandial period is less than in Jolley's study (1978) and the number of episodes/12hr considerably less. This may reflect the younger age range of Sondheimer's patients in whom frequent milk feeds comprise much of the diet, and the resultant effect of the higher pH and buffering capacity of

milk. This may result in failure to detect GOR in the early post-feed period. This explanation is consistent with Sondheimer's finding that apple juice (pH <4) enhances reflux detection in the two hour post feed period. Sondheimer found the best discriminator between symptomatic and asymptomatic reflux was the amount of GOR present in the two hour post-feed period after a clear acid feed. What is noteworthy in these control infants is the very small amount of acidic GOR present. The overall percent pH <4 time of 1.7 +/- 0.5 was very similar to the value obtained in normal adult volunteers (Demeester et al 1980).

Jolley et al (1981) studied the effect of feeding on the frequency and duration of GOR in the 2hr post-feed period. 28 symptomatic and 28 asymptomatic children were studied using both milk and clear acid feeds with a lower oesophageal pH probe to detect GOR. Details of the selection of the asymptomatic children were not given. However, 16 were male, 7 were less than 1yr and 16 less than 3yrs. In asymptomatic children, GOR was frequent up to 2hrs after a clear liquid feed and the pattern of reflux the same regardless of whether the children were more or less than 3yr old. After a milk feed, there were fewer GOR episodes than following apple juice, confirming Sondheimer's findings (1980). Jolley et al (1981) were not able to determine directly whether non-acid gastric contents refluxed in this period. After 2 hours, in the asymptomatic children the GOR frequency was not influenced by the type of feeding. This suggests that by two hrs the pH of

gastric contents had fallen below 4, reminiscent of the time found by Mason (1962) that it takes for gastric pH to fall below 4 in very young infants.

The results of these studies of GOR (Jolley et al 1978 & 1981, Sondheimer 1980) in the >2hr period after a cow's milk feed agree in terms of both the number of episodes with pH<4 per hour and the per cent time pH <4. However, despite similar probe positioning and data analysis there is a substantial difference in the findings for GOR in the <2hr post-feed period in asymptomatic infants. Jolley (1978) reports a more than twelve fold excess in per cent time pH <4 when compared with Sondheimer (1980) (5.9% vs 0.4%) and a similarly large excess in pH episodes <pH 4 (10.2 vs 3.6). The reasons for this difference is not obvious. Interestingly, the results of Jolley's 1981 report in the <2hr post-prandial period following a milk feed are much more in line with Sondheimer's findings (episodes per hr: 0.1 vs 0.3; %time pH <4: 0.4 vs 0.4). These findings highlight the difficulties in comparing different groups of asymptomatic infants. How representative these findings are of those in normal infants is even more uncertain.

Jolley's values for the asymptomatic and symptomatic infants were similar in the first 2hr post-feed period for both milk and acid feeds. This led them to suggest that GOR is frequent in this period in all children. The difference between the two groups was greatest in the second 2hrs period after a feed. In the symptomatic patients, the frequency and duration of GOR, reflected in pH scores, correlated with the presence of oesophagitis.

Boix-Ochoa et al (1980) reported a study of 123 children between 6mths and 6yrs. Included in this group were twenty children aged between 2mth - 3yrs with no symptoms of GOR who served as a comparison group. The pH probe was situated 2.5cm above the LOS determined manometrically. The frequency of episodes, number of episodes greater than 5min and longest episode were computed. The percent time the pH was less than 4, overall and separately for prone, seated and supine positions was also calculated.

The 'normal' group demonstrated some GOR in all three positions, without associated symptoms. In the supine position the number of refluxes was higher, but in the prone position episodes lasted longer. In the seated upright position the number of refluxes was lower and the oesophageal clearance faster. In the study as a whole it was noted that the longest percent time <pH 4 occurred in the prone position. Boix-Ochoa attributed this to slower oesophageal clearance in this position. The results from the 'normal' group is included in table 4.

In a study confined to infancy, Koch and Gass (1981) reported the findings in 8 infants between 5wks and 11mths with recurrent vomiting, and 7 asymptomatic infants of similar ages. The infants were studied with a 3mm probe situated 3cm proximal to the LOS over a 20-24hr period. Values were computed for percent time pH<4, frequency of episodes / 24hr, number of episodes greater than 5min / 24hr, and longest episode and were similar to the findings for adults of Johnson and Demeester (1974). Koch and Gass introduced the concept of oesophageal

clearance, measured as the time taken for oesophageal pH to rise from pH4 to pH6, which they found useful in differentiating between physiological and pathological reflux. In most cases the percent time less than pH4 distinguished the normal from the pathological.

The following table (Table 4), summarises the results on control children from the studies of Koch and Gass and Boix-Ochoa et al, and gives for comparison the data from Johnson and Demeester's normal adult volunteers. Although the studies are of similar duration - 20-24hrs - the data of Johnson and Boix-Ochoa refers to a 24hr period while Koch's refers to a slightly shorter period of 20hrs. Normal formula feeds were used in the studies of Koch and Gass and Boix-Ochoa et al.

Table 4: pH data from adults, children and infants

	Group					
Reflux	(A)		(B)		(C)	
n	15		20		7	
	*					
	Mean	sd	Mean	sd	Mean	sd
Total no of episodes	20.60	14.77	10.60	8.20	15.67	15.54
Time pH <=4 (%)	1.47	1.38	1.86	1.60	.85	.53
No of episodes >5min	.60	1.24	1.73	2.05	.17	.41
Longest episode (min)	3.86	2.68	8.07	7.19	3.55	2.07

(A) Johnson and Demeester, 1974 - adults

(B) Boix-Ochoa et al, 1980 - infants and children

(C) Koch and Gass, 1981 - infants

* mean +/-sd

It can be seen that there is surprising agreement in the amount and frequency of GOR in these three studies despite the wide differences in age ranges.

The studies described have in the main analysed the pH traces in a manner similar to that originally described by Johnson and Demeester (1974) in adults. In order to assess measures of GOR, Byrne and Euler (1981) performed a comparative analysis of 17 different indices of GOR. These were computed from 49 studies in infants and children all suspected of GOR or GOR related problems (including pulmonary symptoms, failure to gain weight or apneic spells). 22 were judged asymptomatic during the observation period. In this study, the probe was sited at 87% of the distance from nose to LOS (ie 13% above the LOS) and an unrestricted diet was allowed. The ages of the two groups were similar and in each mean age was greater than 12 months. Two variables separated the groups with a high degree of reliability - number of episodes pH<4 /24hr (x) and number of episodes pH <4 for greater than 5 min (y) and a simple function involving these two variables was developed (x + 4y >= 50 : diagnosis = GOR).

It is reassuring that some of the analyses commonly used emerge as statistically useful in separating those children with presumed pathological GOR. However, this study illustrates the limitations of using an asymptomatic group as a control group. Many of the asymptomatic group had an earlier history of symptoms identical to those present at the time of observation in the symptomatic group. Thirteen (13/22, 59%) in the asymptomatic group had barium studies showing evidence of GOR.

Even in terms of symptom separation, Euler and Byrne's' tables show overlap between groups (eg 5/22 with weight <3% in controls vs 11/22 in symptomatic group). Conclusions about inter group differences in such apparently similar groups must be interpreted with caution.

As part of a study of the role of GOR in infants with apnea and cyanosis Berquist et al (1984) reported data on 11 control infants and 10 control adults. Feeds were acidified to below pH4, pH probes were sited 13% above the LOS detected by manometry and the sleep posture was horizontal. In this study the controls, both adult and infants, had a decreased frequency and percent GOR <pH4 in sleep when compared with the postprandial period. Table 5 gives the values obtained. The acid nature of the feeds ensured that all GOR was detected. Hence pH indices of reflux, particularly for infants, would be expected to be greater than for those receiving ordinary milk feeds. The values for infants and adults are again quite similar, and provides further confirmation that GOR is present, if infrequent, in controls.

Table 5: pH data from infants and adults given acid feeds

Infants n = 11 Age 13.5 +/- 12.7wks

Reflux	Sleep		Postprandial		Total	
	mean	sd	mean	sd	mean	sd
Time pH <=4 (%)	1.8	2.4	3.8	4.8	3.1	2.8
Longest episode (min)	5.3	6.8	5.0	5.7	8.0	6.3
Episodes /24hr	12.0	12.0	24.0	21.6	24.0	21.6

Adults n = 10 Age 33.5 +/- 3.1yrs

	mean	sd	mean	sd	mean	sd
Time pH <=4 (%)	.6	.3	6.4	3.2	3.0	.7
Episodes /24hr	14.4	4.8	96.0	14.4	43.2	7.2

From this brief review of GOR in normal or more commonly, asymptomatic children a number of common threads emerge.

Asymptomatic GOR occurs throughout the day and night. It is particularly frequent following a feed and seldom occurs during sleep. This is true for adults and children although there may be slightly more GOR during sleep in children. In general, the amount of GOR occurring in asymptomatic individuals is quite small. In adults the normal range is estimated to be up to 50 episodes per day with the pH being <4 for up to 4% of the total time (Demeester et al 1980). There is surprising similarity between pH indices of GOR in adults and asymptomatic infants and children (Table 4). In children and adults the majority of GOR episodes appear to be due to inappropriate, transient and unexplained LOS relaxation.

It is apparent that there are many technical variations among the published studies. Although the probes have been placed in the lower oesophagus the precise positioning has varied. As it is difficult to ensure absolute fixation of a nasal probe and some degree of movement is inevitable it is probable that differences in results from minor variations in the chosen probe placement will not be important. The use of the LOS, determined by oesophageal manometry, as a landmark is probably the best method for siting the probe in a relevant and reproducible position and is probably the ideal to ensure comparability between studies. The pH of feeds is more significant as acidification of feeds enhances the detection of GOR. In the studies discussed this enhancement is a presumed consequence of non-acid reflux which is most likely to be important in studies on young infants receiving frequent milk

feeds. It is difficult to decide on the optimum feed during pH studies but any such study should include an explicit statement of the type of feed given. Similarly, the positioning of the infant does appear to influence the occurrence of GOR and should be recorded.

The major criticism and limitation of the studies on infants and children to date relates to the choice of appropriate controls. In general, controls have been "asymptomatic" children in hospital. The precise criteria for selection are often not given and on some occasions the selected controls have seemed inappropriate. As a consequence information on physiological GOR is scanty. Efforts must be made, within current ethical constraints, to obtain the most appropriate age-matched controls possible, in every study.

3 GOR in relation to pulmonary disease

Three main categories of material can be aspirated into the lung: orally ingested material, oral or upper airway secretion and regurgitated gastric contents (Thach and Menon 1985). The first is well recognised in paediatrics and presents with symptoms such as choking with feeds. This review discusses the relation between aspiration of regurgitated gastric contents and pulmonary disease.

3.1 In adults

Aspiration of gastric contents in adults is a recognised cause of lung abscess and pneumonia and subsequent local fibrosis and bronchiectasis (Belsey 1960).

Over the last 40 years, it has become increasingly clear that aspiration of gastric contents into the lungs can also cause other serious respiratory illness. Mendelson's description (1946) of pulmonary aspiration during obstetric anaesthesia is the classic example. Mendelson described an asthma-like syndrome occurring in 40 patients following aspiration of liquid and recognised this as being due to the irritant action of gastric hydrochloric acid. More recently there has been much interest in the relation between GOR and asthma, particularly nocturnal asthma, and in the possible association of GOR with interstitial fibrosis (Allen and Newhouse 1984).

3.2 In infants and children

The appreciation that GOR is an important cause of pulmonary disease in children is more recent. Massive aspiration of food particles with sudden choking and death is well recognised, but it was only in 1960 that Carré drew attention to the association between nocturnal vomiting and respiratory infections in children with hiatus hernia. In his study of children with hiatus hernia he reported a threefold increase in the number of recorded pulmonary infections if nocturnal vomiting was present. He found no increase in

pulmonary infections with either frequent daytime vomiting or dysphagia. He suggested that many of the pulmonary infections recorded in these children were due to inhalation of vomited material when the patient was in a semi-conscious state.

By 1981 research had confirmed an association between GOR and recurrent or persistent pulmonary disease and Herbst was able to write that "chronic respiratory disease is a well-established complication of gastro-oesophageal reflux" (Herbst 1981). This association had been documented in infants and children with recurrent pneumonias and recurrent acute episodes of obstructive lung disease (Danus et al 1976, Christie et al 1978, Euler et al 1979, Berquist et al 1981). Clinical features reported have included recurrent acute cough, particularly nocturnal cough, wheeze and tachypnea. Strikingly, vomiting was often not a prominent feature and, in many, barium studies showed neither GOR nor evidence of a hiatus hernia. Demonstration of GOR was often difficult and multiple tests were required to confirm its presence. However, despite this difficulty, clinical improvement occurred in a large proportion of cases after effective treatment of the GOR. When these studies were undertaken the methodology of lower oesophageal pH monitoring had not been fully developed. Subsequently, Hoyoux et al (1985) have shown that reflux related chronic bronchopulmonary disease correlated best with GOR detected by pH monitoring. In their report the severity of bronchopulmonary disease was directly related to the amount of GOR implying a dose-response relation.

3.3 Diagnosis of aspiration

The elucidation of a relationship between GOR and pulmonary disease has been hampered by two factors. Firstly, until recently there has been a lack of reliable and sensitive tests for indicating the presence of GOR. The development of techniques for demonstrating GOR, such as prolonged ambulatory lower oesophageal pH monitoring, and the use of multiple tests has helped to place the detection of GOR on a more secure footing. However, demonstration of the occurrence of GOR can only result in an inference that reflux is responsible for the clinical symptoms.

The second and more persisting difficulty has been the lack of a test that will objectively demonstrate pulmonary aspiration. In many cases where GOR reflux is thought to be at the root of pulmonary disease there is often no evidence either from clinical history or X-ray to suggest aspiration (Herbst 1981).

Even in Mendelson's original description of an acute asthma-like reaction following presumed aspiration of liquid gastric contents during anaesthesia, it was noted that the actual episode of aspiration often escaped clinical recognition. The inference that aspiration was responsible for the clinical features followed from animal experiments in rabbits where the clinical, X-ray and pathologic features noted clinically in humans were reproduced by the inhalation of hydrochloric acid. Subsequent animal studies have confirmed that aspiration of large quantities of highly acidic material

causes haemorrhagic pneumonitis similar to a chemical burn. However, such large aspirations are very rare in the absence of an altered level of consciousness.

Actual aspiration of liquid material is seen very rarely during radiological studies. There was optimism that radionuclide scanning might lead to a better test for documenting pulmonary aspiration but unfortunately experience with this test has shown that aspiration is seldom identified. There have been reports of histological (lipid laden tracheal macrophages, Wagener et al 1980), chemical (lactose in tracheal aspirates, Hopper et al 1983) and immunological (raised milk antibody titres, Muller et al 1985) markers of aspiration. However, these have not proved consistently reliable and a satisfactory test to indicate pulmonary aspiration still awaits development.

3.4 Why do only some infants develop pulmonary damage?

There has been remarkably little attention paid to the features which predispose infants or children to develop pulmonary consequences of aspiration. Carré's original study (Carré 1960) suggested that in children nocturnal vomiting was one clinical feature characterising those with reflux related pulmonary symptoms. Subsequent studies have also shown a greater incidence of nocturnal symptoms such as nocturnal cough with or without nocturnal wheeze in those with GOR related pulmonary disease (Hoyoux et al 1985).

Jolley et al (1981) have attempted to find a reliable diagnostic correlate of respiratory symptoms caused by GOR . These workers investigated 41 children less than 6mths with symptomatic GOR by clinical history, by extended lower oesophageal pH monitoring. The infants were divided into 2 groups. The first group of 27 presented with a history of recurrent respiratory difficulties that were considered to be complications of GOR. These included apnea or choking episodes in 20, recurrent aspiration pneumonia or chronic cough in 6 and recurrent wheeze in 1. 25 (93%) of these infants had a history of recurrent vomiting from birth. The non-respiratory group of 14 children had a similar history of chronic vomiting but had no history of recurrent respiratory symptoms. GOR was assessed primarily by prolonged lower oesophageal pH monitoring but in 13 of the children with respiratory symptoms a second pH probe was placed more proximally at the level of T3. A liquid diet without pH adjustment was given and the infants were restrained only during the first 30 minutes. Jolley found acid reflux closely preceding the onset of respiratory distress in

7/17 (41%) infants. Resolution of respiratory symptoms followed effective anti-reflux treatment. Data was presented on two patients illustrating the association of reflux episode (with acid detected by the more proximally placed pH probe) with pulmonary symptoms.

The inability to demonstrate a direct temporal relation between GOR and pulmonary symptoms in every case was not felt to exclude a cause and effects relation since mild symptoms might have been missed or symptoms might have been infrequent. When a clear cause and effect relation between GOR and respiratory symptoms was not evident the mean duration of reflux during sleep (total time pH <4/ No of reflux episodes) was found to provide a sensitive predictor of reflux-induced respiratory symptoms. This index correlated directly with the presence of respiratory symptoms that remitted when GOR was controlled. Hence, it appears likely that prolonged acid reflux episodes during sleep predisposes to pulmonary damage. Jolley's findings accord with the earlier clinical observations of nocturnal symptoms in patients with reflux related pulmonary disease (Carré 1960).

Jolley suggested that the basic problem in GOR related pulmonary disease lay in a dysfunction of the pharyngo-oesophageal clearance mechanism. He hypothesised that this might have been abnormal as a consequence of central nervous system disease or oesophageal abnormality, as in repaired tracheo-oesophageal atresia, or that it might have been overwhelmed by clustering of GOR episodes. However, not

all children with prolonged reflux during sleep develop respiratory complications and hence there must be additional factors leading to GOR related pulmonary disease.

Jolley's study is important for two other reasons. It is one of the few to date to use both a low and a high oesophageal pH probe simultaneously. While lower oesophageal probes are likely to be particularly useful for gastro-intestinal related symptoms such as oesophagitis it is likely that reflux to upper oesophageal / pharyngeal level will be more directly relevant to pulmonary symptoms. At present this approach has not been extensively explored. The second important point is the emphasis placed on pharyngo-oesophageal clearance. While much time has been spent investigating the occurrence of GOR there have been few investigations of oesophageal clearance of reflux, either under normal or pathological conditions. This could be a fruitful area for future research.

3.5 Non-acid aspiration

Jolley's studies (1981) suggest that nocturnal acid reflux is important. Acid aspiration into the respiratory tract has been shown to result in a pathological reaction which resembles a severe chemical burn with haemorrhage, necrosis and granulocyte infiltration in the lung tissues (Wynne and Modell 1977). The severity of the lung injury increases as the pH falls to 1.5.

Non-acid aspirations, however, has also been shown to cause severe functional and pathological abnormalities in animals (Wynne and Modell 1977). In this case the extent and nature of the damage depends on the volume and composition of the aspirate, especially the tonicity and the presence of large or irritating food particles. Of particular interest for the paediatric population is the lung injury caused by aspiration of neutral stomach contents containing small, non-obstructing particles of foodstuff such as milk or partially digested dairy products. In such cases a granulomatous reaction with numerous macrophages is present within 48hrs. In animals, it has been shown that the physiological effects of such an aspiration can be as severe as in animals aspirating HCl of pH 1.8.

Alkaline GOR has been shown to occur in adults (Johnson 1981). However, the frequency of non-acid aspiration is unknown, both in adults and children, and clinically it would be difficult to determine retrospectively whether aspiration was acid or non-acid. However, many aspirations occur during or shortly after a meal, when food in the stomach is only partially digested and the gastric pH may be above 2.5. The observation of the serious consequences of non-acid aspiration may, therefore, be of direct relevance to infants where non-acid aspiration may occur, particularly after a feed. It was noted earlier that there is to date only indirect evidence that such non-acid GOR occurs in infants and children.

3.6 Mechanism of pulmonary damage

As a consequence of the frequent absence of direct evidence of pulmonary aspiration alternative hypotheses have been proposed to explain how GOR causes respiratory disease.

There have been two main alternative suggestions. The first has been that micro-aspiration or "silent" aspiration of refluxed gastric contents may occur. Implicit in this suggestion is the idea that aspiration is confined to the upper airways and does not penetrate to the lower respiratory tract. The presence of micro-quantities of lactose in tracheal aspirates of ventilated premature infants without radiological evidence of aspiration has been demonstrated and would suggest that clinically silent aspiration can occur (Hopper et al 1983). In animal studies, Wynne et al (1981) showed that a small amount of gastric contents caused damage to tracheal mucosa even when the amount aspirated was too small to induce a clinically significant pneumonia. In humans, such damage to the large airways might be sufficient to stimulate airway receptors so as to affect respiratory function and interfere with muco-ciliary clearance. Such effects might cause or exacerbate pre-existing pulmonary disease.

An alternative suggestion is that reflux of gastric contents into the oesophagus, without aspiration into the respiratory tract, may stimula(C) C mucosal receptors and trigge a vagally mediated reflex resulting in alterations in pulmonary mechanics. It has been shown that acidification of the oesophagus in animals and humans increases total lung resistance (Boyle et al 1985). However, in animal studies the

magnitude of the observed response was much less with oesophageal installation of acid than with intratracheal administration. This suggests that, at least in animals, micro-aspiration may be a more important cause of pulmonary irritation than simple reflux into the oesophagus.

4 GOR and apnea

4.1 Original observations

Apnea in infants is usually precipitated by infective, metabolic or neurologic stresses. Towards the end of the 70's at a time of increasing awareness of the pulmonary consequences of GOR, reports started to appear describing an apparent association between GOR and severe and recurring apnea (Leape et al 1977, Herbst et al 1978). There had been earlier reported cases of respiratory arrest and death resulting from GOR (Forshall 1954, Lilly and Randolph 1968) but these had post mortem evidence of pulmonary aspiration of gastric contents. Gross pulmonary aspiration was not a feature in the cases with apnea.

Leape et al described 10 infants <6/12 with recurrent episodes of apnea. All had at least two episodes of respiratory arrest before GOR was confirmed. Five had no history of previous vomiting before the first apneic spell and in 8 GOR was not recognised until an upper GI barium study was carried out. Thus, reflux was occult and recognised only after investigation. The report provided only brief clinical details about the 10 infants. Two infants had other abnormalities

(Pierre-Robin syndrome and subglottic stricture) but apnea disappeared after treatment of GOR despite the continued presence of the anatomic abnormality. One infant had a repaired tracheo-oesophageal fistula (a situation where apneic and cyanotic spells may be related to swallowing inco-ordination and/or tracheal compression). The clinical presentations of these infants were heterogeneous - in the first choking and gasping was followed by cyanosis and apnea; the second had episodes of respiratory arrest preceded by tachypnea and vomiting for two days and had clinical and radiological signs consistent with chest infection; the last was found cyanosed having vomited, shortly after a feed. The possibility of there being mechanisms for the asphyxial episodes other than GOR was not investigated.

In this report, there was no direct demonstration of a temporal relation between apnea and GOR. In all the infants the recurrent episodes of apnea ceased with effective medical or surgical treatment of GOR, suggesting that GOR was important. In the absence of evidence of gross aspiration, the authors suggested that laryngospasm, reflex central apnea or both, consequent upon aspiration of a small amount of gastric contents, might have been the mechanism of respiratory arrest.

Soon after, Herbst et al (1978) described 14 infants presenting as "near-miss" for SIDS. The term "near-miss" SIDS is usually applied to hitherto well infants who experience an episode of sudden "collapse" followed by resuscitative intervention, which in the opinion of the infants' attendants prevented death. Such infants often recover quickly and investigations seldom reveal a convincing explanation of the

event. The 14 infants had cyanotic and apneic spells, starting between 2-4mths of age, which were subsequently ascribed to GOR. Again, only a minority had a history of vomiting (5/14) and in 3 this had been minor. A history of a prior episode of coughing or choking spells was obtained in 5 of the patients. All had abnormalities on CXR (mild perihilar infiltrates 11, aspiration pneumonia 2, right upper lobe pneumonia 1), and severe GOR on barium studies. In 13 frequent GOR was also documented during studies of oesophageal motility and lower oesophageal pH. In 5 infants, an episode of apnea and cyanosis (thought to be due to laryngospasm in 3) occurred during and immediately following a decrease in oesophageal pH. As in Leape's cases effective medical or surgical treatment of the GOR prevented further episodes of apnea. In one infant positioning therapy for GOR was effective for 4/12 but one week after stopping this treatment the infant died. The findings at post mortem were consistent with the diagnosis 'sudden infant death syndrome'.

Neither of these reports makes it entirely clear whether the recurrent cyanotic and apneic episodes occurred during sleep or wakefulness. Herbst et al noted that sleep was not an essential prerequisite of the episodes. Many of the episodes occurred with the parents in attendance when it is likely that the infants would have been awake. The mechanism of apneas is likewise unclear. In a later report, Herbst et al (1979) use the term "laryngospasm" to explain the clinical appearance of an infant with absent nasal airflow but continuing chest movement without objective evidence to define the level of obstruction. It seems probable, therefore, that Herbst was describing obstructive apnea in association with GOR but any

inference concerning the site of obstruction is purely speculative. Neither report gives details about the number of preterm infants, the specific relation of apneic/cyanotic episodes to feeds or comments on the presence of antecedent symptoms such as colds.

Despite these limitations the message "GOR can cause apnea" has evoked an enthusiastic reception. The reports discussed, emphasise the apparent similarities, both clinical and epidemiological, between infants with GOR on the one hand, and infants presenting with "near-miss" episodes for SIDS or dying of SIDS on the other. From these initial reports, the hypothesis was formulated that in a number of infants presenting as 'near-miss' for SIDS (or perhaps succumbing to SIDS) the sequence leading to collapse (or death) was initiated or precipitated by GOR. Intense interest has followed in the possible association between GOR and asphyxial episodes in infants.

While many similarities between 'near miss' infants with GOR and infants dying of SIDS are apparent one difference should be noted. Infants dying of SIDS are usually thought to die during sleep whereas it is inferred in the two reports discussed that GOR precipitated apnea in awake infants.

4.2 GOR in 'near-miss' infants

Following these original observations there have been further studies of the relationship between GOR and apnea. In the main, these studies have concentrated on the 'near-miss'

infant. Such infants are known to have a small but definite increased risk for SIDS (Froggat et al 1971) and some, who have subsequently died suddenly, have had post mortem findings consistent with SIDS. Hence, they are widely regarded as an important human model for SIDS. Since SIDS is widely thought to occur during sleep these studies have tended to concentrate on the impact of GOR occurring during sleep even though careful reading of the original reports of Leape and Herbst might suggest a relation between GOR and apnea in awake infants.

Jeffery et al (1983) investigated 64 infants referred to a special 'near-miss' clinic. The group comprised 58 'near-miss' infants and 6 surviving twins of SIDS victims. A comparison group was not included. GOR was sought using barium studies, pH monitoring and radionuclide gastro-oesophageal ("milk") scans. Severe reflux was identified by each method in 45-50% of the infants studied. For the pH studies severity of GOR was assessed using the scoring system of Johnston et al (1978) whilst on the other tests severity was determined by the anatomical extent of GOR. Seven infants showed direct evidence of aspiration on radionuclide scan. In the first 20 infants studied by pH monitoring the relationship between GOR and sleep state was evaluated. A high incidence of reflux was noted during sleep with episodes occurring in active and indeterminate sleep but never during quiet sleep. Polygraphic studies during sleep were performed to elucidate the inter-relations between breathing, GOR and sleep-state. The major finding was that there was no statistical difference in the number of breathing pauses of greater than 10 seconds which occurred during periods with GOR (oesophageal pH <4) compared with periods without GOR (pH >=4). Similarly there was no

difference in the mean breathing rate in the 20sec before and immediately after reflux, in whatever sleep state GOR occurred.

This study, therefore, demonstrated that reflux was a common finding in the 'near-miss' infant. In the absence of controls it is not possible to be certain that the extent, frequency and occurrence of GOR overall or specifically during sleep are significantly different from a normal population. Despite the common occurrence of GOR, Jeffery et al could not demonstrate a relation between GOR and apnea during sleep. These authors suggested that GOR per se may not be sufficient to cause death but that an additional defect eg defective arousal response, might be required. Such a defect could occur temporarily, perhaps associated with natural "stresses" such as upper respiratory tract infection. Jeffery et al had in fact noted that 45% of their study population had an antecedent history of upper respiratory tract infection.

Macfadyen et al (1983) also demonstrated GOR in 'near-miss' infants. They studied 17 'near-miss' infants (mean age 10wks). In 14 (82%) infants the 'near-miss' episode had been thought to occur when the infant was asleep. All 17 had been well in the 24hrs before presentation with no symptoms of minor coryza or poor feeding and no infant had a history of vomiting. Radionuclide scans demonstrated GOR in 8 infants (47%). Pulmonary aspiration was not noted during any radionuclide scan. In this study there was no systematic attempt to examine the relation between GOR and respiratory variables and no normal or asymptomatic controls were included. A group of 9 infants with suspected pulmonary aspiration was

also investigated and GOR was noted in a similar proportion to the 'near-miss' infants (4/9). The incidence of GOR in 'near-miss' infants in this study is very close to that found by Jeffery et al (1983).

Ariagno et al (1982) reported the findings on 45 infants born at term presenting with a 'near-miss' episode. Strikingly, none of these infants had failure to thrive, vomiting or recurrent pneumonia - conditions commonly associated with significant GOR. Each infant had presented with a frightening event, witnessed by a parent or guardian, in which the infant was presumed asleep and was found pale, limp or stiff, and for which resuscitation was felt necessary. Ariagno was primarily interested in the relation of GOR with apnea. The 45 infants were monitored polygraphically for an average of 18hrs with a lower oesophageal pH probe in situ to detect GOR. Sleep state was inferred by examining the traces for the presence and nature of movement artefact. Nasal airflow was not recorded. A total of 356 pH drops were recorded (mean 8.7 +/- 7.4 per study) in 41 infants. The pH drops occurred most frequently when the patient appeared to be awake (73%) and in 84% of episodes there was movement before and during the pH change. A comparison group was not available for study but as a group these 'near-misses' had significantly more reflux than was present in the normal but older infants and children studied by Boix-Ochoa et al (1980). 341 episodes of apnea >= 10sec were identified in 46 studies. Prolonged apnea (>20sec) was not observed. Whether the apneas occurred during sleep or waking is not stated. Detailed analysis of the temporal relation between apnea, pH drops and movement led Ariagno et al to

conclude that the majority of 'near-miss' SIDS infants had GOR associated with movement during awake periods without any relation to apnea.

In these studies of 'near-miss' infants no attempt was made to select infants especially likely to have GOR. Symptoms or findings suggestive of GOR were specifically noted to be absent in the studies of Macfadyen et al (1983) and Ariagno et al (1982). Both Jeffery et al and Ariagno et al considered the GOR present to be "pathological" though neither included a comparison group of healthy normal infants. The relatively small number of episodes of GOR reported by Ariagno et al and the wide range of values for indices of GOR suggest that in their series most infants did not have excessive or pathological GOR. Neither Ariagno nor Jeffery could confirm a relation between GOR and apnea.

A number of limitations are inherent in all reported studies of GOR prevalence in 'near-miss' SIDS. None give information on carefully matched controls studied under similar circumstances. Thus, it is not clear whether the amount of GOR present in 'near-miss' infants is genuinely excessive. The studies investigating a possible direct relation between GOR and apnea have monitored pH in the lower oesophagus. The possibility exists that only GOR reaching upper oesophageal / laryngeal level is implicated in the causation of apnea. Hence, methods for studying GOR are needed which document the incidence of GOR at different levels over long periods of time. Also, in studies using pH probes the potential importance of non-acid GOR is rarely acknowledged and its possible relationship to cardio-respiratory events ignored.

There is conflict between the earlier reports of apnea related to GOR (Leape et al 1977, Herbst et al 1978) and the later studies of Jeffery et al (1983) and Ariagno et al (1982). Are these apparently discrepant observations reconcilable? Part of the answer may lie in the difference in cardio-respiratory response to GOR in different states of arousal.

4.3 Specific cardio-respiratory consequences of GOR

During sleep

Some subsequent studies have focused either on specific groups (infants with GOR and apnea, Walsh et al 1981; infants with awake apnea, Spitzer et al 1984), or specific episodes (regurgitation, Menon et al 1985) in an attempt to confirm a relation between GOR and apnea.

Walsh et al (1981) compared the frequency of brief apneas during periods with GOR with that during control periods without GOR in 14 infants (5 preterm and 9 term) selected for study on the basis of abnormal GOR scores and a history of prolonged apnea. Six of the 13 infants had a history of a 'near-miss' episode while the remaining one was the twin sib of a SIDS victim. Of the 13 'near-miss' infants 6 were awake at the time of the prolonged apnea, 6 were asleep and in one the state was not known; 5 were preterm and 8 term. Vomiting was noted in only 7 infants. Each infant was studied for 14-16hrs using combined polygraphic and lower oesophageal pH monitoring to examine the temporal relation between GOR and apnea. The

infants slept for between 5-9hrs of the monitoring. Respiratory pauses (cessation of airflow) longer than 3sec were noted and classified as either central or obstructive apnea. An episode of GOR was defined by a pH reading less than 4 for a minimum of 15sec and GOR scores were calculated using the scoring system of Jolley et al (1978). In the study, 63 episodes of GOR were observed in the 14 infants with a median duration of GOR of 203sec (range 15 - 2551sec). This seems a small overall number of GOR episodes in a group of infants selected because of abnormal GOR and monitored for a prolonged period. Obstructive apnea was present in seven infants with the longest apnea noted being one of 6.8sec which terminated spontaneously.

Obstructive apnea occurred more frequently during GOR segments than during control segments. However, this primarily reflected the data on two infants. Brief obstructive episodes occurred at GOR onset in only 15.9% of all recorded GOR episodes but were statistically commoner during the onset of GOR episodes than during the onset of control segments. Walsh did not specify the state of the infant when obstructive episodes occurred and, in particular, did not give the proportion of obstructive episodes which occurred while the infants were awake.

Walsh et al (1981) concluded that, in the majority of instances, apnea and GOR were not temporally related. However, they felt that examination of the individual data did not allow a complete rejection of the GOR / apnea hypothesis for in isolated infants there may have been a significant temporal relation; for example, one infant showed obstructive apnea 3 times as commonly during GOR segments as during control

segments. It is also worth noting that in a study of apnea occurrence, Abreu e Silva et al (1985) noted no OA in 10 normal infants studied on 31 occasions. Hence, the mere presence of OA in Walsh's group may be of pathological significance.

Walsh et al (1981) acknowledged two technical limitations surrounding their conclusion. First, the use of lower oesophageal pH monitoring may have been inappropriate to study the GOR / apnea relation as apnea may not be a consequence of GOR unless it reaches proximal oesophageal or laryngeal receptors. Secondly, all the infants were given normal formula with pH in excess of 5. They could not exclude the possibility that apnea might have occurred in relation to reflux of non-acid gastric contents.

In Walsh's group of infants GOR occurred during awake periods (61.9%), in quiet sleep (28.6%) and during active sleep (9.5%). GOR during sleep lasted significantly longer than during wake periods, a finding which has been noted previously as identifying children with respiratory symptoms secondary to GOR (Jolley et al 1981). These findings on state at occurrence of GOR compare with the data of Jeffery et al (1980) whose report of 18 'near-miss' infants and 2 SIBS concentrated on the state of the infant at occurrence of GOR. Jeffery's studies using prolonged polygraphic and lower oesophageal monitoring revealed that 73% of GOR episodes occurred during wakefulness, 16% during active sleep, 10% during indeterminate sleep and none during quiet sleep. The finding of frequent GOR while awake agrees with Walsh et al (1981) and other reports

discussed earlier. However, the observations on the occurrence of GOR with respect to quiet and active sleep differ and cannot be readily reconciled.

While awake

It has been noted that many studies have not commented on the infant's state at the occurrence of apnea. Spitzer et al (1984) make it clear that this is an important variable to consider in their study of 15 infants who had apnea while awake. They delineated a clinical presentation of awake apnea occurring within an hour of a feed with a characteristic history. Typically an awake infant after a feed suddenly stared straight ahead and stopped breathing. There was an associated colour change and stiffening, sometimes with opisthotonus. This was followed by hypotonia. With stimulation the infant returned to normal. In all cases there was no history of tonic clonic episodes and coughing or choking was absent. This subgroup comprised 7% of all the infants being evaluated for apnea. The 15 infants, of age range 6-22wks, had all been born at term, and none had a history of birth asphyxia or neurological disease. Clinical regurgitation was present in one third. Lower oesophageal pH monitoring with simultaneous polygraph recording of nasal thermistor, heart rate and thoracic impedance was performed over 24hrs. A comparison group of 9 age matched infants was also studied. While the latter did not have the same clinical presentation as the 15 index infants, 6 had sleep apnea with GOR on Barium studies and 3 were SIBS of SIDS reported to have frequent regurgitation after feeding.

All 15 index infants had pathologic GOR documented by 24hr pH study. Thirteen had some degree of obstructive apnea during periods of GOR; eight had at least two separate episodes of prolonged obstructive apnea (>=15sec) during periods of GOR, while in five obstructive apnea was usually less than 15sec duration and associated with increased thoracic impedance and elevation in heart rate. In two infants apnea could not be demonstrated during the hospital investigation. Prolonged central apnea was not seen in the 24hr recordings but one child had excessive periodic breathing. Interestingly, there was no significant correlation between duration and frequency of GOR and severity of associated apnea. Central apnea did not occur simultaneously with GOR while obstructive apnea did. In addition, obstructive apnea did not occur in the absence of GOR although not every episode of GOR was associated with OA. Of the control infants, only 1 had significant GOR and none had any OA. In view of the their clinical histories, the lack of significant GOR on study in the control infants is somewhat surprising.

Spitzer and his group felt that they had defined a subgroup of infants with a specific history and investigative findings. In this group OA occurred while awake and appeared to be directly associated with GOR.

Spitzer sited his probe in the lower oesophagus and hence the true anatomical extent of GOR associated is not known. He does not specify whether there was regurgitation associated with OA. In order to try and assess the importance of regurgitation in the genesis of apnea Menon et al (1985) have reported detailed studies of the cardio-respiratory events

occurring at the time of regurgitation. This is highly relevant to the present discussion since, during regurgitation, gastric contents come in contact with upper airway chemoreceptors. Stimulation of these receptors, at least in animal studies (Boggs et al 1982), can result in apnea.

Menon et al (1985) examined 10 infants (9 preterm) to determine whether regurgitation might be a factor in the pathogenesis of apnea. The nine preterm infants (gestational age 28 - 36wks) were studied at a postnatal age of 2-4wks while the one term infant was studied at 1wk postnatal age. All had histories of post-feed regurgitation and apnea of prematurity or idiopathic prolonged apnea. They were studied in hospital and a comparison group was not available. Polygraphic monitoring included nasal airflow detection and pharyngeal pressure measurements. Sleep state was assessed by clinical observation. 44 regurgitations occurred, at least one in each infant, and 100 prolonged (>20sec) apneas were observed. Eight prolonged apneas occurred during post-regurgitation epochs and the group mean frequency of prolonged apneas following regurgitation was greater than during inter-regurgitation control periods. The type of apnea was not always given but for the 8 following regurgitation 5 were mixed, central and obstructive, and 3 obstructive. Using a binomial statistical model, Menon found that both prolonged (>20sec) and short apnea (>3sec) occurred much more frequently during regurgitation than during control periods without regurgitation. However, the majority of prolonged apneic spells (92%) were not associated with regurgitation. Most short apneas and all prolonged apneas

following regurgitation were mixed or obstructive. Seven episodes of nasal regurgitation were noted of which 4 were associated with apnea of brief duration.

Menon et al concluded that regurgitation was a significant predisposing factor for both short and prolonged apnea and suggested that this was mediated through upper airway chemoreceptors. While state was not defined precisely 6/8 prolonged apneas coinciding with regurgitation were associated with gross motor activity suggesting wakefulness. The fact that 9/10 infants were premature might also have been an important factor in the observed association. Laryngeal stimulation with water and some other liquids in newborn animals (Downing and Lee 1975) and humans (Perkett and Vaughan 1982) has been shown to result in sustained apnea. This apneic response to fluids in the larynx diminishes with age and is replaced by coughing as the chief response in adult animals (Bartlett 1985). Hence, premature infants may be particularly prone to develop apnea in response to regurgitation.

The frequency of prolonged apneas in Menon's study is extraordinarily high. Apneas longer than 20 seconds are rare even in studies of high risk infants. For comparison, in Ariagno's study 345 apneas >=10secs were identified in 45 infants with 'near-miss' episodes monitored for a mean of 16 hrs each. Apneas longer than 20secs were not observed. However, Menon et al found 100 prolonged apneas in 10 infants monitored for a mean of 2-3hrs each. This suggests that his findings were a feature of the particular group studied rather than of more general relevance in the age range when SIDS is most likely.

There would seem to be growing evidence, that at least for OA, GOR and apnea are occasionally related. Additionally, this GOR / OA relation would seem to be a feature of awake infants. Obstructive apneas are frequently found in 'near-miss' infants, term or preterm, with evidence of GOR whereas in normal infants OAs are probably rare (Abreu e Silva et al 1985). All of the reports lack appropriate normal controls to provide a true basis for comparison.

4.4 GOR in other groups of infants at increased risk for SIDS

A number of epidemiological studies have provided evidence that the risk of subsequent SIDS is increased in certain groups. (Froggat et al 1971, Peterson et al 1980). Groups identified as being at high risk include 'near-miss' infants, siblings of SIDS victims and premature infants. These infants, particularly the 'near-miss' group, have been studied as providing a human model for SIDS. Although the relevance of the 'near-miss' model has been questioned (Stanton and Oakley 1983), the 'near-miss' group has been the group most commonly studied in the investigation of the putative relation between GOR and apnea as outlined above. Information from other 'at risk' groups is scanty.

Infants after neonatal intensive care

Premature infants with a history of respiratory distress are one alternative 'at risk' group. A report from Herbst et al (1979) described the finding of apnea, bradycardia and persisting pulmonary abnormalities in association with GOR.

Herbst's group described 14 infants (9 preterm and 5 term) with chronic respiratory distress starting at birth, and the contribution of GOR respiratory distress, apnea and chronic lung damage resembling bronchopulmonary dysplasia. Symptoms of GOR were common and in all 14 patients frequent reflux was noted on barium swallow. Apnea had started in the first week of life and was attributed to the effects of GOR. All the infants had pulmonary complications at birth, mainly RDS, and had received respiratory support. Intensive medical treatment of the GOR had been associated with a prompt decrease and ultimate cessation of apneic spells in 4/5 term infants and in 4/9 preterms. In six in whom medical treatment of GOR had failed there was dramatic improvement after surgical treatment. Chest X-ray changes which resolved with treatment of GOR were ascribed retrospectively to the effects of chronic aspiration. In five patients, studied in detail to document the sequence of apnea-bradycardia-GOR episodes, apnea occurred immediately after GOR and in some cases was associated with upper airway obstruction. In these infants, the installation of 0.5ml of 0.1M HCl acid (but not dilute formula or water) into the mid-oesophagus induced mixed apneas, whereas installation of acid in asymptomatic infants did not effect respiratory pattern or heart rate. Herbst et al suggested that stimulation of laryngeal and pharyngeal receptors induced "laryngospasm"

(obstructive apnea) and that chronic aspiration was responsible the mechanism for pulmonary changes. Herbst et al suggested that oesophagitis might "sensitise chemoreceptors" in the oesophagus but did not speculate on the significance of the cardio-respiratory abnormalities induced by installation of acid into the mid-oesophagus.

This report, therefore, described a group of abnormal, mainly preterm, infants with significant neonatal respiratory disease, requiring respiratory support, and chronic respiratory distress to which GOR was judged to have contributed. The limited clinical details provided make it difficult to be sure that acute respiratory distress, respiratory support, the paraphernalia of neonatal intensive care (including the use of nasogastric and nasojejunal feeding) and, perhaps, also therapeutic agents such as theophylline preparations, did not actually predispose to GOR, and that the situation described is not a "chicken and egg" with significant neonatal respiratory illness leading to GOR which in turn increased the likelihood of further respiratory damage. The dominant problem in this group appears to have been persisting respiratory damage rather than apnea. Hence, it is more difficult to draw conclusions about the relevance of this report to the question of GOR associated apnea.

Menon et al's (1985) study of the cardio-respiratory associations of regurgitation also related predominantly to preterm infants (9/10 were preterm) all of whom had "recovered from respiratory distress syndrome", gave a history of apnea of prematurity or idiopathic prolonged apnea, and were in hospital at the time of study. Perhaps infants recovering from

respiratory distress and neonatal intensive care have a high incidence of both apnea and GOR, and the two are interrelated. It may not be appropriate to extrapolate these findings to other infant populations.

These studies certainly suggest that GOR has a role in perpetuating respiratory symptoms in premature infants recovering from a variety of respiratory disorders.

SIBS of previous SIDS victims

Subsequent siblings, particularly if a surviving twin, also have a small increase in risk of subsequent SIDS. The reasons underlying this increased risk have not been defined.

Many of the studies discussed here have included siblings. However, the numbers have been small. There has been no systematic attempt to separate SIBS from other "at risk" infants. The relation between GOR and apnea in this group has not been examined specifically.

4.5 Other reports of apnea with regurgitation

Case reports have appeared describing apnea and bradycardia where the postulated mechanism of cardio-respiratory events have included GOR.

Schey et al (1981) reported four 'near-miss' infants with apnea and bradycardia and a radiological appearance of oesophageal dysmotility. The four infants were all born extremely preterm and had developed cardio-respiratory complications of prematurity. All had received nasoenteric feeding. Oesophageal strictures or hiatus hernia were noted in three. The symptoms, observed in the first three months, included "seizure-like activity" (generalised spasms followed by total flaccidity), bradycardia or cardiac arrest, and apnea or complete respiratory arrest. Oesophageal dysmotility was observed during barium swallow and accompanied or immediately preceded such symptoms in 2 patients. GOR and aspiration into the airways was not observed. While Schey et al acknowledged that GOR might have occurred, as GOR and other causes of oesophageal irritation (including the presence of nasoenteric feeding tubes) are primary factors in provoking oesophageal dysmotility, they considered that oesophageal dysmotility was the key feature, and attributed the associated cardio-respiratory abnormalities to an outburst of vagal activity resulting from oesophageal dysmotility. The possible significance of prematurity and neonatal respiratory distress in the aetiology of the episodes is not known.

Fontan et al (1984) described a term female infant with diffuse oesophageal spasm associated with apnea and bradycardia. The infant had repeated episodes characterised clinically by the following sequence; a look of apprehension, restlessness, hyperextension of the neck and back, apnea and bradycardia. The episodes of bradycardia were frequent, usually while the infant was asleep but also when awake and active. The association with oesophageal spasm was documented with

physiological measurements of both oesophageal and cardio-respiratory function rather than radiological appearance. Apnea, bradycardia, oesophageal spasm and significant GOR were all demonstrated. Central and obstructive apneas lasting up to 10 seconds were variably associated with oesophageal spasm. The oesophageal manometry findings were typical of older patients with diffuse oesophageal spasm. Bradycardia occurred independently of apnea and both apnea and bradycardia were not temporally related to decreases in oesophageal pH. Hence, GOR was not the direct cause of the cardio-respiratory abnormalities. Anticholinergic medication resulted in a decrease in the number of episodes of apnea observed and bradycardia was not observed after treatment. The findings suggest that bradycardia was mediated by a vasovagal reflex mechanism. Although apnea was not seen in the absence of oesophageal spasm, obstructive and central apneas were not closely related to individual oesophageal contractions. The nature of the relation between the two could not be defined.

These two reports suggest that apnea and bradycardia can occur in association with oesophageal spasm independently of GOR. However GOR, present in these cases, may have had an important role in causing the oesophageal spasm. The clinical descriptions of "seizure-like activity" in the first and episodes of apprehensive look, restlessness and hyperextension in the second are reminiscent of Spitzer et al's (1982) description of awake apnea due to GOR. However, Spitzer found no evidence of oesophageal spasm in his infants during oesophageal manometry studies.

Plaxico and Loughlin (1981) described two preterm infants who developed apnea and bradycardia primarily during feeding in association with nasopharyngeal reflux. The diagnosis was established by observing the swallowing mechanism using cine-fluoroscopy while the infant ingested a dilute barium meal. In both children velopalatine insufficiency was demonstrated and apnea and bradycardia coincided with nasopharyngeal reflux. They suggested that nasopharyngeal reflux was a consequence of swallowing dysfunction and that apnea may have resulted from either airway obstruction or as a reflex induced by the presence of milk in the nasopharynx. This report differs from the earlier reports in that apnea is related to nasopharyngeal regurgitation and not GOR. The important features were that the infants were premature and that the episodes were related to feeding, when the infants were presumably awake. The suggested mechanisms of apnea (airway obstruction or reflex induced apnea) are similar to those considered in infants with GOR and apnea. The nature of the apneas was not recorded in this patient but their association with the early onset of bradycardia suggests that they were obstructive.

Another interesting picture is found in children who have had corrective surgery for oesophageal atresia and tracheo-oesophageal fistulae. These children frequently have swallowing and breathing abnormalities throughout their first years of life. Such problems may be due to stricture at the anastomosis, poor oesophageal motility or recurrent tracheo-oesophageal fistula. However, there are reports of infants with repeated life-threatening cyanotic and apneic spells usually in association with feeding (Filler at al 1976,

Cook and Bush 1978). These episodes usually started with stridor or a cough and can progress to cyanosis, apnea and loss of consciousness and occasionally death. Investigations have shown that such spells are due to tracheal compression by anteriorly placed structures. Wailoo et al (1979) have examined the tracheas in patients dying with tracheo-oesophageal fistula and found deficiency of cartilage in 30 of a series of 40. Hence, tracheomalacia is a common finding in such infants and is clinically manifest as variable degrees of expiratory stridor. 'Sudden death episodes' are related to intermittent complete airway obstruction. Such episodes are preventable by aortopexy. While the group of patients with previous fistulae will be easily identified, this problem is of relevance to the GOR apnea hypothesis. Firstly, GOR could conceivably precipitate or accentuate airway obstruction and apnea in such circumstances because of direct pressure from a filled oesophagus compressing the trachea. Secondly, infants with tracheal obstruction from minimal tracheomalacia or aberrant innominate artery have presented as 'near-miss' for SIDS. In such infants, it can be difficult to diagnose the presence of an airway problem (Jeffery et al 1983). Infant body plethysmography, which is not widely available, allows airway problems to be readily diagnosed from inspection of tidal breathing pressure flow loops. In the absence of such sophisticated tests asphyxial episodes might be erroneously attributed to GOR.

4.6 "Symptoms" without 'near-miss' episodes

Minor symptoms such as snuffles, cough, irritability, vomiting diarrhoea, sleepiness, skin rash, change of cry, and fever have been noted more frequently in SIDS victims before death than in matched control cases (Carpenter et al 1979). In a study (Stanton et al 1978) of 145 SIDS victims 85 (59%) had recent symptoms, predominantly respiratory compared, with 40 (26%) of 154 controls. The possible relevance of this finding to the aetiology of asphyxial episodes is not known. However, Steinschneider (1972, 1975, 1977) has documented prolonged episodes of apnea during sleep in association with nasopharyngitis and the clinical observations that some infants with 'blocked' noses have difficulty breathing when the nose is blocked has suggested that nasal obstruction is one possible mechanism contributing to apneic episodes.

Do minor illnesses exacerbate GOR, and perhaps augment its cardio-respiratory effects? There have been no systematic attempts to examine these possibilities by documenting the frequency and duration of GOR and cardio-respiratory abnormalities in infants with minor symptoms. However, there are some hints that minor symptoms might be important in the apnea / GOR context.

In their original cases, Herbst et al (1978) noted a clustering of the cases of reflux-induced apnea in the winter months and speculated that infants were more likely to reflux gastric contents because of the gagging or coughing associated with upper respiratory infections which are common in winter.

Five of their infants did have a history of "prior coughing or choking" but whether this related to upper respiratory infection was not made clear.

In Jeffery's study (1983) an episode of 'minor' illness frequently preceded the 'near-miss' event. In 45% of their infants this took the form of an upper respiratory illness with snuffles and a blocked nose. They suggested that since GOR was common in their 'near-miss' group of infants; an additional problem such as a defective arousal response might be necessary to cause apnea. Defective arousal responses have been described in animals secondary to sleep fragmentation (Bowes and Phillipson 1980). Many parents testify to the disturbed nature of their infant's sleep during 'colds' suggesting a similar mechanism might apply.

Abreu e Silva et al (1986) have recently described cardio-respiratory abnormalities, including prolonged and obstructive apnea, during upper respiratory illness and metabolic alkalosis in infants not otherwise at increased risk for SIDS. In such circumstances GOR could act as an additional stress. It is conceivable that the sum of such stresses influences respiratory control and results in abnormalities of sufficient severity in some infants to precipitate a major, possibly fatal, asphyxial episode. If these suggestions are correct then it may be important to study risk groups of infants during the course of apparently "minor" illnesses symptoms if insight is to be gained as to the cause of asphyxial episodes.

It has also been shown in relation to upper respiratory infections and metabolic alkalosis that cardio-respiratory abnormalities are a feature of the illness itself and not of the recovery phase (Abreu e Silva et al 1986). This may be important for research studies in that if an infant is studied after an acute illness then abnormalities present during that illness may have resolved.

4.7 Mechanisms

One attractive feature of the hypothesis that GOR may be cause of cardio-respiratory abnormalities is the degree of biological plausibility associated with the idea. A number of potential mechanisms by which GOR "causes" cardio-respiratory abnormalities have been recognised and discussed. These are brought together and summarised here. The mechanisms suggested to explain pulmonary complications of GOR may also be of relevance in the GOR apnea context.

4.7.1 Airways obstruction

The simplest and clearest example of GOR resulting in apnea and asphyxia is when pulmonary aspiration of refluxed material leads to obstruction of the air passages. Massive aspiration can result in complete airways obstruction; obstructive apnea and the rapid development of asphyxia follow.

Apart from massive aspiration, however, there are number of other potential mechanisms whereby airways obstruction might occur. One alternative possibility is that a minor degree of tracheal obstruction is present, perhaps because of tracheomalacia. Then additional posterior pressure from a full oesophagus during feeding or GOR might cause partial tracheal obstruction. Partial obstruction can become complete if the pharyngeal airway collapses when sub-atmospheric pressure is generated by augmented inspiratory efforts (Tonkin et al 1979). In this scenario GOR may have a indirect role by increasing partial tracheal obstruction. Alternatively, there could be a more fixed anatomical obstruction related to vascular structures; an additional minor degree of obstruction might then result in complete tracheal occlusion. It is of interest that Jeffery et al (1983) recognised 4 infants in whom tracheal obstruction was thought to be the major factor responsible for a 'near-miss' episode. Two had repair of a tracheo-oesophageal fistula repair and had some degree of tracheomalacia and two had substantial narrowing of the lower trachea caused by innominate artery compression. It was not made clear whether GOR was present in any of these infants.

Nasopharyngeal reflux, described by Plaxico and Loughlin (1981) in two preterm infants provides another possible mechanism by which reflux can result in apnea. While their observations linked nasopharyngeal reflux, secondary to velopalatine insufficiency during feeding, with apnea the mechanisms they suggested to account for apnea (airway obstruction or a reflex induced by the presence of milk in the nasopharynx) could equally apply to material refluxed to oropharyngeal level.

Even when aspiration does not result in complete airways obstruction, aspiration can result in intense chemical inflammation with resultant interference with pulmonary gas exchange and development of severe hypoxia (Wynne and Modell 1977).

4.7.2 Local Reflexes

Several lines of evidence have suggested that the induction of apnea by GOR might be mediated by stimulation of reflexes. Reflexes which might fulfil such a role have been demonstrated at pulmonary, laryngeal and oesophageal level.

Stimulation of pulmonary reflexes can be brought about by 'micro-aspiration' or 'silent aspiration'. This has been described earlier as a mechanism by which GOR can trigger wheeze. Such a phenomenon has been demonstrated in animal experiments (Wynne et al 1981) and the presence of micro-quantities of lactose in tracheal aspirates of ventilated premature infants suggests that clinically unrecognised aspiration can occur in humans. In this situation micro-aspiration may be sufficient to stimulate airway receptors to affect respiratory function. Activation of tracheal irritant receptors situated in the upper airway epithelium has been shown to produce vagally mediated reflex bronchoconstriction. It is not known whether apnea can result from micro-aspiration, but it is clear that micro-aspiration is a possible mechanism whereby alterations in breathing patterns occur.

The best established evidence for a reflex leading to apnea comes from studies of laryngeal stimulation in baby animals. Laryngeal closure can be elicited by a wide variety of respiratory stimuli and manoeuvres (Bartlett 1985). Both mechanical and chemical stimuli applied to the larynx have been found to elicit immediate glottic closure and in newborn animals particularly, an apneic response occurs. In such animals, laryngeal stimulation with water or certain other liquids placed in the larynx results in sustained apnea (Downing and Lee 1975). Breathing resumes when the offending substance is washed from the larynx with normal saline. In such cases laryngeal closure does not always occur (Boggs and Bartlett 1982). This response has been found in several species including humans (Perkett and Vaughan 1982) and is mediated by the superior laryngeal nerve. The apneic response to fluids in the larynx diminishes with age and is replaced by coughing as the chief response in the adult animals. This change with age apparently reflects a maturation in the central nervous system because adult animals have laryngeal receptors that respond to water and other materials much as those in neonates (Boggs and Bartlett 1982). It is obvious that this response will protect the lungs of baby animals from aspiration but it has been pointed out that the resultant reflex apnea may be so profound that it is potentially dangerous and there has been speculation that reflex apnea in humans might be one cause of SIDS (Downing and Lee 1975).

The last level at which reflex activity might originate is in the oesophagus. It will be recalled that Herbst et al (1979) in their study on infants with pulmonary disease, reported five

infants where installation of 0.5ml of 0.1M HCl acid (but not dilute formula or water) into the mid-oesophagus induced mixed apneas. Also, in adults Mansefield and Stein (1978) showed that acidification of the oesophagus could increase total pulmonary resistance in the presence of oesophagitis. While evidence suggests that stimulation of oesophageal receptors may not be a potent way of inducing bronchospasm (Tuchman et al 1984) the importance of its relation to apnea is unknown.

The suggestion that oesophageal spasm may precipitate cardio-respiratory abnormalities (Schey et al 1981, Fontan et al 1984) is significant in this context although the receptors concerned could be different. Presumably GOR is primarily concerned in the first mechanism and of secondary importance in the second - perhaps by precipitating oesophageal spasm.

It can be readily appreciated that GOR may have an important role in each of these reflex mechanisms because it provides a means whereby gastric contents can come in contact with the appropriate receptors.

4.7.3 Anaphylaxis

In 1960 Parish et al (1060) put forward the hypothesis that sudden infant death could be explained by a modified anaphylactic reaction to the foreign antigen in cow's milk. The basis of the hypothesis was the development by an infant of an anaphylactic sensitisation as a result of the alimentary intake of large amounts of cow's milk. Thereafter, regurgitation of some stomach contents in a sleeping sensitised infant, with

inhalation of a small amount into the lung, could trigger an immediate anaphylactic reaction. The anaphylactic reaction resulted in death but was "modified" due to the deep sleep of the infant.

There has been considerable supporting evidence for this hypothesis from investigations of a guinea-pig experimental model (Devey et al 1976). Despite the high plausibility of the hypothesis it has been extremely difficult to prove in humans because SIDS cases are not seen alive and evidence from post mortem has provided little evidence either to support or refute the hypothesis.

In summary, it can be seen that there are a number of plausible mechanisms whereby GOR might lead to apnea. Which, if any, are of greatest importance in infants, remains to be determined.

4.8 GOR as a consequence of cardio-respiratory events?

Relatively little attention has been paid to the suggestion that GOR is a consequence rather than a cause of cardio-respiratory events. The studies available have focused on GOR and its in relation to bronchospasm. In recent years there has been emphasis on the role of drugs, particularly theophylline preparations, in the causation of GOR. Berquist et al (1981) have found that GOR is induced in most normal adults

who achieve therapeutic serum theophylline levels. There has been little exploration of the alternative hypothesis that respiratory events might precipitate GOR.

The major driving force for GOR is transdiaphgramatic pressure. It is simple to speculate that increased transdiaphgramatic pressure associated with airways obstruction could overcome the LOS and result in gastric contents being pumped into the oesophagus. Such a sequence of events can easily be imagined as occurring in obstructive apnea. It might also account for the association between movement and GOR noted by Ariagno et al (1982). They found that the majority of 'near-miss' infants had GOR episodes associated with movement during awake periods. In 84% of precipitous drops in pH movement occurred before and during the drop. Movement has also been associated with GOR in Barium studies where it is likely that tensing of the abdominal muscles during movements leads to an increase in transdiaphgramatic pressure sufficient to overcome lower LOS pressure, and to result in GOR.

While such speculations are plausible other evidence suggests that any role GOR may have is as the cause rather than the consequence of respiratory events. Firstly, the reports suggesting that an association exists have usually found that effective treatment of GOR results in cessation of cardio-respiratory abnormalities (Leape et al 1977, Herbst et al 1978). Herbst, for example, describes one striking example where cessation of treatment for GOR was followed within a week by the infant's death. Although this could have been entirely fortuitous the findings at post mortem were consistent with the sudden infant death syndrome. Secondly, the studies that have

demonstrated a relation between GOR and obstructive apnea (Walsh et al 1981, Spitzer et al 1984, Menon et al 1985) indicate that GOR precedes the occurrence of obstructive apnea.

Hence, while there is a theoretical basis for the suggestion that GOR follow cardio-respiratory events, the evidence to support this idea is not presently available. Where a relation has been shown GOR has preceded cardio-respiratory abnormalities.

5 Conclusion

This review has traced the development of medical interest in GOR in infancy and childhood through the early work on the occurrence of GOR, past the developing appreciation of its role in pulmonary disease, to the current interest in the role of GOR in the causation of apneic / asphyxial episodes in infants. The last area forms the subject of this thesis. A number of points emerge in relation to this area.

1. GOR can occur in normal infants and children. Unfortunately, since information on GOR in normal infants is limited as a consequence of ethical constraints, the extent and frequency of GOR in normal infants and children is uncertain. The effects of important factors such as age, gestational and chronological, have not been systematically assessed. Much of the information that is quoted comes from studies in asymptomatic infants. Inspection of the

published clinical details of such infants leads one to suspect that they are often an inappropriate substitute for normal infants.

2. While it seems likely that assessment by pH probe, using pH 4 as the indicator level for GOR, is probably valid in infants and children there is a need for systematic evaluation, particularly in infancy where the effects of milk feedings may significantly alter the pH profile of the stomach with respect to time. This may be relevant to the occurrence of apnea and pulmonary damage following aspiration.

3. In infants and children GOR is seen most commonly during waking hours. It is least frequent during sleep. The precise phases of sleep during which GOR occurs is not clearly established. GOR may also be related to movements or manoeuvres which increase intra-abdominal pressure.

4. GOR is not usually due to persistently low LOS pressure but is most frequently associated with transient inappropriate relaxation of the LOS. The reasons for this relaxation are not known.

5. It is suspected that GOR is an important predisposing cause of pulmonary disease in infancy and children. The assessment of the role of GOR in pulmonary disease has been significantly hampered by the lack of a test which directly, reliably and sensitively indicates that pulmonary aspiration has occurred. The demonstration

that GOR is an important factor in pulmonary disease in an individual case is often difficult. At present, the best method for assessing whether GOR is likely to be a factor is an extended lower oesophageal pH study. The presence of "significant" GOR leads to the inference that pulmonary aspiration may be occurring. The factors which lead a particular infant with GOR to develop pulmonary consequences have not been clearly delineated. The most important factor to emerge so far is nocturnal reflux. pH probes situated in the upper, as opposed to the lower, oesophagus may in the future provide a better assessment of GOR reaching upper oesophageal / laryngeal level and help to clarify the factors leading to pulmonary disease.

5. GOR is found frequently in 'near miss' infants. There is some evidence that the amount of GOR present in such infants is excessive but there are no really well controlled studies to put this question beyond doubt.

6. The available evidence suggests that there is no temporal relation between GOR and central apnea or between GOR and apnea during sleep. However, there is some evidence for an association between GOR in awake infants and obstructive apnea. This evidence comes from two studies. In one, a group of infants under 8mths were shown to have OA's in association with GOR while awake soon after a feed. In the other, a group of mainly premature infants recovering from respiratory distress with apneas, both short, long, central and obstructive apneas, occurring with regurgitation. These

studies illustrate the importance of considering factors such as the state of the infant, the type of apnea, the degree of prematurity and the presence or absence of vomiting in assessing the possible relation between GOR and apnea. When explicit statements about such factors in study populations have not been made this has caused difficulty in interpreting results. Greater attention to the presenting clinical features might serve to highlight groups where reflux is of clinical importance.

7. Suggestions and speculations relating GOR and cardio-respiratory abnormalities have come from animal studies and clinical case reports. Which, if any, are of greatest importance is not known. The possible hazards of additional factors such as minor respiratory illness in precipitating or exacerbating GOR and its postulated cardio-respiratory consequences have not yet been systematically approached.

A brief history of the development of knowledge on GOR in childhood and infancy has been presented. Information on the pulmonary consequences of GOR has been described in detail with particular emphasis on the possible association of GOR and apnea. The significant studies in this area have been presented and discussed and areas of confusion or contention highlighted. Some of the information reviewed only became available during the course of the investigations presented in this thesis. Though much is now known, even more remains uncertain.

CHAPTER 3 Page

AIMS

CHAPTER 3

AIMS

1 Background to current research

Since SIDS is now the major cause of post-neonatal infant mortality in developed countries any potential cause or contributing factor attracts considerable interest. The possible association, outlined earlier, between GOR and apneic episodes for which the infant received cardiopulmonary resuscitation led to the hypothesis that GOR might be a "cause" of SIDS. This has sparked off considerable research, including the present study, into the relationship between GOR and apnea.

As it is not yet possible to identify and study in advance infants who will die suddenly, unexpectedly and inexplicably no direct answer to the question whether GOR is causally related to SIDS can be given.

In an attempt to circumvent this basic limitation, epidemiological methods have been used to define populations of infants at increased risk for SIDS. Several groups have been identified as being at increased risk including 'near-miss' for SIDS and sibs of SIDS victims (Froggat et al 1971, Peterson et al 1980). It must be emphasised that the degree of increased risk for each group is controversial and it is not yet clear

whether the 'within' group risk is uniform. Also, the factors underlying the increased risk have yet to be defined in any of the 'at risk' groups.

Despite these limitations "at risk" groups are often studied as potential models for SIDS. This is particularly so for the 'near-miss' group which in some studies has been shown to be at considerably increased risk for SIDS. This group has become widely regarded as a possible human model for SIDS and has been viewed as an important and potentially informative group by researchers looking for abnormalities which might cause, precipitate or predispose to SIDS. The finding, for example, of frequent GOR in 'near-miss' infants in a number of studies has already been discussed. However, a cautionary note has to be sounded about extrapolations from 'near miss' infants since it is by no means definitely established that the 'near-miss' group is an appropriate model for SIDS (Stanton and Oakley 1983).

An assessment of the importance of GOR in the 'near-miss' group and in the wider context of SIDS has been considerably hampered by a lack of information about the occurrence of GOR in appropriate normal controls. Thus it is not yet clear, for example, whether the frequency and duration of GOR in the 'near-miss' infants is greater than that present either in other 'at risk' groups or in normal infants. It is also unclear whether within the 'near-miss' group there are subgroups, perhaps identifiable by additional clinical features, such as prematurity or symptoms such as a history of choking episode or "colds", in which GOR is a particularly important aetiological

factor in the asphyxial episode. The observation of a group of infants with post-feed awake apnea precipitated by GOR (Spitzer et al 1983) suggests this might be the case.

Unfortunately, too, the information available from controls is both limited and difficult to interpret. Ethical constraints have been a major limitation to performing the appropriate studies in normal infants and lack of uniformity in methodological detail has rendered comparison of the studies available difficult. For example, there are no agreed standards on the length of study, positioning of the pH probe in the oesophagus, the positioning of the infant or the pH of feeds (acid or non-acid) to be used. The ages of control subjects, both gestational and chronological, in published series have covered a wide range often with few in early infancy. Many of the available controls have been asymptomatic infants or children in hospital, and careful scrutiny of the clinical descriptions suggest that these children are often closer to the study populations than to normal infants. Also, the methods of data analysis have varied from study to study although here at least there is some agreement on the most useful indices for describing GOR.

There is, therefore, a clear need for information from appropriate "control" infants in any study of the role of GOR in precipitating cardio-respiratory abnormalities. Given that it is ethically difficult to justify studying "normal" healthy infants alternative groups must be considered.

A number of possible alternative comparison groups can be considered. Subsequent sibs of SIDS victims have been shown to be at slightly increased risk for SIDS (Peterson et al 1980). Moreover, in this situation, there is often considerable, and natural, parental pressure for reassurance that their babies are "normal". These two considerations make investigation of siblings of SIDS justifiable. In the absence of symptoms suggestive of GOR, such as frequent vomiting, the sibling group might prima facie be expected to have a prevalence of GOR similar to that in normal infants. Consequently, they constitute one alternative group of infants where, a priori, excessive GOR would not be expected.

A second potentially important group comprises those infants who have experienced 'events' similar to those noted in the 'near miss' infants but which did not appear life-threatening or lead to resuscitative intervention. Such 'events' include choking episodes, minor apneic episodes and blue or pale episodes with spontaneous recovery. Clinically, this group often seems to overlap with the 'near miss' group and in some instances clear separation is not possible. Such 'events' have similarities to the minor, predominantly respiratory, symptoms which have been observed with increased frequency before death in retrospective studies of SIDS victims.

Infants with upper respiratory infections, metabolic alkalosis and congenital stridor have all been identified as having abnormal breathing patterns (Abreu e Silva et al 1986). The functional consequences of apparently "mild" illness therefore may be greater than is generally suspected. Summation

of such stresses may result in profound abnormalities of respiratory control sufficient to lead to a major asphyxial episode, presenting perhaps as SIDS or "near-miss" for SIDS. The frequency of GOR and the reports of apnea in relation to GOR suggest that GOR may be another important "stress". Perhaps GOR provokes abnormal breathing patterns in a similar way to the above conditions. The question then arises whether GOR occurs in infants with minor symptoms or 'events' or whether GOR is a specific feature in 'near-miss' infants and, perhaps, those dying of SIDS. Infants with minor symptoms do not frequently come to medical attention as compared to those with more dramatic occurrences such as brief and self-terminating apnea. An 'events' group, therefore, constitutes a similarly relevant - and more accessible - comparison group.

A third possible group includes those infants with recurrent or persistent vomiting (and by implication significant GOR), who have no other clinical features attributable to GOR, for example, the infant who possets frequently but continues to thrive. Differences between such infants and 'near-miss' infants might highlight those features which make the latter apparently more vulnerable. They represent a third "control" group to compare with the 'near-miss' group. However, the causes of vomiting are various and more than one cause may be present in a particular infant. For example, in an infant with GOR, vomiting may be exacerbated by an intercurrent viral upper respiratory infection. In such a case, the exogenous factor (the URTI) might be sufficient to precipitate cardio-respiratory abnormalities, irrespective of the presence or absence of GOR. Alternatively, the aberrant cardio-respiratory responses produced by two factors in

combination might exceed that of either in isolation. Where endogenous and exogenous factors coexist their relative effects on cardio-respiratory variables may be difficult to distinguish. Hence, this potentially heterogeneous group of infants must be regarded circumspectly as a comparison group.

Apart from the assessment of the frequency and severity of GOR in particular groups of infants, any relation between GOR and cardio-respiratory abnormalities must also be considered. Research in this area has concentrated on 'at risk' groups, particularly the 'near-miss' group, and has attempted to define the effects of GOR on cardio-respiratory variables such as apnea. Here also, there is a need for comparative studies. For example, it would be particularly informative to compare different groups of infants with proven GOR to determine whether associated cardio-respiratory abnormalities were peculiar to a particular group of infants.

A schematic presentation of the likely characteristics of the index ('near-miss') group and the three comparison groups selected is as follows:

Group	Cyanosis/apnea during sleep	Antecedent Symptoms	Cardio-respiratory abnormalities	GOR
'Near-miss'	++	+/-	+/-	+/-
Siblings	-	-	-	?
'Events'	+	+/-	+/-	?
Vomiters	-	+/-	?	?

++ all
+ most
+/- some
- none

So far as a study of the prevalence of GOR is concerned, the sibling group is the best alternative to a group of normal infants. A lesser prevalence of GOR in the sibling group relative to the 'near-miss' group could distinguish the 'near-miss' infants from siblings, and by implication from normal infants. Similar or increased GOR in siblings would be unexpected but could then be an important factor in the increased risk status of siblings.

The non life-threatening 'event' group is a less satisfactory comparison group and clearly is not an ideal alternative to a "normal" group. Its similarity to the 'near-miss' group leads one to question whether the prevalence of GOR within it is also high. However, any significant difference in frequency and severity of GOR between this and the 'near-miss' group would support the notion that GOR is a particular hazard in 'near-miss' infants.

In the infants with recurrent vomiting, the frequent occurrence of GOR would be anticipated. A decreased prevalence of GOR in vomiters when compared with 'near-miss' infants would emphasise further the potential significance of GOR in the 'near-miss' group.

In any study of GOR, the investigative methods selected must take into account their inherent theoretical and practical limitations. When more than one method is used their comparability must be considered and assessed. At present, the barium swallow is the most widely used and readily available test for the detection of GOR. Though useful for detecting structural abnormalities and for observing the swallowing

mechanism (Herbst 1981) barium studies have significant disadvantages. They are less sensitive than other methods in the detection of GOR (Macfadyen et al 1983) and involve a significant radiation dose. In addition, the results depend on the procedure adopted for the study and the skill and experience of the radiologist. The relative lack of sensitivity is partly due to the limited time available for observation because of the radiation dose associated with prolonged fluoroscopy. The density and viscosity of barium may also influence its behaviour within the lumen of the oesophagus and stomach and affect the amount of reflux which occurs. Consequently, barium studies were not considered ideal for the present research.

A prolonged pH study with a probe sited in the lower oesophagus to detect changes in acidity is the most sensitive test currently available for the detection of gastro-oesophageal reflux. The technique is suitable for use in detailed polygraphic studies and for this reason has been the method of choice in several published studies of the relation between GOR and respiratory events particularly during sleep. However, this method has a number of potential limitations. Gastric acid output is less in infants than in adults and the acid produced may be partially neutralised by the effects of frequent milk feeds (Mason 1962). Thus, post-feed episodes of reflux might be 'non-acid' in nature and would not be detected in pH studies. These studies involve the placement of a probe in the oesophagus, usually via the nasopharynx, and whereas studies in awake adults (Malmud and Fisher 1980) suggest that a tube in this area does not alter the likelihood of reflux, comparable studies have not been undertaken in sleeping

infants. The effects of probe placement on arousal, oesophageal dynamics and the work of breathing in infants remain unquantified. To these limitations must be added a lower degree of parental acceptability when any such 'invasive' studies are contemplated on symptom-free infants. Despite these caveats, pH monitoring is the best and most suitable method for detecting GOR presently available.

The limitations of the two methods described have in part been the stimulus to the development in the last 10 years of radionuclide techniques for the assessment of GOR in infants and children (Heyman et al 1979). Radionuclide techniques allow reflux to be detected as it occurs using physiological fluids, without the placement of oesophageal probes. Radionuclide scans represent the most physiological approach available to the detection of reflux and have the two particular advantages that reflux can be monitored over a much longer period than is possible by barium study, without any increase in the radiation dose, and that the detection of reflux is independent of the pH of the refluxing fluid. A disadvantage is a phase delay between the occurrence of reflux and its detection as it takes some seconds for the gamma camera image to appear. Radionuclide techniques are, therefore, suitable as sensitive screening tests for the occurrence of GOR (Macfadyen et al 1983) but are less well suited than pH studies for the elucidation of physiological interrelations.

In the present research, radionuclide scanning was the method employed to detect GOR in the studies of prevalence. pH monitoring was the method for subsequent sleep polygraphic studies in selected infants with GOR, to assess the relation of GOR and cardio-respiratory variables.

In selecting a method for detecting GOR it is important to define or state what constitutes 'significant' or pathological GOR. Current concepts of normal and pathological reflux have been reviewed in Chapter 2. The comparability of different methods for detecting GOR is also pertinent. 'Significant' reflux on one test should be similarly recognised by any other test used. There are inevitable difficulties when the basis for the detection of reflux differs between tests. If the ideal of complete congruence between methods is not achieved the reasons underlying any discrepancies in the assessment of 'significant' GOR should be understood.

2 Questions posed

Certain unanswered questions about the postulated relationship between GOR and cardio-respiratory events such as apnea represent the background to this thesis.

1. How common is reflux?

As discussed, gastro-oesophageal reflux is common in 'near miss' infants, even in the absence of significant vomiting. What is not clear is whether the prevalence and

severity of reflux in 'near-miss' infants is different from that obtaining in normal infants. As it is not ethically justifiable to employ techniques which are 'invasive' or involve exposure to radiation on completely normal infants one aim of this research was to assess the occurrence of GOR in groups of infants who could not be regarded as totally normal and to compare the findings in each to those in a 'near-miss' index group in an attempt to answer this question indirectly. The choice of groups has been described. Three broad categories of infants were selected for study: 1. asymptomatic sibs of SIDS victims; 2. infants who had experienced non-life threatening 'events' but recovered without resuscitation; 3. infants whose principal problem was persistent vomiting not associated with any respiratory problems. These were the main comparison groups.

Two additional smaller groups, investigated because of clinical problems possibly attributable to reflux, were also included in the study. One comprised children with severe mental retardation and the other infants with respiratory problems thought to be due to recurrent aspiration. Infants with severe mental retardation are known to have a very high prevalence of gastro-oesophageal reflux; a similar finding was anticipated in infants with suspected aspiration.

Radionuclide scans were used to assess the frequency of GOR in the groups defined. This method provided a sensitive and physiological approach to reflux detection. The low dose of isotope used made it suitable for use in infants and its non-invasive nature made it very acceptable to parents.

Facilities for radionuclide studies were established and easily available in the department of Medical Physics in the Leicester Royal Infirmary.

During the course of the radionuclide scans additional observations were made of some factors which could influence the occurrence of GOR, including time elapsed since feeds, body position and state of wakefulness.

2. GOR and cardio-respiratory abnormalities?

The second major aim of the research focused on the possible relation between GOR and cardio-respiratory events, especially apnea.

Two approaches were used.

A) A group of infants was monitored for apnea and bradycardia during the course of radionuclide scanning. Cardio-respiratory variables were monitored using a non-invasive 3 channel system for heart rate, and chest and abdominal movements. This, combined with the radionuclide scan, allowed the assessment of the cardio-respiratory effects of reflux. However, the method of monitoring respiration had inherent limitations. The absence of an airflow sensor meant that obstructive apnea could not be detected reliably. Any temporal relation between reflux and apnea was also difficult to assess precisely. Finally, the infant did not always sleep throughout the course of a radionuclide scan. As any relation

between GOR and apnea may be greatest during sleep, this was an important period to study. To take account of these limitations a second approach was used.

B) A subgroup of infants with significant GOR on radionuclide scan was studied during sleep at night using polygraphic techniques for monitoring sleep state, respiration and heart rate. In these studies, lower oesophageal pH monitoring was the method employed to detect GOR for both logistic and technical reasons. This approach allowed precise timing of the sequence of events related to episodes of reflux. It was anticipated that the temporal relation between GOR (detected by pH probe) and any cardio-respiratory abnormalities occurring during sleep would be defined.

3. How do scan and pH methods of GOR detection compare?

While radionuclide scans and lower oesophageal pH monitoring are both sensitive methods for detecting GOR it must be recognised that they measure different aspects of reflux. pH probes detect acid reflux whereas radionuclide scans indicate reflux of gastric contents, irrespective of pH. Since it seemed likely that in infants some GOR, especially in the post feed period, might be 'non-acid' discrepancies between the two tests were expected. As both methods were employed in the studies undertaken it was essential to compare the two methods. Therefore, simultaneous pH monitoring was performed on a number of infants during the course of radionuclide scans, to provide a direct comparison of the methods.

In performing these studies episodes of vomiting were also recorded to assess their relation to GOR detected by the two investigative methods.

3 Hypotheses tested

Three hypotheses were tested in this research.

i) The first hypothesis was that 'near-miss' infants have a greater than 'normal' frequency and duration of GOR. The difficulties in studying a normal population of infants and the definition and selection of suitable alternative infant groups for comparison to an index group of 'near miss(C) Cants have been outlined. If GOR was present in significant excess in the 'near miss' group when compared with other groups it would provide support for the notion that 'near miss' episodes might occur as a direct consequence of GOR. Conversely, if GOR was not present in excess in the 'near-miss' group then it would suggest that other differences between the groups were more important in the aetiology of cardio-respiratory abnormalities which precede or follow 'near miss' events. GOR might then be of secondary importance or have no special significance.

The first part of this research was designed to test this hypothesis by comparing the frequency and severity of GOR detected by radionuclide scan in 'near-miss' infants with that detected in the other infant groups studied. Before completing this study an experimental assessment of the analytical sensitivity of radionuclide scans was also performed.

ii) The second hypothesis was that GOR causes cardio-respiratory abnormalities, particularly during sleep, in 'near-miss' infants. It was appreciated that the crucial factor in determining outcome might not be the presence of significant GOR, but rather the nature of the infant's response to the occurrence of GOR. If the infant groups could be distinguished by their response to GOR and not by the amount of GOR recorded, it would support the theory that the infant's response to GOR was abnormal.

iii) The third hypothesis was that non-acid GOR occurs in 'near-miss' infants. The confirmation that such non-acid GOR does occur has important implications for studies of the detailed relation between GOR and cardio-respiratory abnormalities. Most detailed studies of this question to date have used pH probes to detect GOR and a pH below 4 as indicating GOR. Such an approach assumes that it is only acid reflux which causes abnormality. Animal studies have shown that aspiration of non-acid material is as harmful to the respiratory system as aspiration of acid fluid and there is no reason to suspect that in infants non-acid material is any less harmful. A priori it would seem as likely to cause cardio-respiratory abnormalities as acid reflux.

This hypothesis is testable by performing simultaneous pH and radionuclide scan studies. The use of a pH independent method along with a pH dependent one allows the pH of refluxes detected by scan to be measured. By this means, any episodes of non-acid reflux should be detectable.

In summary, the three hypotheses were:

1.'Near-miss' infants have a greater than "normal" amount of GOR.

2. In 'near-miss' infants GOR is responsible for cardio-respiratory abnormalities during sleep.

3. In 'near-miss' infants non-acid GOR occurs.

Within the constraints of the experimental methods and design these three hypotheses were felt to be testable.

CHAPTER 4 Page

METHODS

CHAPTER 4

METHODS

1 Plan of Investigation

In order to test the hypotheses set out in the previous chapter it was planned to study four principle groups of infants. These groups were infants presenting as 'near-miss' for sudden infant death, infants with "events" such as episodes of choking or blue or pale episodes usually resolving spontaneously or with minor stimulation (non life-threatening "events"), subsequent sibs of SIDS and infants with recurrent possetting who were otherwise well. In addition, two small groups were studied where GOR was strongly suspected on clinical grounds: a group of four infants with severe mental retardation in whom reflux had proved difficult to demonstrate radiologically; and a group of seven infants where recurrent pulmonary aspiration was suspected.

In the first instance, it was planned to monitor all the infants for GOR using radionuclide gastro-oesophageal scans to assess the frequency of GOR in the 'near-miss' group, where reflux had been reported to be common, and to compare it with the frequency in the other groups. It was also planned that selected infants from each group would have additional studies during the course of the radionuclide scans. One subgroup was to have simultaneous pH monitoring during the scan in a study designed to determine if episodes of reflux were always acid in nature. A second subgroup was to have cardio-respiratory

monitoring throughout the course of the scan to see if any temporal relation between reflux and apnea or bradycardia could be detected. Along with these studies it was planned to perform more detailed polygraphic sleep studies, including lower oesophageal pH monitoring, on selected infants from each group, shown to have significant GOR by radionuclide scan. The polygraphic studies would permit a more precise assessment of the relation between GOR and cardio-respiratory abnormalities during sleep.

2 Patients

2.1 Selection

The infants with 'near miss' events presented to paediatricians at the Leicester Royal Infirmary or Leicester General Hospital with a history of sudden unexpected collapse usually associated with apnea, pallor or cyanosis. These alrming episodes had resulted in resuscitative intervention, varying from stimulation by shaking to full scale cardiopulmonary resuscitation. In their parents' view the child would have died without such intervention. Admission to hospital followed. There a full history was obtained from parents and a thorough clinical examination of each infant completed (Simpson and Macfadyen 1986). Comprehensive investigations to elucidate the cause of the presenting episode included a full infection screen, EEG, ECG, CXR and metabolic studies. A barium swallow and radionuclide gastro-oesophageal scan were performed to exclude abnormalities of swallowing and GOR.

The infants with non life-threatening "events", who also presented to paediatricians at the above hospitals, were usually current or recent in-patients. They had a variety of symptoms such as choking during feeds, blue spells and short stop breathing episodes from which they had recovered speontaneously or with minor stimulation at most. A brief outline of their presenting histories is given in appendix 1. There was sometimes a history of recurrent possetting in these infants suggesting that GOR was a potential factor in their symptoms.

The infants with a history of troublesome possetting were clinically suspected of having GOR and were investigated as part of their clinical care to confirm or refute this diagnosis. Other possible explanations for recurrent vomiting had been excluded.

The next group comprised SIBS of previous sudden infant death victims. As discussed in the previous section, it was considered ethical to study these infants given their known increased risk for SIDS and a possible causal relation between GOR and SIDS. Parents of SIBS were referred from a variety of sources and were initially contacted by one person (JYP) as soon as possible after birth. The nature, details and purpose of the proposed studies were explained. If informed verbal consent was obtained and the parents agreed to participate, arrangements were made to perform the radionuclide scan study, when possible, 4-8wks after birth.

The remaining two small groups investigated by radionuclide scan were suspected of having clinical symptoms related to GOR. In 4 infants with significant mental retardation, GOR was suspected as a cause for pulmonary or neurological symptoms even although barium studies of the upper GI tract had been negative on more than one occasion. In the other group of 7 infants, recurrent pulmonary aspiration was suspected clinically and it was hoped that direct evidence of aspiration might be obtained by radionuclide scan.

Table 6 summarises the details of the infants studied by radionuclide scans. Table 7 documents the number of infants from each clinical group having additional studies, either at the time of the scan or later at night. Appendix 1 gives brief details of the presenting clinical problem of each infants. Appendix 4 tabulates which studies each infant underwent.

2.2 Ethical considerations

The Leicestershire District Health Authority Committee on the Ethics of Research approved the experimental protocols. For all the SIBS of previous SIDS victims and in those infants where the studies were not being performed as part of the infant's normal medical care informed verbal consent was obtained from the parents after a detailed explanation of the experimental aims and procedures. Informed verbal consent was obtained for all infants taking part in polygraphic studies during sleep.

Table 6: Details of infants studied by scan

		Sex		Gestation	Age at study	
Diagnosis	n	M	F	<=37 wks	Mean (yrs)	Range (yrs)
'Near-miss'	22	14	8	1	.281	0.096 - 0.877
SIBS of SIDS victims	12	8	4	0	.260	0.038 - 1.156
Non-life threatening "events"	29	15	14	7	.208	0.025 - 0.858
Recurrent possetting	8	5	3	3	.338	0.093 - 0.622
Mental retardation	4	3	1	1	1.792	1.277 - 2.173
Suspected tracheo-bronchial aspiration	7	4	3	2	.593	0.126 - 0.989
Total	82	49	33	14	.365	

Table 7: Additional studies performed in infants having scans

	Infants	Studies during scans		Later studies
Diagnosis	n	Respiration	pH study	Sleep c pH
'Near-miss'	22	8	8	7
SIBS of SIDS victims	12	6	2	2(3)*
Non-life threatening "events"	29	12	11	7(10)**
Recurrent possetting	8	3	4	0
Mental retardation	4	0	3	0
Suspected tracheo-bronchial aspiration	7	1	0	1
Total	82	30	28	17 (21studies)

Respiration = respiratory monitoring during scan

pH study = pH monitoring during scan

Sleep c pH = Later polygraphic sleep study

* 1 infant studied x2 ** 1 infant studied x2, 1 x3

3 Radio-nuclide gastro-oesophageal scans ("Milk scans")

3.1 Scan procedure

Details of feeding

All the infants were fasted for at least four hours before a radionuclide scan. They were brought to the nuclear medicine department in the Leicester Royal Infirmary on the morning of the study ready to receive their first feed of the day.

Each infant was then fed freshly prepared Tc99m Sulphur colloid mixed in a small amount of his/her normal feed (either formula or expressed breast milk). The isotope mixture was always given by bottle. In the early studies, the isotope was mixed with 30ml of milk but in the later studies the volume of milk was reduced to 5-15ml. The radio-label was always mixed with part of the feed, rather than the whole, to ensure the infant received all the label even if the feed was not completed. This approach also ensured that the mouth, pharynx and oesophagus were washed clear of radio-isotope before the scan was started.

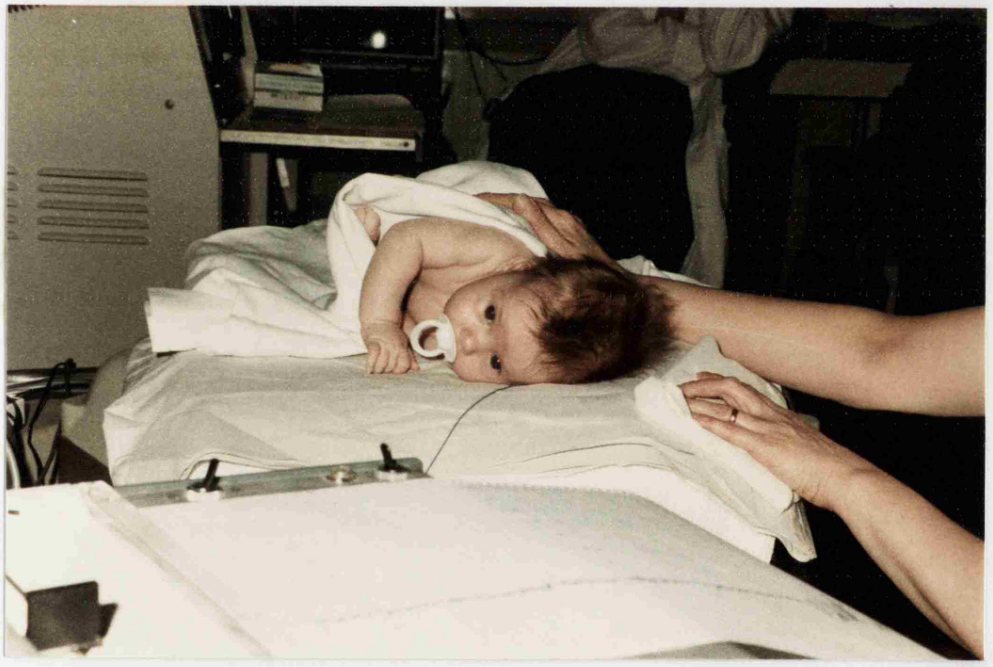
After taking the isotope milk mixture, the infant completed the remainder of the feed (by bottle or from the breast). The infant was then winded and settled on the gamma camera head (Figure 1). A dummy was offered if the infant was accustomed to one, and restless without it. At this stage most infants would settle and fall asleep. They were usually asleep for at least part of the scanning time. Sedation or restraint was not used.

Occasionally the infant failed to complete a feed and then became unsettled during the course of the scan. If this happened the scan was temporarily stopped and the rest of the feed offered. This settled most infants allowing the scan to be continued.

If radioactivity persisted in the naso-pharynx after reflux a swallow of non-radioactive liquid was given to clear the pharynx. Care was also taken to remove any of the infant's clothing or coverings contaminated by spillage or vomiting of radioactive material during the study. Both of these measures were taken to ensure the absence of "hot spots" on the scan, arising from surface contamination, which might be wrongly interpreted as GOR or pulmonary aspiration.

No attempt was made to induce reflux by manoeuvres such as application of external abdominal pressure.

Figure 1: Infant positioned on gamma camera head for radionuclide scan



Patient positioning

The infant was placed lying on the gamma camera face in one of four positions; supine, prone, right or left lateral positions. No particular order was used for the starting position. Subsequently the infant was turned every ten to sixteen minutes to one of the other positions until the infant had been in each position twice. This permitted an assessment of the effects of position on the amount of reflux.

Time and Duration of scan

The scan began as soon as the infant had completed the feed and was settled in position on the gamma camera. This usually took no more than 5-10min from the end of the feed. Information was then collected every minute for between eight and sixteen minutes in each of the four positions (supine, prone,left and right lateral). This was repeated until each position had been examined twice. The radionuclide scan studies lasted on average 110 +/-17min (mean,sd) and the mean dose of isotope administered was 7.76 +/- 0.66MBq (mean,sd).

Recording of information

Once the infant had been placed directly on the gamma camera face and the precise position adjusted to ensure that the mouth, pharynx, oesophagus and stomach were all included in the camera's field of view the study was started. These areas were then observed continuously on the gamma camera's monitor

screen. Each study was supervised and all the observations recorded by one person (JYP) who was present throughout the study.

During each minute while the scan was in progress the following observations were made and recorded - the occurrence and extent of GOR, body position, and state - whether asleep or awake - and presence of restlessness. No attempt was made to distinguish between active and quiet sleep phases by behavioural criteria. It was not, therefore, possible to assess from isotope studies whether reflux had occurred during active or quiet sleep. Finally, a minute-to-minute recording of the time was made.

The gamma camera was set to accumulate counts for sixty seconds every sixty seconds. The results were displayed on a monitor screen and stored in the gamma camera computer (ie one sixty second frame was collected every sixty seconds). The information was then transferred onto floppy disc at the end of each study to provide a long term record. In addition selected representative images (including those showing evidence of reflux) were transferred to X-ray film to provide a visual record of the scan. These X-ray films were assessed independently by the duty radiologist.

3.2 Gamma camera and collimator

All the radionuclide scans were performed in the Department of Nuclear Medicine in the Leicester Royal Infirmary using a Siemens ZLC gamma camera and computer. Initially, the scans were performed with a low-energy all purpose collimator (NEMA sensitivity 6.0 counts/sec per uCi). For the later studies a high sensitivity collimator was used (NEMA sensitivity 10.2 counts/sec per uCi). This collimator is 1.7x more sensitive. However, only a small change in the detection threshold for reflux resulted from this change (from between 2-5ml.sec to between 3.4-8.5ml.sec). Thus the results from the two collimators were considered to be comparable (see Chapter 6 and Appendix 2).

3.3 Isotope

Type and preparation

All the scans were performed using Tc99m sulphur colloid. The isotope is not absorbed by the oesophageal mucosa and, except in severe oesophageal motility disorders, is rapidly cleared from the oesophagus (Malmud and Fisher 1982). The bulk of this isotope is thought to bind to sites on coagulated milk protein and is not absorbed by the infant. Free pertechnetate, which is readily absorbed, is present in only small amounts, (around 1.3%), in such a milk / colloid mixture. This is important as absorption of free pertechnetate is undesirable because it increases both the radiation dose to the infant and the background body activity (Heymann et al 1979).

The isotope was always prepared immediately before use by the Pharmacy Department of Leicester Royal Infirmary.

Amount of radiation

The amount of isotope used in any such study represents a balance between an acceptable level of exposure to radiation and a dose offering an adequate lower limit for reflux detection.

In these studies approximately 8MBq (250uCi) Tc-Sulphur colloid was used (mean 7.76MBq, sd 0.66MBq). This gave an estimated reflux detection threshold in the region of 2 - 5ml.sec (see Chapter 6 and Appendix 2). This dose allowed adequate visualisation of episodes of reflux in the infants studied regardless of the weight of the infant or volume of feed ingested.

Dosimetry

The radiation dose in a 'milk' scan has been estimated in two published studies using amounts of isotope similar to that used in these studies. Heymann et al (1979) used isotope doses between 150-1000uCi and estimated the absorbed radiation to be 300-500mR to the stomach, 17-36mR to the gonads and 33-56mR to the body in toto. The thyroid dose was considered negligible

because there was minimal free pertechnetate. Macfadyen et al (1983) used an isotope dose of 150uCi (5.55MBq) and estimated the maximal radiation dose as follows:

Whole body	4.8 x 10^6 C/Kg
Bowel	19.35x 10^6 C/Kg
Thyroid	Negligible

These doses compare favourably with the exposure in a Barium swallow study with fluoroscopy and are lower than in a radionuclide liver scan (Macfadyen et al 1983, Heymann 1979). The radiation dose was therefore considered to be within acceptable limits.

3.4 Classification of reflux on scan

McCauley et al (1978) have described a radiological classification of gastro-oesophageal reflux for use in Barium studies which has been widely followed. It is based primarily on the extent of retrograde flow of barium into the oesophagus. The grades are:

1 = reflux into the distal oesophagus only

2 = reflux extending above carina but not into cervical oesophagus

3 = reflux into cervical oesophagus

4 = free persistent reflux into cervical oesophagus with a widely patent cardia

5 = reflux of barium with aspiration into trachea or lungs

McCauley found it practical and clinically useful to condense the grades into two categories: 'minor' reflux (grades 1 and 2) and 'major' reflux (grades 3-5).

On radionuclide scans, as opposed to Barium studies, precise details of surrounding anatomical structures cannot be delineated. The abbreviated scale is therefore a more appropriate classification of GOR on scan. Using this classification, reflux on milk scan was assessed as "moderate" reflux (involving only the lower oesophagus and equivalent to minor reflux on the above scale) or "severe" reflux (extending to the upper oesophagus or larynx and equivalent to major reflux). Examples of each are shown in Figure 2 (a & b).

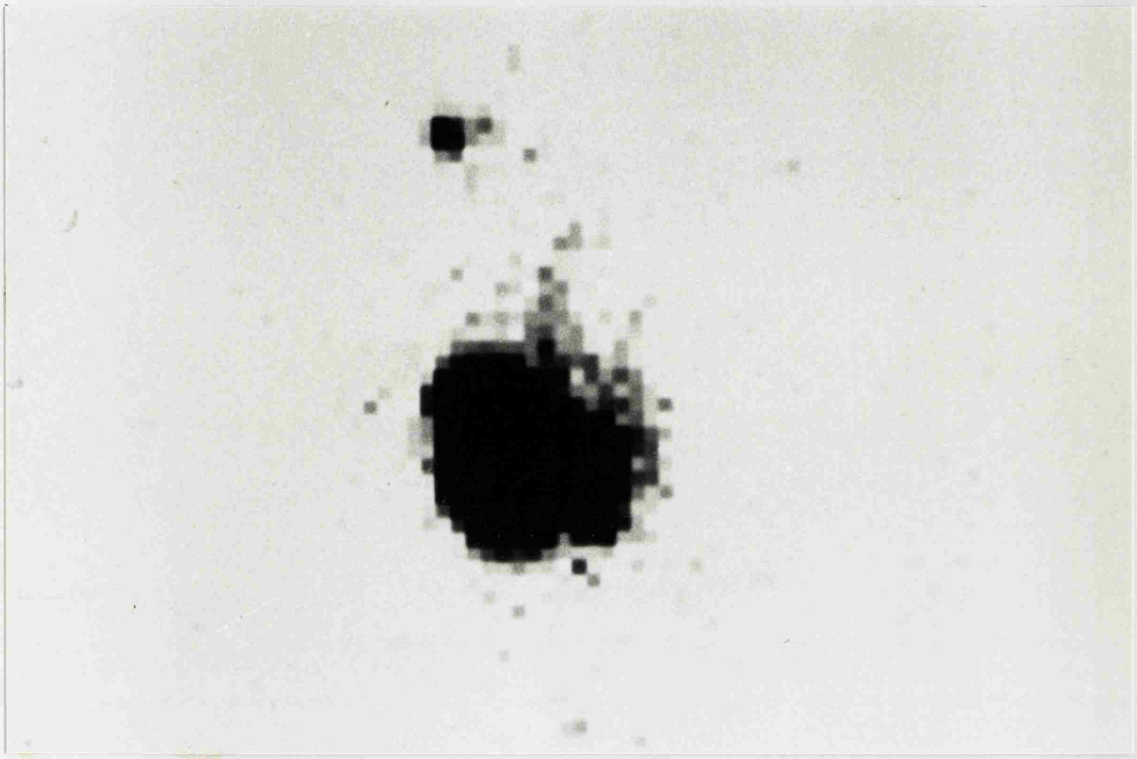
In these studies a scan was counted as positive if one frame in the two hour study showed reflux (major or minor). This convention was adopted following Seibert et al (1983) who compared radionuclide scans with lower oesophageal pH studies and showed that one positive frame on a 1 hour scan study correlated with significant reflux on subsequent 24 hour lower oesophageal pH study, the technique widely regarded as the "gold standard" for the diagnosis of GOR. Seibert's study was not precisely comparable to the present one, as a smaller isotope dose was used. This is discussed in more detail in later chapters.

This method of reporting by counting positive frames gives a measure of the time that refluxed material is present in the oesophagus. If GOR is not cleared from the oesophagus promptly as a consequence of abnormal oesophageal clearance then the infant may have many positive frames arising from only a few

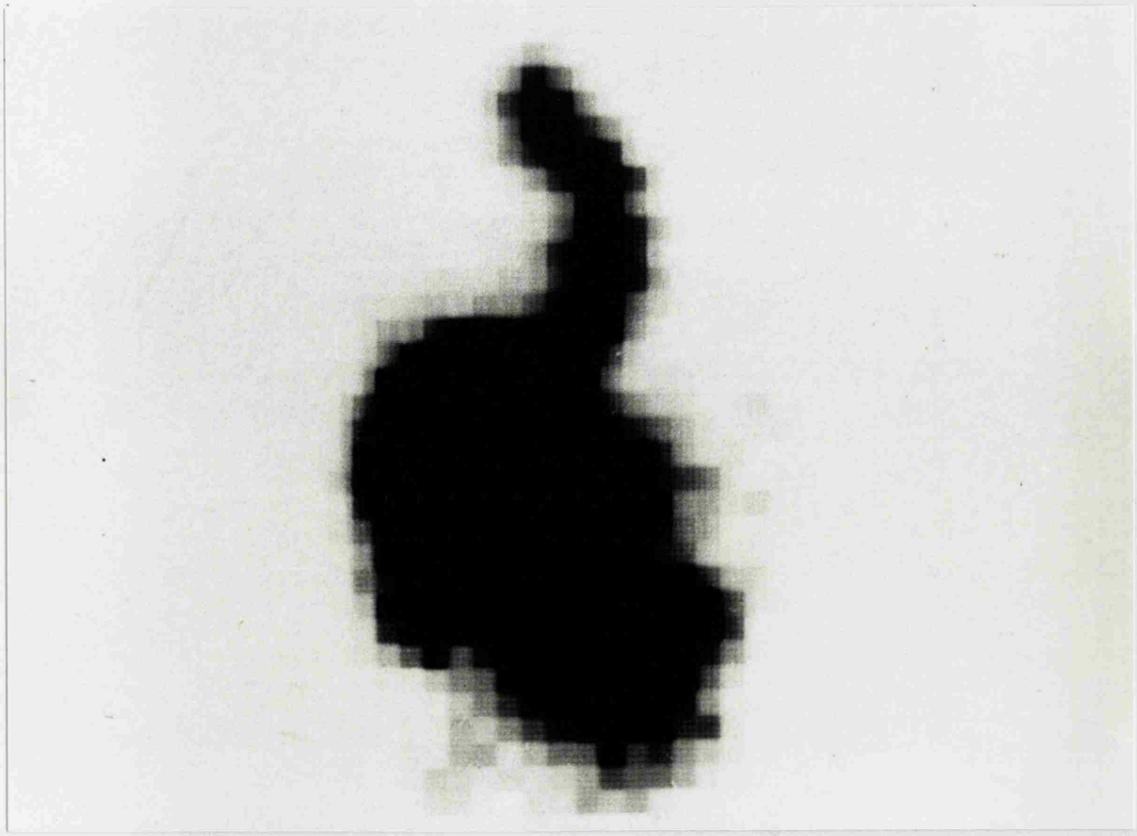
episodes of reflux eg an infant could have a single episode of reflux lasting 20 frames. To avoid this potential source of confusion, the number of separate episodes of reflux was computed, in addition to the number of frames during which reflux occurred.

Figure 2: Radionuclide scans showing GOR a) moderate and b) severe

a



b



4 pH probe studies

4.1 Methods

Instrumentation

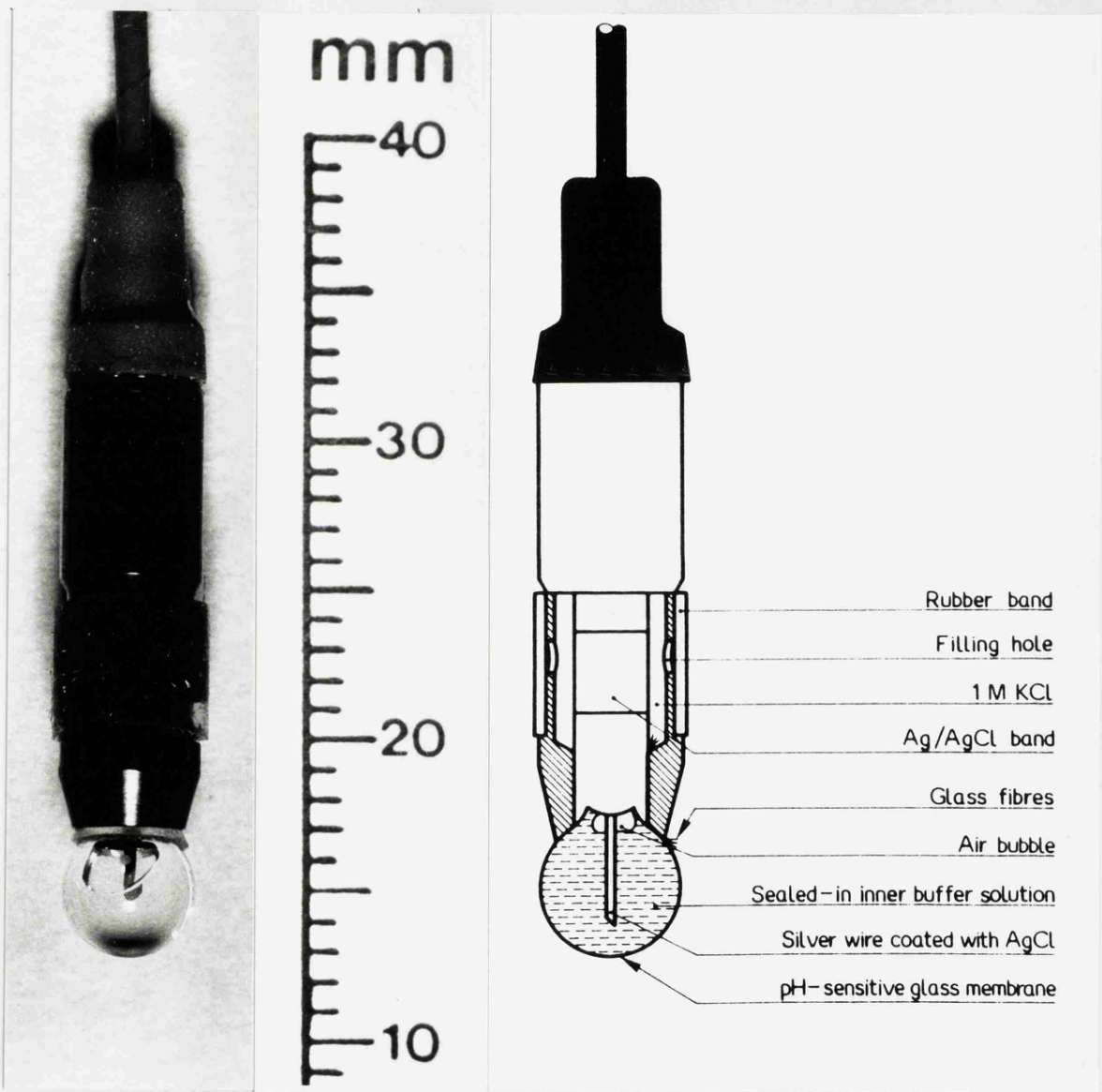
Lower oesophageal pH was measured using a Radiometer GK2801C stomach pH electrode (Radiometer, Copenhagen) with a Radiometer PHM75 clinical pH meter (Figure 3).

The GK2801C pH electrode is a micro pH probe designed for prolonged and accurate measurement of gastric or oesophageal pH. The probe tip has dimensions of 4.5mm x 25mm and is attached to 1.0mm x 2.5m low-noise cable (Figure 3). These small dimensions allowed the probe to be passed orally in even the smallest infants. The probe consists of a glass pH electrode and a tiny inbuilt adjacent silver/silver chloride cell which functions as an internal reference cell. Consequently an external reference electrode is not required. This allows the probe to be calibrated in vitro before use, a feature which greatly facilitates the calibration process. The associated PM75 pH meter is a galvanically isolated meter designed for clinical pH measurement in the oesophagus and gastrointestinal tract.

In the present studies, the output from the pH meter was interfaced to a Servoscribe flat bed ink recorder to provide a permanent analogue record of a study for subsequent analysis. The recorder was run at a paper speed of 10 mm/min. For most night studies the recorder was, in addition, interfaced to the Mingograph (Elema Schonander) polygraph recorder used for

recording data relating to sleep state and cardio-respiratory variables. This recorder was run at a paper speed of 1cm/sec. This faster paper speed allowed precise timing of changes occurring in the physiological variables under study and facilitated comparisons between them.

Figure 3: Radiometer GK2801C pH electrode



In any physiological recording system, such as the lower oesophageal pH system used in the present studies, the object is to obtain a record which is an exact analogue of the physiological event. In assessing the accuracy of any resulting measurements three general questions must be considered: 1) what is the static accuracy? 2) what is the dynamic accuracy? and 3) what is the physiological reactance? (Fry 1960)

Static accuracy is the reliability of the instrument in recording stationary or extremely slowly varying events and implies two qualities, stability and uniqueness. Stability implies freedom from a drifting base line and a drifting gain factor while uniqueness implies that the system will respond uniquely to any statically applied signal regardless of the way the signal is applied. With a variable, such as oesophageal pH where the pH changes are often relatively slow, static accuracy is of prime importance.

The static accuracy of a system may be studied by observing the response of the system to various static input signals over a period of time. This can be done by turning the system the system on, allowing the recorder to run at a very slow speed and applying known static signals of progressively increasing and then decreasing values periodically throughout the period of observation. From this both the stability of the base line and the calibration factor can be checked.

With the pH system described above the pH drift at pH 7.38 in vitro was measured at 0 pH units/hr. At pH 4.03 the drift in vitro was .03 pH units/hr. In use in vivo, the measured mean pH of the pH 7.38 standard buffer at the end of a study (which

usually lasted around 4hrs) was 7.42 giving a mean pH drift of 0.04 pH units over the course of a study ie approximately 0.01 pH units/hr (Table 8). This represents a satisfactory level of static accuracy.

The dynamic accuracy of a recording system is the fidelity with which the response of the system will simulate the dynamic event being measured. The dynamic accuracy is governed by the noise level of the system and the dynamic response of the system. In the case of a pH transducer the noise is electrical arising principally from the electronic amplification of the system, though there may be components due to bio-electric noise. An assessment of the noise level can be made obtained as a by-product of the test for static accuracy by inspection of the baseline trace both in vitro and in vivo. For the pH system used the noise level was very low. Figure 4 illustrates typical traces.

The dynamic response of a recording system may be determined by driving it with a known input wave and observing its response. A sine wave is commonly used for this purpose. Intuitively, the uniformity of amplitude response and the absence of phase lag of the recorded wave indicates the ability of the system to follow rapidly changing phenomenon. For many systems, including pH transducers, no suitable sinusoidal wave generator is available. Fortunately, in certain systems the response to a step change in input has a relatively simple and unique relationship to the frequency response of the system. In an overdamped system, like a pH recording system, subjected to a square input wave the record will slowly rise to the new value without oscillation and the frequency response can be

computed from this non-oscillating curve. In general, for overdamped systems this information is usually reported as a time constant. For the pH electrode used the total response time depends on the response time at the glass membrane (very fast) and the stabilisation of the liquid-junction potential which is entirely dependent on the composition of the sample. The manufacturer reports that when a GK2801C stomach pH electrode stabilised in a neutral buffer is moved to a 0.1 M HCl solution, more than 98% of the response will occur within a few seconds (98% response <25sec at 37degC), while the remainder will be achieved after several minutes. Figure 5 demonstrates the response observed on testing in the laboratory. There is an almost instantaneous change in pH with 98% of the response occurring within 2sec. For the purposes of timing pH drops in relation to simultaneously recorded cardio-respiratory events this pH recording system, therefore, gives a suitably rapid indication of change in pH. An assessment of the extent of the change is less important and hence the slower development of the full scale response is satisfactory.

The remaining question is the "physiological reactance" of the system ie the effect, usually undesirable, of the recording system on the physiological event being measured. There are two aspects to this. The first is the distortion of the physiological event due to flow of mass or energy from the organism in and out of the recording probe of the system. A good recording system would have a sensing probe offering a high resistance to this flow. In this respect this glass pH electrode is almost ideal as the input impedance is >10^12 ohms. There is, therefore, essentially no energy flow from the

system to the probe. The second aspect of physiological reactance is of particular relevance to pH studies on infants but is much more difficult to assess. What effect does the pH probe have on the physiology of the infant's oesophagus? Does its presence alter the state of the infant and the frequency, duration and severity of GOR? Unfortunately, there is little information on this important questions in the literature. The few adult studies available suggest that the presence of a probe in the oesophagus does not influence GOR (Malmud and Fisher 1982). Unfortunately, there is no information available for infants, either awake or asleep. This problem is discussed further in the section on limitations of methods.

Consideration of the pH recording system with respect to the above factors suggests that on all counts (apart form uncertainty surrounding the question of physiological reactance) it was adequate for the proposed studies.

Table 8: In vivo drift in pH probe measurements

28 pH studies

Standard pH (37 degC)	Measurements n	Mean pH after 4hrs (37 degC)	2sd	Range High	Range Low	Mean drift in pH
7.38	27	7.42	.10	7.52	7.30	+.04
4.03	17	4.00	.14	4.12	3.85	-.03
1.10	3	1.09	.06	1.13	1.07	-.10

Figure 4: pH recordings showing low instrument noise level

a) in vitro & b) in vivo

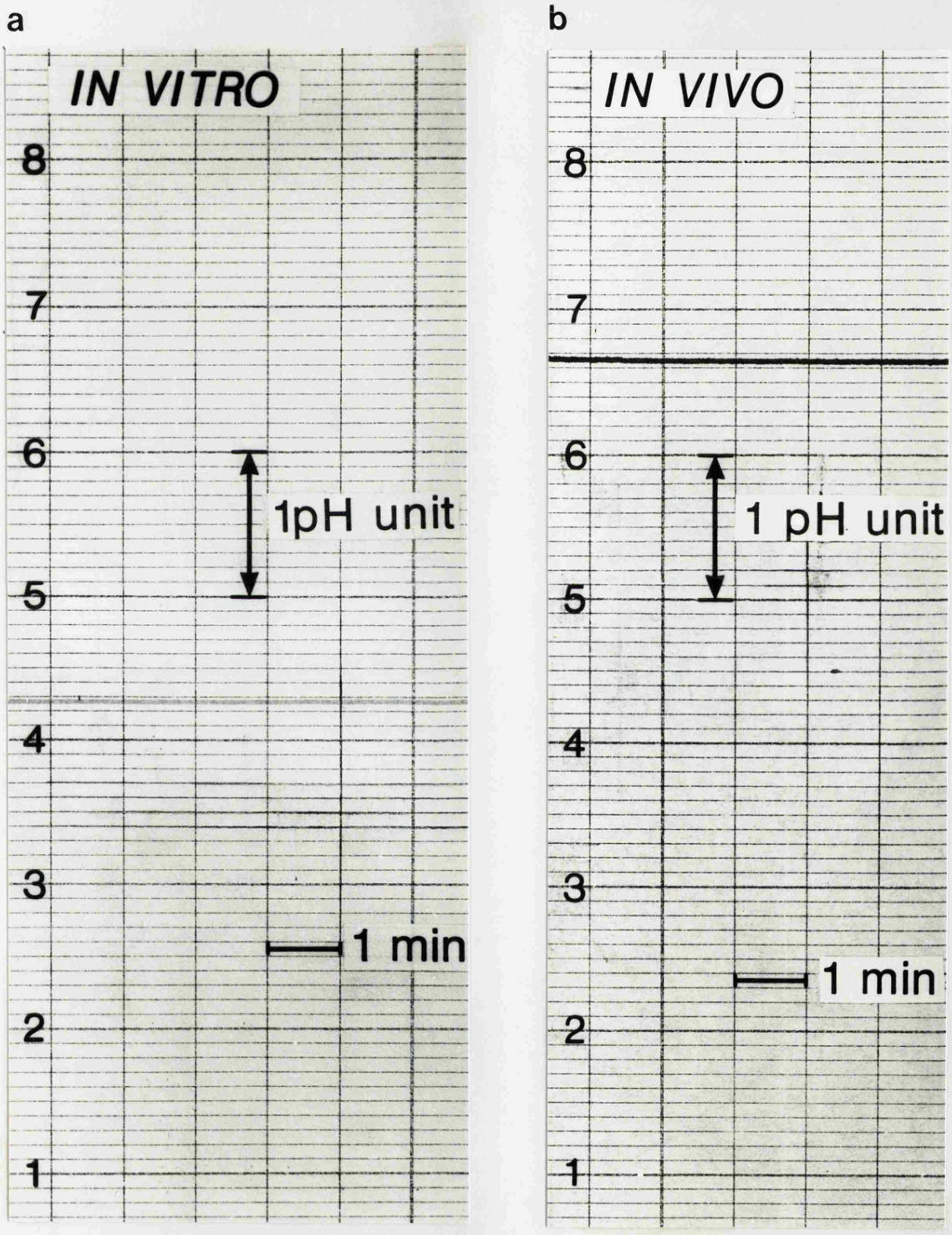
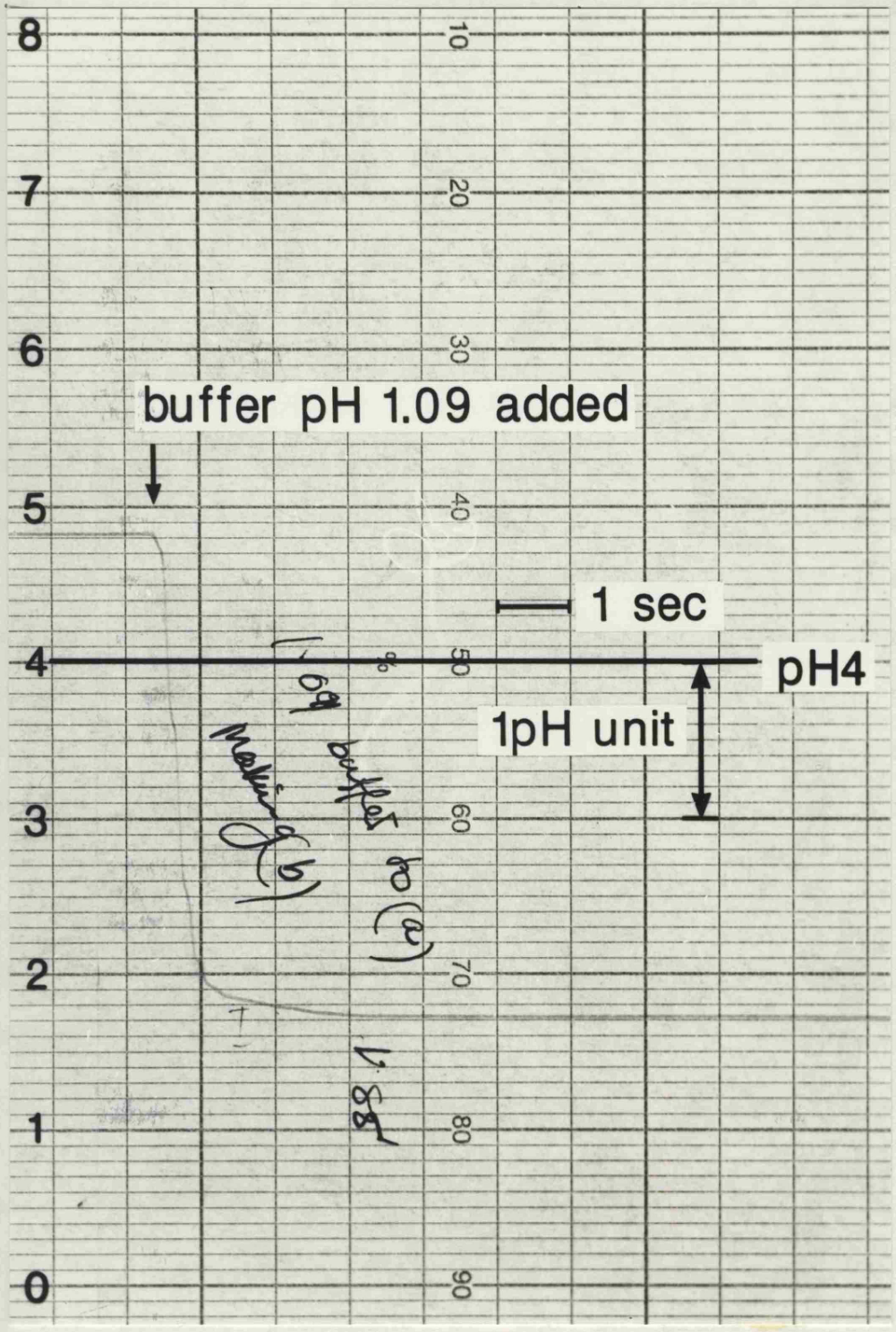


Figure 5: Dynamic response of pH probe to step change in pH



Sterilisation and calibration of pH probe

Before each study the pH probe was sterilised by immersion in a freshly prepared 1:80 sodium hypochlorite solution for at least 1 hour. It was then calibrated and rinsed in distilled water before it was positioned in a patient. A two point calibration was performed in vitro using standard commercially available precision buffers (Radiometer) maintained at 37degC in a water bath. The pH of the buffers used were of pH 7.383 and pH 1.1.

At the end of a study, the probe was advanced into the stomach to determine the pH of gastric contents. The probe was then removed from the patient and checked for instrumental drift by measuring the pH of the standard solutions used for the original calibration. The pH at the end of a 4hr study is listed in table 8. As discussed, the mean pH measured against the pH 7.38 standard buffer at the end of the studies (usually around 4hrs duration) was 7.42 giving a mean pH drift of 0.04 pH units over the course of the studies. The largest drift recorded from the calibration value of pH 7.38 was 0.14 pH units. Thus, in use, the pH probe was highly stable and accurate.

Positioning of probe

The precise placement of the pH probe in the lower oesophagus has to be considered. The most consistent and logical method for determining the appropriate position for the probe in the lower oesophagus is that described by Sondheimer

(1980). This involves placing the pH probe in the lower oesophagus at a constant proportion of the distance from mouth - or nose - to the physiological lower oesophageal sphincter (determined by manometry). Normally, a proportion (usually 13%) is subtracted from the distance from mouth or nose to LOS, placing the probe above and in constant relation to the LOS.

Unfortunately, the position of the lower oesophageal sphincter can only be determined precisely by manometric studies as there are no constant anatomical landmarks. Facilities for oesophageal manometric studies are not widely available particularly for use in infants. This problem can be circumvented by using a nomogram developed by Strobel et al (1979) for use in infants and children, relating height and distance from mouth (or nose) to lower oesophageal sphincter. The nomogram was based on 124 measurements in 119 North American infants and children ranging in age from 3wks to 235mths. The regression equations relating height and oesophageal length had a correlation coefficient, $r > 0.92$. Thus, the probe can be consistently positioned in the lower oesophagus without the use of oesophageal manometry. This method was, therefore, adopted to position the pH probe in the lower oesophagus. Before each study, the infant's length in centimetres was measured using a neonatal stadiometer (Harpenden). The distance from mouth to lower oesophageal sphincter was calculated using the nomogram and a mark was placed on the probe at 87% of the length from its tip. The probe was then passed orally to this mark. Once in situ the probe was fixed to the infant's face using micropore tape (3M). Normally, it took a few minutes for the infant to settle and

become accustomed to the presence of the probe. The infant was then given a feed, after which he / she would usually drift off to sleep.

In contra-distinction to most lower oesophageal studies the pH probe was passed orally. The oral route was deliberately chosen to avoid any interference with respiration caused by obstructing the infant's nasal airway with resultant increase in nasal resistance.

Acid content of feeds

For these studies the infants were fed normal feeds of either breast milk or ordinary formula both of which usually have pH around 6.5. No attempt was made to acidify the feeds to enhance the detection of GOR.

4.2 Analysis of pH recordings

As outlined earlier, a lower oesophageal pH <4 has been widely used as the pH criterion indicating the occurrence of GOR. There are no studies to confirm that this is an appropriate level to use in infants and young children. This practice was followed in these studies and reflux was defined principally as a fall in pH from pH>=4 to pH<4. If any error arises from using this convention it is likely to lead to an under estimate of the occurrence of GOR, because of failure to detect non-acid reflux.

A problem arises when small frequent fluctuations in the pH level occur around pH 4. This could result in many tiny pH variations around pH 4 being counted as episodes of reflux. This can be circumvented by insisting that any new drop is not counted until the previous drop has ended or until a further definite and substantial fall in pH (>=1pH unit) indicates that another has occurred. The criteria for the end of a pH drop were defined as a rise in pH of at least 1pH unit to a pH level above 4, from the lowest level recorded in any drop (Figure 6). This ensured that tiny variations around pH 4 were all counted as one episode of GOR.

Because of the possibility that the pH of refluxing material might not always fall below pH 4, especially in the post-feed period, it was felt important to note the many occasions where a substantial fall in pH (perhaps of 2-3 pH units) occurred without the pH falling below pH 4 (Figure 7). Thus those drops where the pH fell by >=1pH unit, but did not fall below pH 4 were also analysed. These are considered separately from drops to below pH 4 in the final analysis.

Figure 6: pH drop illustrating definitions used in analysing pH traces

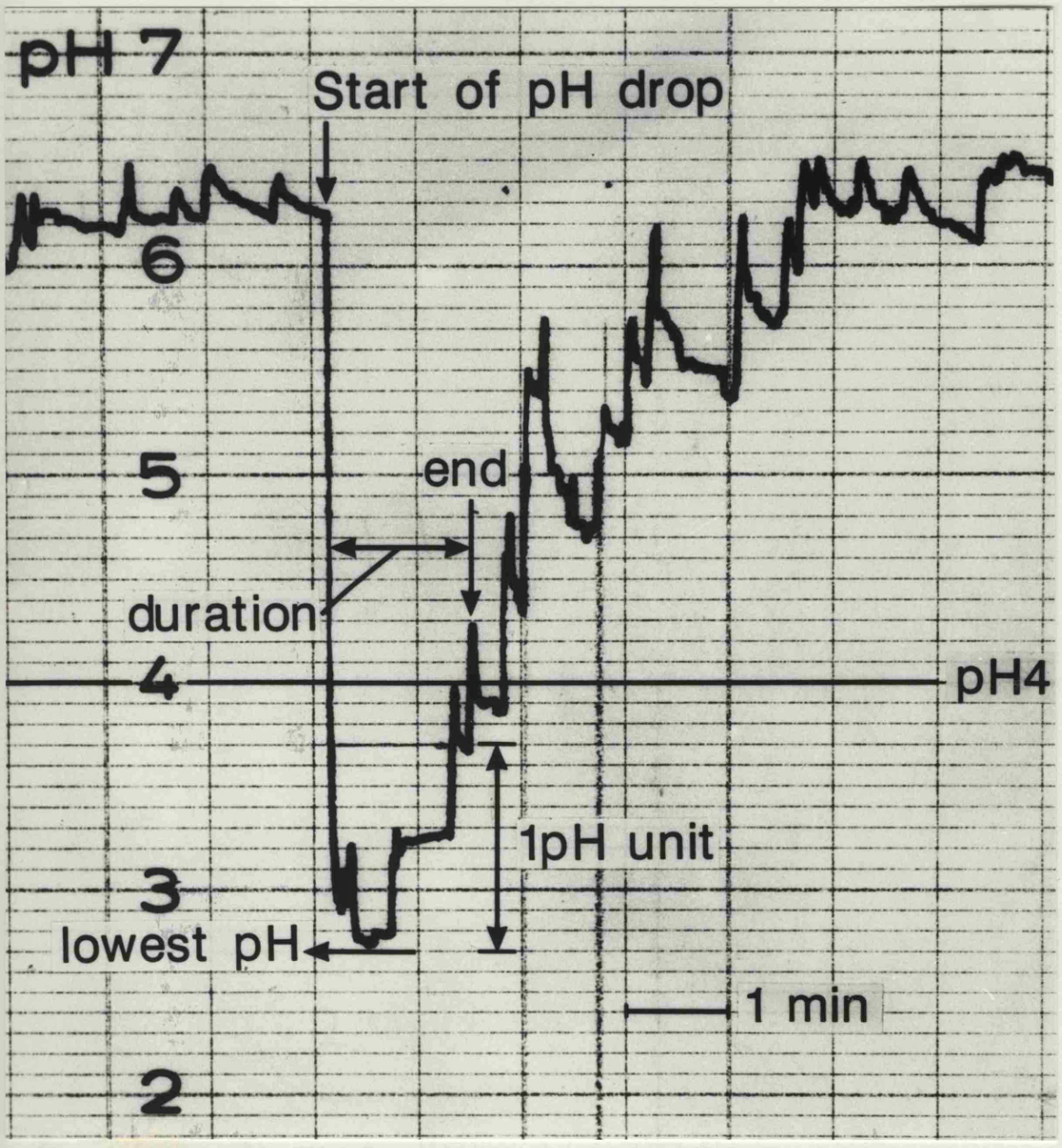


Figure 7: pH drops >1pH unit - a)pH always above 4 and
b)pH always below 4

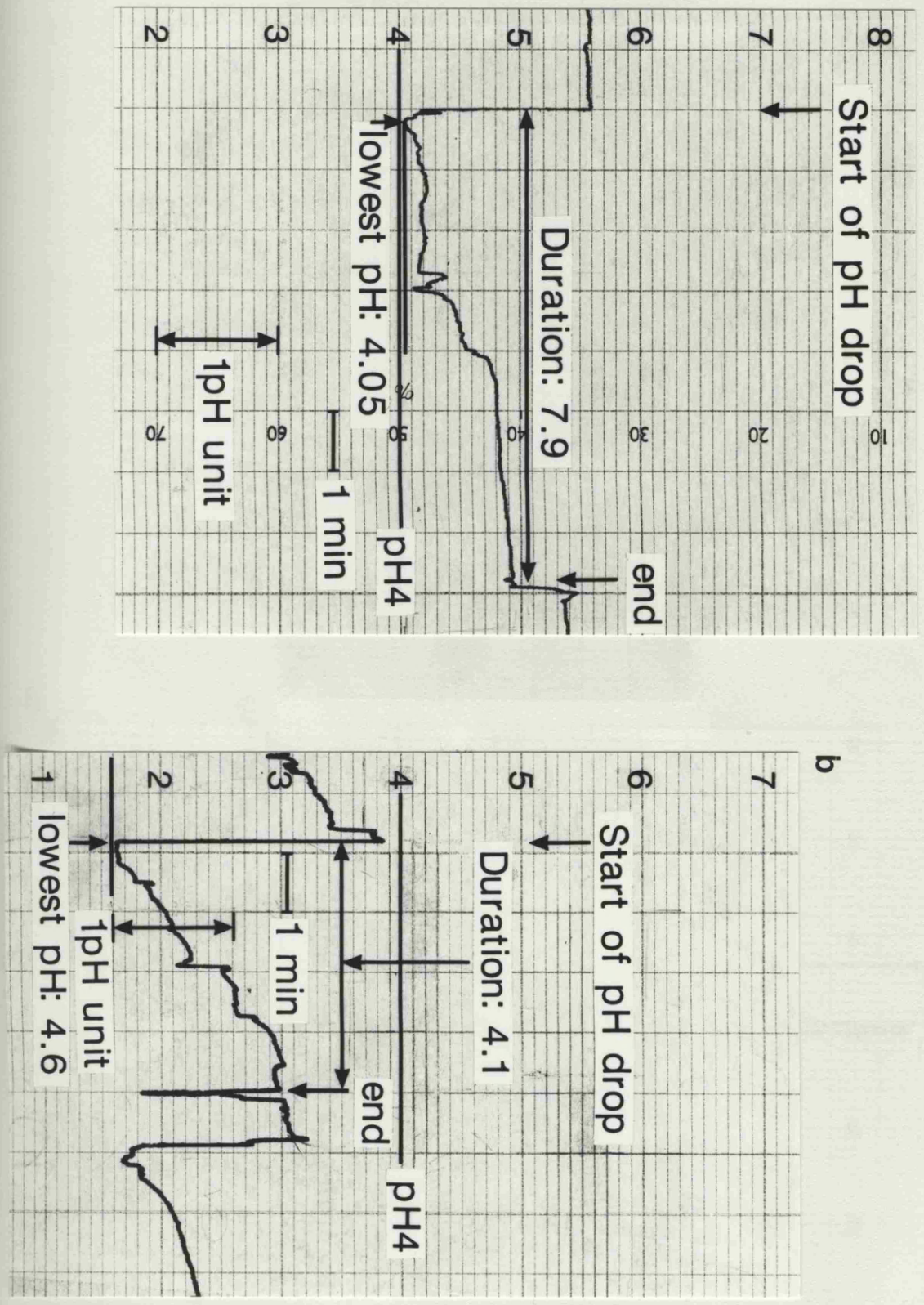
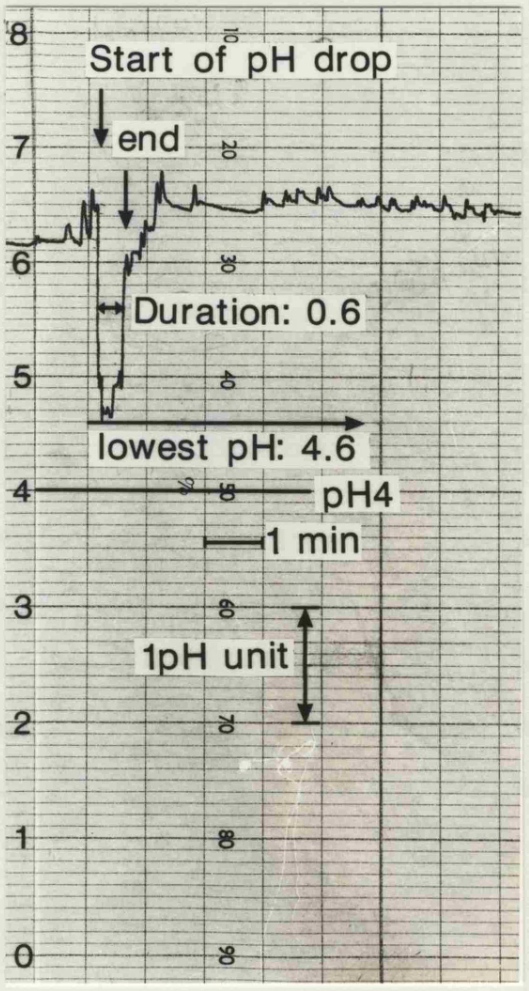


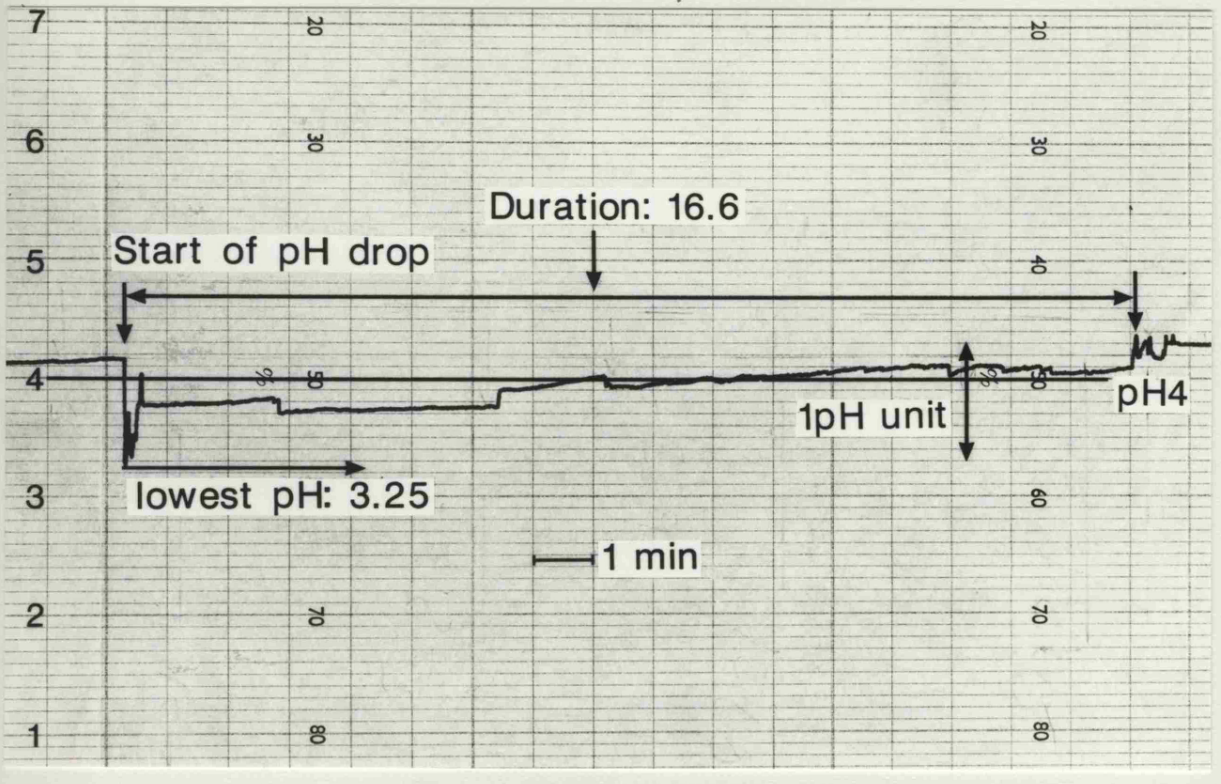
Figure 8: pH drops: a) >=1 unit and

b) from pH>4 - <4

a



b

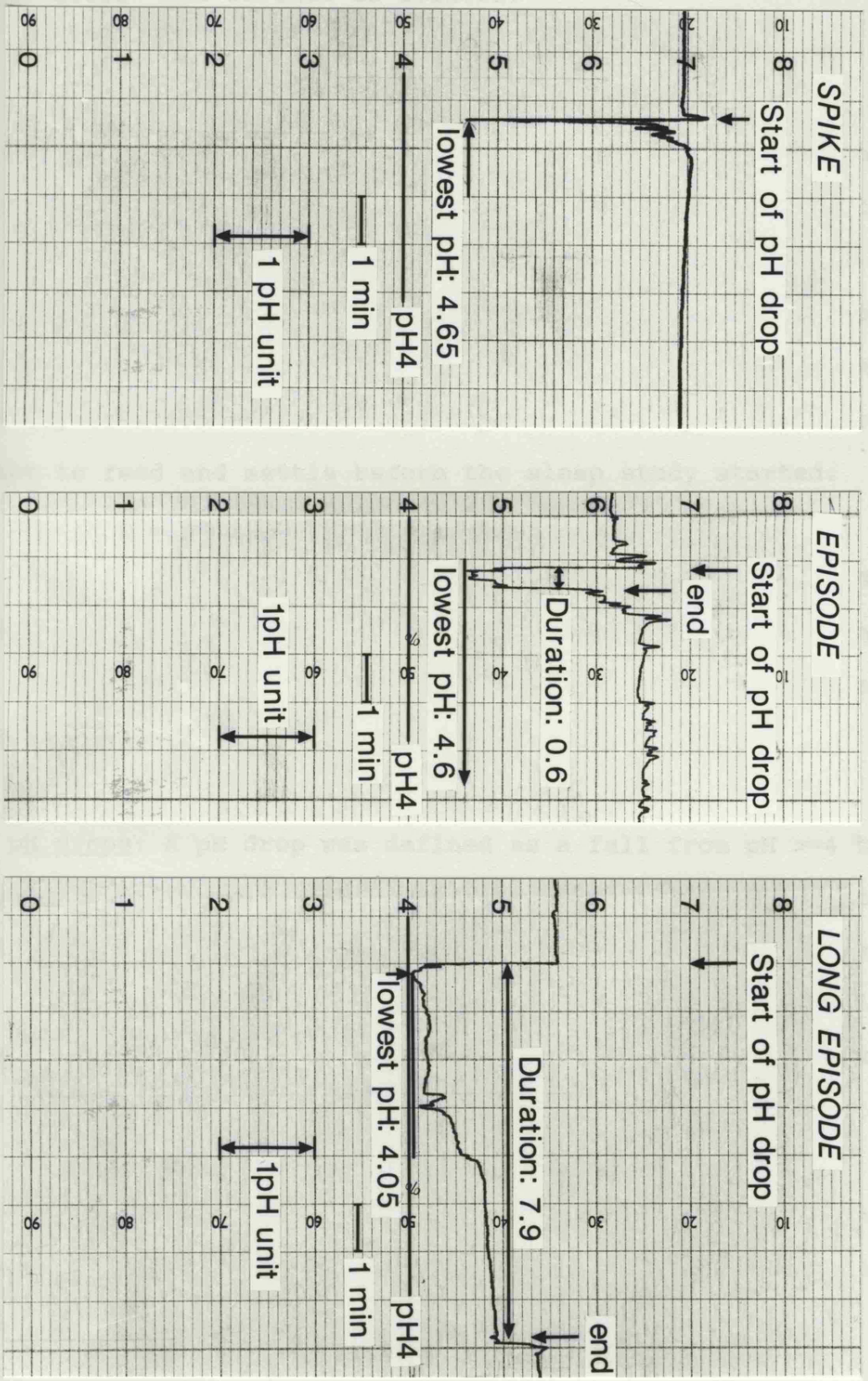


Length of drops

In many pH studies the time elapsed before a pH drop was counted as such is not listed. A review of those studies where a minimum length of time was specified suggested that the paper speed of the recorder was often the main determinant of the minimum time before reflux was said to have occurred (Jolley et al 1978, Sondheimer 1980, Euler and Byrne 1981).

To avoid imposing an arbitrary view on how long a drop had to last before being counted and analysed all pH drops in the present studies were noted. Those lasting less than 15sec were classified as "spikes" while those greater than or equal to 15sec were classified as "episodes". For each recording, the recorder paper speed of 15 seconds equivalent to 2.5mm made it easy to separate spikes from episodes (Figure 9).

Figure 9: pH drops: spikes and episodes



Definition of a pH drop

The duration of a pH study and the magnitude and duration of pH 'drops' was defined as follows:

1. Duration: In the polygraphic studies, the duration of a pH study was taken from the time the probe was in position and reading to the time of its removal. A sleep study was timed from when the infant was settled and asleep to the time when the study was stopped and the infant wakened. The sleep studies were therefore of shorter duration than the pH studies as it normally took some time after the probe was in position for the infant to feed and settle before the sleep study started.

For the studies comparing radionuclide scans and pH measurements the study was timed from the start to the end of the scan procedure. This facilitated the comparison of the two methods in simultaneous studies.

2. pH drops: A pH drop was defined as a fall from pH >=4 to pH <4 or a fall >=1 pH unit. The beginning of a drop was indicated by the initial fall in the pH, and its duration until the pH had risen by >=1 pH unit from the lowest point to at least above pH4 or until the next fall of >=1 pH unit occurred (Figure 6,7 & 8).

3. Duration of pH drop: pH drops were classified depending on duration as either spikes (lasting <15sec) or episodes (>15sec: 15 sec = 2.5mm at paper speed of 10mm/min) (Figure 9).

a) Spike = <15sec (<2.5mm at 10mm/min)

a) Episode = >15sec (>2.5mm at 10mm/min)

pH calculations

From each trace the following measurements and calculations were made:

1. Total duration of pH recording
2. Percent recording with pH<4
3. Number of episodes of 5min or more duration with pH <4
4. Duration of longest drop with pH falling to pH <4
5. Number of pH drops >1 pH unit for drops.
   Subdivided into drops where
   i) pH fell from pH >4 but did not fall below pH4
   ii) pH fell from pH >=4 to pH <4
   iii) pH fell from pH < 4 and remained pH <4.
6. Stomach pH recorded at the end of the study.
7. Standard buffer pH values checked at the end of the study

These criteria were chosen to conform with indices used commonly in reporting lower oesophageal pH studies (Jolley et al 1978, Sondheimer 1980, Euler and Byrne 1981). Fortunately, there is a broad degree of consensus in lower oesophageal pH studies in the values which are reported. In this research, no attempt was made to derive an overall reflux score; rather the various indices were reported individually.

5 Other methods

5.1 Respiratory monitoring during scans

Description of system

Respiration was monitored during the course of radionuclide scans using a system, developed in the Department of Medical Physics at Edinburgh University, for twenty four hour recording of heart rate and respiration in infants. This system was developed to enable cardio-respiratory monitoring to be carried out in the home. With this system heart rate, chest and abdominal movement are all recorded simultaneously. Such an approach has been shown to improve the detection and quantitation of central apnea and facilitate the interpretation of any coincidental heart rate changes.

Instrumentation

Simultaneous recordings of the electrocardiogram and respiratory signals from the thorax were obtained using a single pair of adhesive ECG electrodes applied on opposite sides of the chest of the chest on the anterior axillary lines at the level of the nipples. The ECG and trans-thoracic impedance signals from these electrodes were recorded on a Healthdyne Infant Monitor incorporating a Medilog I 24-hour, 4-channel ambulatory tape recorder (Oxford Electronic Instruments Ltd.).

The other respiratory signal was obtained using a Graseby MR10 Respiration Monitor (Graseby Dynamics, Park Avenue, Bushey, Herts.) The soft plastic sensor capsule was taped firmly to the anterior abdominal wall. Air pressure variations within the capsule associated with abdominal wall movement are transmitted along a fine plastic tube to the monitor. This instrument was modified to provide a continuous analogue electrical signal representing the pressure waves within the capsule which was recorded on the third channel of the tape recorder in the Healthdyne monitor together with the ECG and thoracic impedance signals.

Analysis of data

For analysis, the magnetic tapes were replayed at a speed sixty times faster than the original recording speed and the ECG and the two respiratory signals were fed to solid state electronic buffer memories which allowed signals to be captured at any time during analysis. A specially trained Senior Physiological Measurement Technician continuously monitored the signals during replay.

Apnea detection

The two respiratory signals were fed to a purpose-built analyser which compared the amplitude of each of the respiratory waveforms with a threshold which had been adjusted by the operator to 25% of the amplitude of the respiratory signal during a calibration period in which the infant was at rest and breathing quietly. Even during a period of quiet

breathing the size of breaths could vary so the calibration was approximate. It was assumed that movements less than a quarter of this breathing level were probably not associated with significant ventilation and could be discounted as 'breaths'. The analyser could be used to measure the time between successive breath detections in either channel (chest or abdomen) taken together. The duration of an apneic pause was therefore the period during which neither thoracic nor abdominal channel had detected a breath. The apnea analyser could also be set to generate an output automatically whenever the breath-to-breath interval exceeded a chosen value. In the present studies the breath-to-breath interval was set at 3sec and apneas lasting were noted. An electronic timer within the analyser accumulated the total time during which the analysis was in progress.

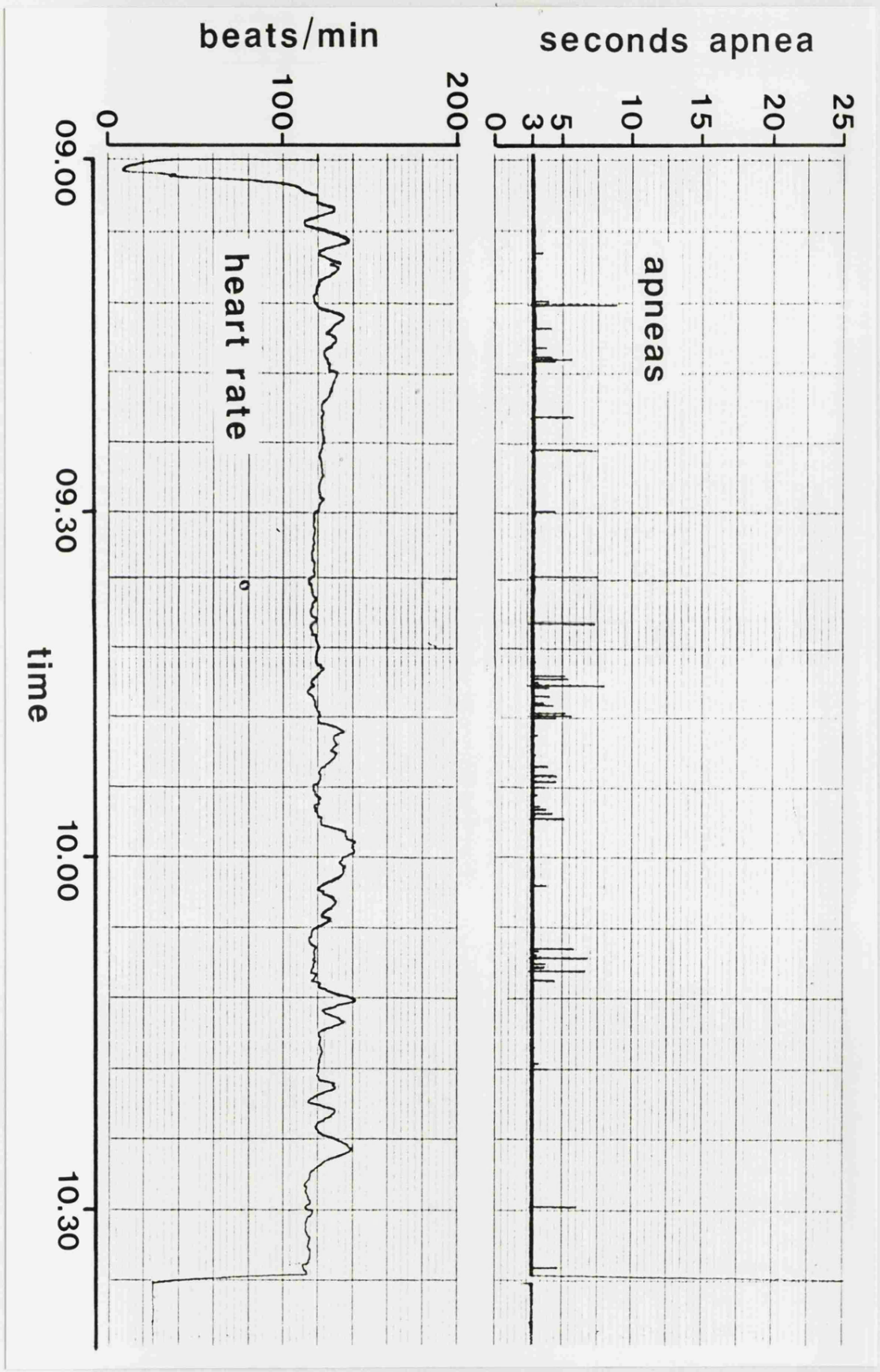
Each time an apnea was detected the analyser output was used to freeze the whole system stopping the tape replay and the progress clock and capturing in the buffer memories the last forty seconds worth of ECG and respiratory waveforms. These signals could then be further examined on an oscilloscope and printed out as a two-channel respiratory trace with the corresponding ECG signal. The operator could freeze the system manually for detailed inspection of disturbances noticed on the monitor screen and could also stop the progress clock while allowing the tape replay to continue past any periods in which the quality of the recorded signals was inadequate due to recording artefacts. At the end of the tape the progress clock could be read out to obtain the total record duration actually analysed for that patient.

Bradycardia

For these studies, bradycardia was arbitrarily defined as a heart rate of <80 bpm for >=10sec measured as sequential R-intervals. This ensured that any bradycardia was significant and not merely a function of beat-to-beat variation.

Figure 10 shows a typical respiratory tracing obtained using this system.

Figure 10: Typical respiratory tape



5.2 Polygraphic sleep studies

Procedure

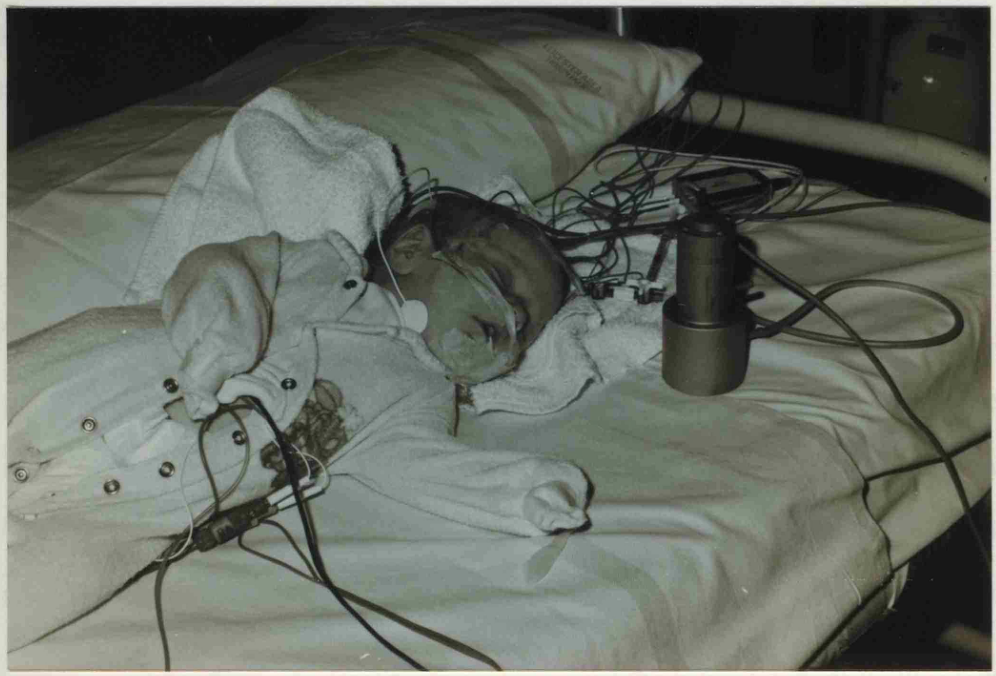
The procedure and methods for monitoring sleep and cardio-respiratory variables in infants have been described elsewhere (Abreu e Silva 1982) and are only briefly outlined below. The technique used for monitoring lower oesophageal pH has been described (section 4). The following is a description of the procedures and methods used.

All the studies were carried out between 2200 and 0500 and were performed by one person (JYP). The infants were monitored in a quiet dimly-lit laboratory used exclusively for sleep studies sited close to the main paediatric wards. The mean ambient temperature of the laboratory was maintained at approximately 23degC. The subject's were either in-patients or outpatients attending specially for the purpose of the studies.

At the outset, the infant's height was measured by stadiometer, and the distance to place the pH probe above the lower oesophageal sphincter calculated. Before the last evening feed, the pH probe was passed orally to the appropriate level and taped in place and the chest and abdominal electrodes were positioned. The parent or nurse in attendance then gave the infant his/her usual evening feed. After this the infant was settled to sleep, lightly clothed and unrestrained. Where possible the infants were settled in a left lateral position for ease of monitoring. Electrodes to record eye movements, sub-mental muscle activity, and brain electrical activity were

placed when the infant was asleep. Thermocouples to monitor nasal airflow at the nose and the electrode to measure transcutaneous oxygen tension were applied carefully during periods of quiet sleep to minimise the likelihood of disturbance. Despite the presence of monitoring equipment (Figure 11) the infant usually settled to sleep fairly readily.

Figure 11: Infant during night monitoring



Equipment

Electro-oculogram (EOG) was recorded by disposable self-adhesive electrocardiogram electrodes (C-50-S, Medicotest, Denmark). A difference exists in electrical potential between the anterior and posterior parts of the eye and the polarity changes as the eye moves: recordings of these potentials constitute the EOG. Two pairs of electrodes were placed beside the outer canthi of each eye and eye movements were recorded from each diagonal pair. A minimum gain of 10mm for 1.0uV was used.

Electromyogram (EMG) was recorded by the same type of electrodes as was used to detect eye movements (C-50-S, Medicotest, Denmark). The two electrodes were attached symmetrically beneath the chin on the area overlying the digastric muscle. A minimum gain of 5mm for 1.0uV was used. The amplitude of the signal is directly proportional to the degree of muscle tone. Bursts of muscle activity associated with muscle activity are also indicated by EMG recordings.

The electro-encephalogram (EEG) was recorded from two channels (B1/9 Silver/ Chloride, Laboratory Equipment, Croyden, England) placed sagitally in the frontal and parietal regions (Fz-Pz).

The electrocardiogram was recorded from electrodes placed on the left and right side of the chest and the right leg.

Respiratory movements were recorded using two systems. Chest movements were recorded using the Cambridge Respiration Monitor (Cambridge Medical Instruments, Ltd., Cambridge) which monitors breathing by means of magnetometers which detect respiratory movements of the thoracic cage. The magnetometers consists of plastic encapsulated copper wire coils placed on the chest. One coil is energised by an alternating current. This creates an electro-magnetic field which induces a voltage in the other coil dependant on the distance between them. The signal varies as the two coils move together or apart as the result of respiratory movements. Following amplification, the signal from the "receiver" coil is rectified, smoothed and recorded as an indicator of respiration. The magnetometer coils do not make contact with patient. No skin preparation or electrode jelly is required. The sensors were attached using micropore tape to areas where breathing seemed to produce maximal relative sensor movement. They were placed either symmetrically at the mid-clavicular lines or at the costal margins. Occasionally, abdominal movements were monitored using a second pair of magnetometers attached anteriorly and posteriorly at a level midway between the xiphisternum and umbilicus.

More frequently, abdominal movements were monitored using a modified MR10 infant apnea monitor (Graseby MR10 Respiration Monitor, Graseby Dynamics, Park Avenue, Bushey, Herts.). In this monitor a pneumatic capsule is attached to the skin of the abdominal wall by micropore tape. Respiratory movements produce a deformation of the capsule and the resultant

pneumatic signal is detected electronically by the monitor. A signal output was taken to an appropriate amplifier and then displayed in analogue form on a multi-channel recorder.

Usually both chest and abdominal movements were recorded. Their presence proved a satisfactory indicator of respiration when compared to simultaneous recordings of airflow. When airflow was present, the airflow respiratory pattern was always closely mirrored by one or other respiration recording, and usually both.

Airflow was measured at the nostril using one or two thermocouples. The principle underlying their use is based on the Seebeck effect, whereby thermal energy is converted into electrical energy at the junction of two dissimilar metals forming a closed circuit current when exposed to different temperatures. As environmental temperature changes, a net electromotive force is generated which induces a continuous electrical current proportional to the change in temperature. This electrical signal is amplified about 10,000 times and recorded as a graphic signal. The thermocouples were type Z2, poly-tetrafluoroethylene insulated, twin-twisted, 0.2mm diameter wires, terminating in an exposed welded hot junction bead (Lab Facility Ltd., Hampton, Middlesex). The wires were made of two different alloys: nickel-chromium and nickel-aluminium. The use of alloy wires ensured a fast response. The amplifier (Ancom, Cheltenham) was designed to accept a differential input with a high immunity to noise and a high gain to amplify the low input. It maintained these characteristics over a wide temperature range. The thermocouple-amplifier system was assembled in the laboratory

of the Department of Child Health, University of Leicester. In use, the thermocouples were carefully placed in the nasal airstreams and taped in position on the infant's upper lip using micropore. Figures 12 & 13 illustrate episodes of central and obstructive apnea observed in simultaneous thermocouple and magnetometer recordings.

Figure 12: Polygraph trace showing a central apnea

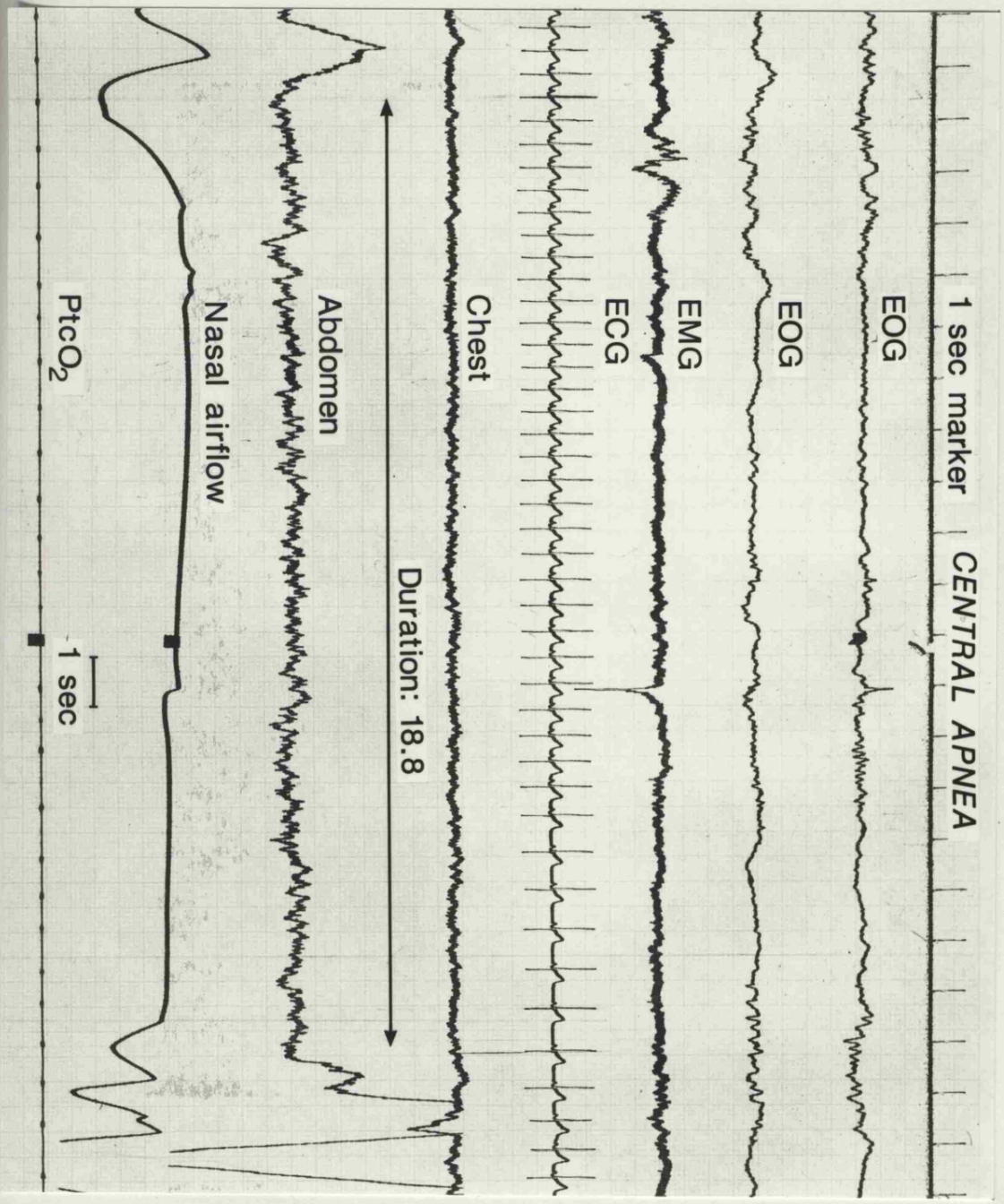
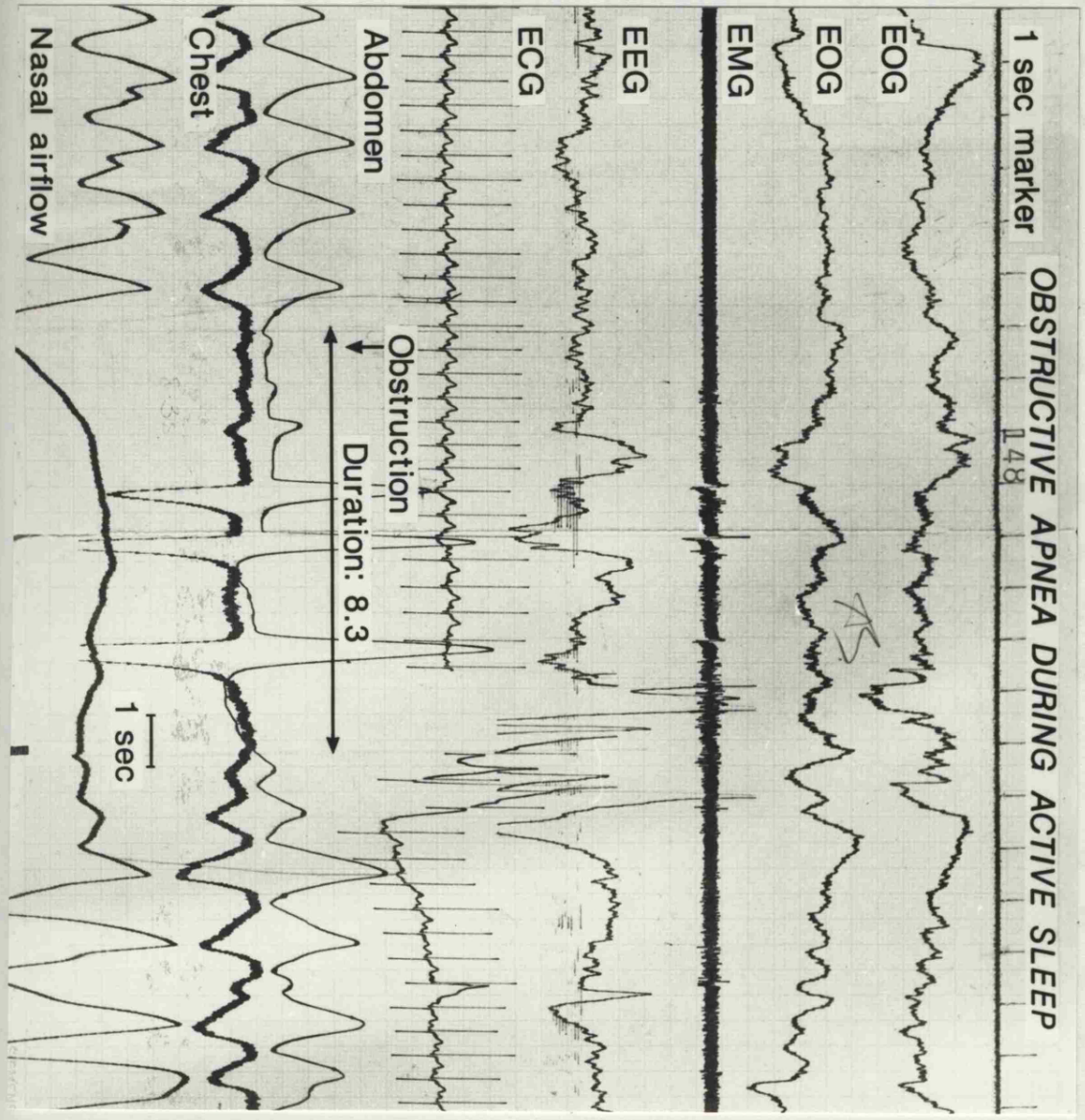


Figure 13: Polygraph trace showing an obstructive apnea



Transcutaneous oxygen tension (PtcO2) was measured on the skin surface by the Draeger Oximeter and Transoxide (Dragerwerk, A6, Lubeck, West Germany). This measurement is based on a polarographic technique and the instrument uses a modified Clark electrode. In practice, the electrode was placed on the skin of the abdomen using a self-adhesive electrode with the instrument set at a working temperature of 44degC. After placing the electrode, PtcO2 dropped rapidly until vasodilation produced by heating had taken place. It then rose gradually until a steady plateau was reached after about 10-15min. The electrode was never attached to the same site for more than four hours to avoid burning the infant's skin. Transcutaneous oxygen values were recorded continuously on thermo-sensitive chart paper at a speed of 10mm/sec. The instrument was calibrated before every study. Previous studies using the oximeter had shown the mean drift to be of the order of 1.5mmHg per hour. Maintenance of the electrode head, including membrane changing, storage and maintenance was carried out carefully in accordance with manufacturer's instructions.

Oesophageal pressure was monitored in one infant on an exploratory basis. This was done using an oesophageal balloon following the method of Beardsmore et al (1980). The pressure was measured using a Gould Statham transducer with appropriate amplifier.

The outputs from the various transducers were recorded on an Mingograph 8 channel jet recorder (Elema Schonander). The recorder was run at 1cm/sec. pH and PtcO2 were also recorded separately at slower recorder speed. In the later studies the

sleep phase data was recorded separately on to an SLE EEG recorder linked by an electronic timer to the main Mingograf recorder.

Analysis of records

Sleep

Each sleep record was divided into successive 30-second periods. These epochs were then analysed visually and scored as either awake (Aw), indeterminate or transitional sleep (Is), quiet sleep (QS) or active sleep (AS). Epochs where more than half showed evidence of body movement were classified as indeterminate sleep. The scoring criteria were based on the definitions suggested by Rechtschaffen and Kales (1968) and Anders et al (1971). Table 9 outlines the system adopted for analysing sleep state and tabulates the features of the various sleep phases. It provided a relatively non-complex framework which could be learned with practice and applied by a non-expert in sleep physiology with little sacrifice of precision. For that reason, further subdivision of QS and AS phases was not undertaken. In these studies, transitional sleep was divided further depending on whether more than half an epoch showed evidence of movement (ISm) or not (ISt).

To further ensure consistency, all the records were scored for sleep phase blind by one experienced observer (Dr. U Macfadyen). Respiration, one of the variables under study, was not included in the assessment of sleep phase. All recordings

were analysed for sleep state and cardio-respiratory variables.

Table 9: Variables used to define sleep states

State	EEG	EOG	EMG
Awake (AW)	Relatively rhythmical and containing faster elements (theta or alpha according to age). There should be no spindles, K complexes or other recognisable EEG patterns of sleep	Blinks or other eye movements occur	High amplitude, sometimes with movement artefacts suggesting prolonged motor activity. During periods without much movement, a least one transitory disturbance every 30 seconds is present.
Intermediate, indeterminate, transitional (IS)	Shows mixture of delta, theta and alpha (according to age slower or faster waves are more prominent). May be weak signs of EEG spindling but no definite spindles or K complexes. Transitory (episodic) high voltage rhythmical slow activity is also included.	May show occasional eye movement	Amplitude lower than during wakefulness; there may be transient increases in amplitude and movement artefact.
Quiet sleep (QS)	Slower than during wakefulness, equal to or slower than in indeterminate sleep; amplitude higher than in indeterminate sleep; presence of sleep spindles or K complexes.	No rapid eye movements	Lower than during wakefulness; equal to or lower than in indeterminate sleep. May be short interruptions by indeterminate sleep pattern (less than half an epoch) and transitory increases in EMG.
Active sleep (AS)	Relatively rhythmical containing faster elements (theta or alpha according to age). No spindles or K complexes present but occasionally they might occur within an epoch; brief reversals in the pattern of IS or QS.	Rapid eye movements present	Low voltage, occasional transitory increases and general movement artefacts.

Apnea

Definitions of apnea

Central apnea was defined as a pause in breathing during which there was neither air flow nor respiratory movements (Figure 12). In the present polygraphic studies, only episodes of central apnea of six seconds or longer were reported. Six seconds was chosen arbitrarily to facilitate comparison with previously reported studies. There were no episodes of prolonged central apnea (>20sec).

Obstructive apnea was defined as an episode during which breathing movements (thoracic and /or abdominal) persisted in the absence of airflow at the nose (Figure 13). Episodes could be of any length but were reported only if they were >=3sec in duration. There was often a steep fall in PtcO2 following obstructive apnea. Episodes of apparent obstructive apnea where breath holding occurred (and hence airflow was absent) during gross body movements were distinguished as carefully as possible and were not recorded as obstructive apnea. Episodes where central apnea ended by continuing into obstructive apnea were classified as mixed apneas and were included with obstructive apneas for the purpose of tabulation.

The duration of apnea, central, obstructive or mixed, was measured from the end of the last breath before cessation of airflow to the start of the next, from thermocouple tracings. Each apnea was measured individually and the corresponding

sleep state noted; the apnea of longest duration in each study was also recorded.

Measures of apnea

Four indices of central apnea were calculated for each study:

1. apnea index
2. apnea attack rate
3. apnea percent
4. mean duration of apnea.

The apnea index is defined as the ratio of the total duration of apnea (seconds) to the total duration of sleep phase (seconds) expressed as a percentage. Apnea attack rate is the ratio of the number of apneic episodes during a sleep phase to the total duration of the sleep phase (seconds) and apnea percent the percentage of epochs (30 second periods) during which at least 1 apneic pause was initiated. These indices and the mean duration of apnea were calculated for each sleep stage - AS, QS, IS, and total. These indices only relate to recorded episodes of central apnea. In general, obstructive apnea was very much less common and details of any such apneas were noted separately for each infant.

The duration of periodic breathing, defined as two apneic periods of 3 seconds or more within 20 seconds of each other (Parmalee et al 1972) was measured from the beginning of the first apnea until the end of the last. The following indices

were calculated: number of periodic breathing events per 100 minutes of sleep and total duration of periodic breathing in minutes per 100 minutes of sleep.

Each page of the sleep record, representing 30 seconds (1 epoch), was scored into one of four phases depending on electrical and behavioural criteria. These were:

1 Active sleep

2 Quiet sleep

3 Indeterminate sleep

4 Awake

Episodes of central apnea - cessation of respiratory movements and airflow for >=6 seconds - were noted. For each apnea, the sleep phase was noted and the duration measured. The respiration rate and the heart rate were calculated from the beginning of the fourth minute of continuous sleep for AS and QS.

The following indices were calculated for each sleep phase and for the total record:

$$1\ \text{Apnea Index} = \frac{\text{Total duration of apnea during sleep phase}}{\text{Total duration of sleep phase}} \times 100$$

$$2\ \text{Apnea attack rate} = \frac{\text{Number of apneic episodes}}{\text{Total duration of sleep phase}} \times 100$$

3 Apneic episode of longest duration

4 Mean duration of apneic episodes

5 Apnea per cent (= Percentage of epochs during which at least one apneic pause was initiated).

6 Per cent sleep for each sleep phase

Movements and PtcO2 Dips

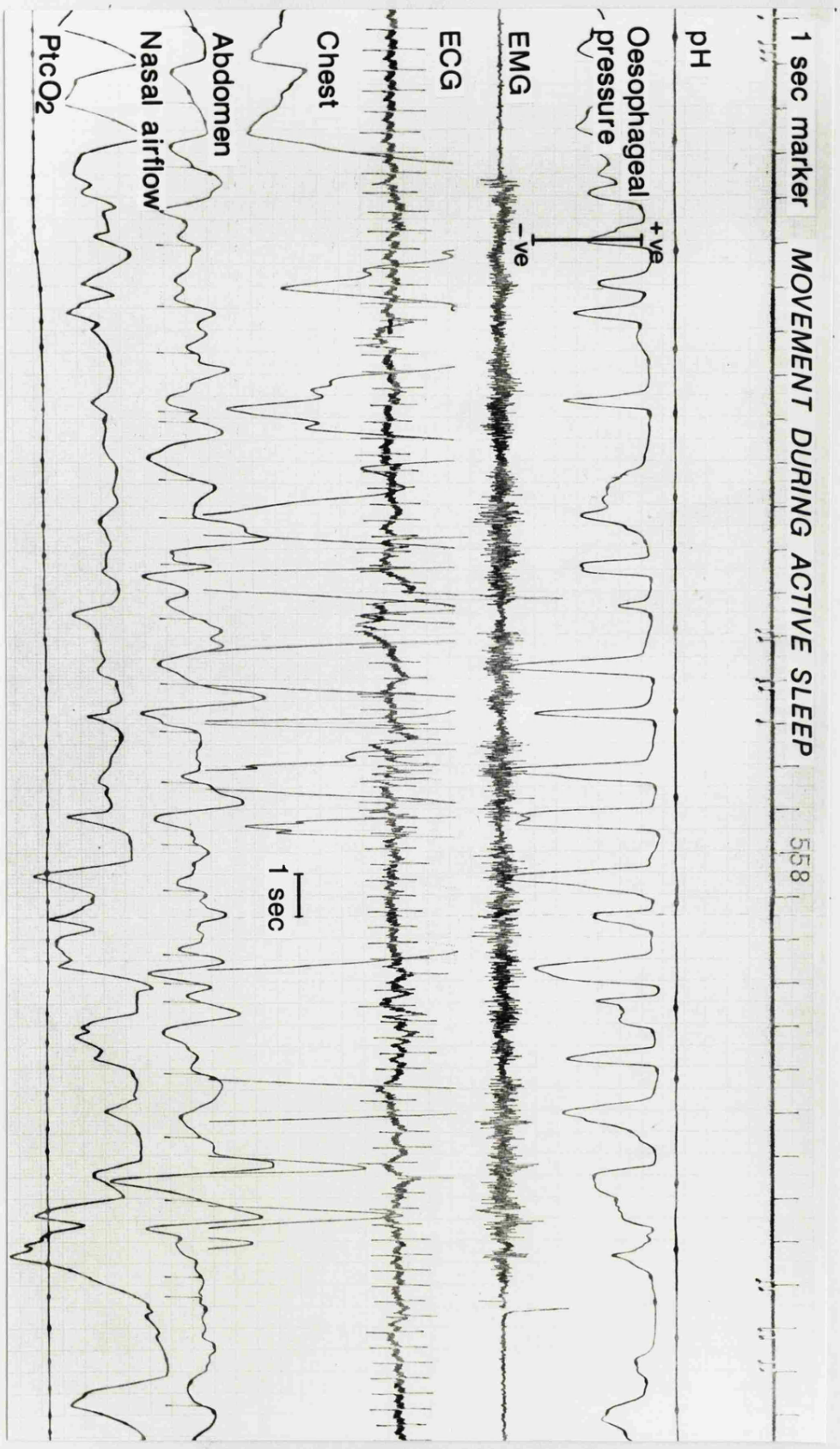
Gross body movements were noted both at the times of recording and also subsequently when the records were analysed. Such episodes were easy to recognise, particularly from EMG recordings (Figure 14). The number of gross body movements and their total duration in minutes in each study, both expressed per 100 minutes of sleep time, were computed for each sleep phase and for the overall study.

Transcutaneous oxygen values were recorded continuously on thermo-sensitive chart paper at a speed of 10mm/sec using the method outlined. PtcO2 dips >=5mm Hg were noted. The times of these dips were marked on the polygraphic and pH tracing and the dips were then related to events occurring on either side of the dip.

Bradycardia

In the sleep studies, bradycardia was again arbitrarily defined as a heart rate of <80 bpm for >=10sec measured as sequential R-R intervals. This definition was used to ensure that any bradycardia was significant and not merely a function of beat-to-beat variation. No bradycardias of this magnitude were observed in any sleep study.

Figure 14: Polygraph trace showing typical body movement



pH, cardio-respiratory variables and movements

For each pH drop that occurred during sleep a number of observations were made from the polygraphic trace after the precise time the pH drop commenced had been marked on the polygraphic trace:

1. Sleep state: The sleep state during which a pH drop occurred was noted. It was also noted whether an episode of reflux 'crossed' a sleep phase or lay entirely within one sleep phase.

2. Respiration: the pattern of airflow and respiratory movements were noted at the start of the pH drop and in the preceding and following 60 sec and were recorded as:

a) present and apparently normal airflow and respiratory movements

b) central apnea - absence of airflow and respiratory movements

c) obstructive apnea - absence of airflow with continuing and often exaggerated respiratory movements

d) interrupted airflow with normal respiratory movements

3. Movement: the presence of gross body movement, activation of the EMG or both were noted at the onset of the pH drop and in the 60sec before and after the onset.

4. PtcO2 dips: any dips of 5mm Hg or more in the minute before or the minute after a pH drop were noted.

5. Other events: the presence of any other event such as a cough or vomit was noted.

In the initial studies the pH trace was only recorded on a flat-bed single channel recorder. When analysing the traces it proved extremely time consuming to ensure a precise match between the respiratory traces and the separate pH trace running at a slower speed. To facilitate the precise matching of polygraphic and pH traces the output from the pH meter was additionally interfaced onto the polygraph recorder. Thereafter, it was straightforward to observe the timing between the respiratory and pH variables.

Once the events surrounding the occurrence of each pH drop had been analysed, the process was repeated for central apnea, obstructive apnea, body movements and PtcO2 drops in turn. Again, the events surrounding the incident event were noted for the minute before and after and the results tabulated.

5.3 Statistical Methods

Standard descriptive statistics (mean, median, standard deviation, standard error of mean and range) were used to summarise data.

The Spearman Rank correlation coefficient was used to test the relationship between amounts of GOR detected by different methods of analysis and between GOR and various cardio-respiratory abnormalities.

Apart from these instances, statistics were not employed. In particular, the techniques of statistical inference were not used.

6 Limitations of methods

There were several potential sources of error in relation to each part of this study. The extent to which potential sources of error influenced the accuracy and reliability of the results obtained in these studies cannot be computed directly. Wherever possible attempts were made either to quantify or to circumvent the potential impact of these possible errors. The following limitations are acknowledged.

6.1 Radionuclide scan studies

Certain limitations of radionuclide scanning became apparent during the course of the studies.

Firstly, it was observed that possetting was not always detected by the gamma camera. This had important implications as it suggested that other significant episodes of GOR, not marked by vomiting, might pass undetected by radionuclide scan. To investigate this an in vitro simulation study was performed (see Chapter 6 and Appendix 2). In this study simulated refluxes of varying duration and volume were recorded by the gamma camera. From the results of this simulation it became apparent that there was a lower limit below which reflux went undetected by the gamma camera. This limit was quantifiable and was determined by a number of factors including the duration and quantity of reflux. Although the limit was low (2 - 5ml.sec) it was probable that the vomits which the gamma camera failed to detect did not reach this limit. However, this limit was not felt to be a major source of error in the radionuclide

scan studies. The results of this simulation study were published (Paton et al 1985) and the paper is bound as appendix 2.

A second limitation was noted in the detection of reflux extending only into the lower oesophagus. Here the presence of high activity in the adjacent stomach occasionally made the diagnosis of reflux difficult. The effect is analogous to taking a photograph into the sun when objects round the edge of the sun are poorly defined, lost in the brilliance of sunlight. Similarly, it was difficult to assess the occurrence of small refluxes into the lower oesophagus because of the activity in the adjacent stomach. This error would result in under recognition of small amounts of reflux into the lower oesophagus.

In the radionuclide scan studies the occurrence of GOR was assessed visually. This involved direct observation of each scan frame as it 'developed' on the gamma camera screen during the course of the scan. Positive frames were copied onto X-ray film at the end of the study. The films were then reviewed to determine whether the initial impression of the presence of GOR was correct. Other published studies have used electronic processing of the collected data to detect the presence of GOR. From the in vitro simulation study described it was found that such processing did not improve the sensitivity of reflux detection and accordingly this technique was not used in the present studies.

The possibility of the observer over-interpretating the radionuclide scan data was also considered. All the scans were assessed at the time of performance and then reviewed again later to confirm agreement with the initial interpretation. In addition, they were reported independently by a consultant radiologist. A comparison of the assessments is given later (Chapter 5). From this, it was considered that an acceptable level of agreement was present confirming that significant over-interpretation of the scans was not occurring.

6.2 pH probe studies

The limitations of pH studies must be considered with respect to a number of questions.

Firstly, what alterations does the presence of the recording instrument cause to the function of the organism? In this case, does the presence of the probe alter the state of the infant or degree of arousal and the frequency, duration and severity of GOR. As discussed, there is no information about this in the literature in relation to sleeping infants. Information from adult studies suggests that the presence of a probe in the oesophagus does not influence the occurrence of GOR (Malmud and Fisher 1982). The effects of a probe on oesophageal dynamics is unknown. The presence of a probe may also influence the infant's arousal threshold with possible effects on the occurrence of reflux and the infant's response to it. Direct observation of the infants during the course of these studies and the comments in published reports suggest that young infants adapt rapidly to the presence of a tube in

the upper airway passages. In most cases the infants settled to sleep quickly and satisfactory sleep records were obtained suggesting the infants were not greatly distressed by the presence of the pH probe.

Secondly, it has to be recognised that lower oesophageal pH monitoring for GOR using pH 4 as a marker of GOR measures the reflux of acid gastric contents into the oesophagus and hence presupposes that gastric acid is produced in sufficient quantity to maintain the gastric pH at least below pH 4. If acid is absent or insufficient in volume (either absolutely or relatively) to lower the pH of gastric contents to below pH4 GOR will not detected. This problem was not encountered during the sleep studies but in one infant during the combined scan and pH studies the gastric pH at the end of the study had not fallen below pH4 (infant no. 41), suggesting an inability to produce sufficient gastric acid. The fact that normal neonates may not lower the gastric pH below 4 for two hours following a feed (Mason 1962) has already been discussed. In general in young infants, there is liable to be a period of variable duration when the amount of gastric acid is relatively insufficient to acidify a milk feed. It is not sufficient to measure the gastric pH at a particular point in time to confirm that a pH below 4 has been achieved, since gastric pH values are likely to be varying continuously with time. This problem was partly overcome in these studies by defining a pH drop to include drops >=1 pH unit. This ensured that drops of this amount were noted irrespective of whether the pH fell below 4 and hence allowed at least those episodes of 'non-acid' reflux associated with a pH fall greater than 1 pH unit to be noted. However, even this would fail to take account of refluxes

associated with a smaller pH drop. Hence, the possibility of 'non-acid' reflux is an important potential limitation which might result in an underestimate of the occurrence of reflux. Obviously, any direct consequences of GOR, eg on respiration, might then also be overlooked.

In these studies, no attempt was made to ensure that gastric pH was always below pH 4 by acidifying the infant's feeds. A more direct attempt was made to assess the prevalence of 'non-acid' reflux by performing a comparative study involving simultaneous radionuclide scan and lower oesophageal pH studies. This is reported in chapter 6.

Thirdly, pH monitoring gives no indication of the volume of material refluxed into the oesophagus. Similarly other factors such as bile or pepsin, which may harm the oesophagus, are not measured. The speed of acid clearance from the oesophagus cannot be assessed since pH measurements cannot distinguish between multiple episodes of GOR with incomplete clearing of acid and a single episode with very slow clearance of acid from the oesophagus. Whether these are important factors must await future studies.

6.3 Respiratory monitoring during scans

This method of respiratory monitoring only monitors respiratory movements and does not include any airflow sensors. It, therefore, only reliably detects cessation of respiratory movement ie central apnea. Obstructive apnea, where respiratory movements continue and are often exaggerated but airflow is

absent, can only be detected when airflow sensors are used. Hence, with this method of respiratory monitoring it is not possible to make definitive comments about the presence or otherwise of obstructive apnea. However, OAs are usually associated with the rapid onset of significant bradycardia. Thus the presence of significant bradycardias may provide indirect evidence of the occurrence of OA. The reliable detection of obstructive apnea requires detailed polygraphic monitoring including both respiratory movement (chest and abdomen) and airflow sensors. Methodologically, this is a much more complex undertaking.

The calibration procedure for breathing relied on the operator choosing an appropriate period of quiet breathing. Since the size of breaths could vary from second to second the calibration was approximate. When quiet breaths were large and amplifier gain low small breaths might be missed and false apneas reported. Conversely if a period of quiet breathing was chosen when amplifier gain was high cardiac impulses were seen as small breaths and "real" apneas missed. If the chosen thresholds appeared to be giving a grossly erroneous interpretation of the data then a recalibration was performed. Therefore, for short apneas the method has to be regarded as giving a good approximation, rather than a precise estimate, of the number of apneas.

6.4 Sleep studies

The effect of the measuring instruments on the infants' sleep has already been mentioned in relation to the pH studies; similar strictures apply to polygraphic studies. In general, as has been noted the infants' slept satisfactorily despite the presence of the monitoring equipment.

There were a number of more practical limitations in the polygraphic recording system. Firstly, the Mingograph recorder had only 8 channels. This was barely sufficient for the information which was to be recorded (sleep phasing, respiration, airflow, pH and PtcO2 data). For the initial studies, for example, the pH data had to be recorded on a flat bed recorder only. Precise matching of records subsequently proved time consuming and was prone to error. The problem of lack of recording channels was overcome by linking two 8 channel recorders using a crystal-controlled timer/marker to synchronise the two recorders giving in effect a 16 channel recorder. Thereafter, it was easy to observe the temporal relation between changes in respiratory and pH variables.

A second limitation was the presence of a small degree of timer error in the Mingograph recorder. After careful calibration this was reduced to less than 5%. However, even a small degree of error rendered the precise timing of events more difficult to assess. Again, this problem was effectively overcome by linking the two 8 channel recorders using the crystal-controlled timer.

Further, limitations arise in relation to the analysis of the polygraphic traces from sleep studies. This was tedious and time consuming taking up to 5 days for an full analysis. No systematic study of inter-observer error in the assessment of sleep phasing was undertaken in this study as only one person had been fully trained in this area (Dr U Macfadyen). She undertook the sleep phasing of each record. In the assessment of apnea, central and obstructive, body movements and pH drops the initial analysis was completed by JYP. Each individual event was then reviewed and the measurements checked. Where dubiety existed a second independent observer repeated the measurements. All the studies were reviewed on two or more occasions to ensure as far as possible a consistent interpretation of events. No formal assessment of inter-observer error in analysing the data was performed and it has to be acknowledged that minor variations are likely.

CHAPTER 5 Page

THE DETECTION OF GOR BY RADIONUCLIDE SCAN

CHAPTER 5

THE DETECTION OF GOR BY RADIONUCLIDE SCAN

1 Assessing radionuclide scans

Every frame of each radionuclide scan was assessed as positive or negative during the course of the study by two observers (including JYP). At the end of each study all the frames were reviewed. Selected frames, usually including those thought to be positive, were copied onto X-ray film. These static films were subsequently reviewed by JYP as a check on the initial assessment of the scan and the films were also submitted for routine reporting by radiologists (of varying expertise). This provided a separate and independent assessment.

Eighty radiologists' reports were available for comparison with the researcher's assessments. These reports of the static films were compared with the "dynamic" assessments made as the scans developed and showed agreement in 63 (77%) and disagreement in 17 (21%) (Table 10). Of the disputed results, 2/17 (12%) static films were judged positive by the radiologist while 15/17 (88%) were judged negative. Review of the 15 studies judged negative by the radiologist from inspection of the static films showed that in 9 studies the dynamic assessment of reflux was judged either to be moderate, or severe but present in fewer than 3 frames out of the whole study. In the remaining 6 studies the "dynamic" assessment

documented severe reflux present in more than 3 frames. Figure 14 presents selected frames from one of the four cases reported as negative by the radiologist, for review. Reflux is clearly present.

The increased "sensitivity" of the initial observer compared to the radiologist is attributed to the observer being present throughout the scan and assessing and comparing the frames as they develop on a frame by frame basis. In this way episodes of reflux are more readily distinguished from background activity.

Overall, it was concluded that there was an acceptable level of agreement between the "dynamic" assessment of reflux made during the scan and the subsequent reporting of static records by the radiologist. The degree of discrepancy that was noted was attributed to direct assessment being more sensitive than subsequent review. It was, therefore, concluded that the "dynamic" assessments did not represent a significant over-interpretation of the occurrence of reflux.

Table 10: Comparison of assessments of GOR on radionuclide scans

82 Scans

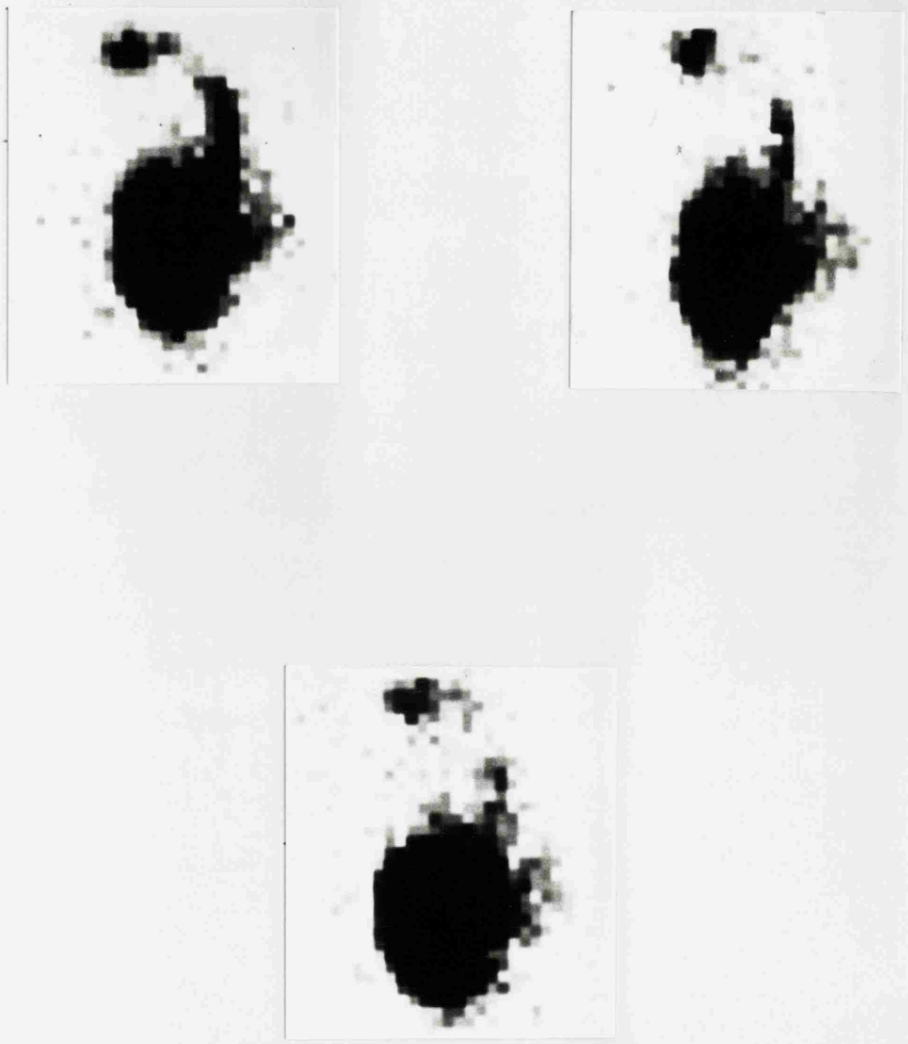
Assessment of GOR: "Real-time" assessment v retrospective radiological review

Agreement	Disagreement	Not Known
63 (77%)	17 (21%)	2 (2%)

Disputed reports n = 17	Reflux present	Reflux absent
"Real-time" assessment (JYP)	15*	2
Retrospective review (Radiologist)	2	15

* Of disputed positives, "real-time" assessment indicates that GOR was moderate in 4 and severe in 11. Of the latter, there were fewer than 3 severe frames / study on 5 occasions.

Figure 15: Selected scan frames from infant no.20, showing GOR



2 How common is GOR?

Frequency of reflux

Table 11 summarises the results of the scans for the various groups studied. The mean dose of isotope administered to each infant was 7.76 +/- 0.66 MBq (mean,sd). The average number of frames in each study was 110 (sd = 16). As a frame lasts one minute each study represented just under 2hrs of scanning. Since each scan started as soon after the feed as possible each scan relates to the two hour period following a feed.

GOR was present in 80% overall, with 70% showing reflux to upper oesophageal level ("severe" reflux). In each group reflux to the upper oesophagus was common but was least frequent in the SIB group. These results confirm that is GOR common in 'near miss' infants. However, GOR was common in each group including the symptom and SIB group.

Table 12 lists the number of positive frames per 60 frames, for both severe and moderate GOR. The data has been normalised to / 60 frames (60 frames = 60 minutes) to take account of the variation in study lengths.

From Table 12 there are many more frames per 60 frames showing severe reflux as opposed to moderate reflux. This surprising finding may be partly explained by the difficulty in distinguishing moderate amounts of radioactivity in the lower oesophagus from the much larger amounts of radioactivity in the adjacent stomach, with probable consequent underestimation of

the occurrence of moderate reflux. Alternatively, it may be that once GOR has occurred it is not confined to the lower oesophagus but spreads easily throughout its length.

The mean and median number of frames showing reflux per 60 frames in those studies where GOR occurred is also tabulated in Table 12 and it can be seen that for each group the mean is substantially higher than the median. This is due to the skewing effect of a small number of infants in each group with large amounts of GOR and is reflected in the large standard deviation of the means and the wide range of values. From consideration of the median values, GOR is commonest in the infants with mental retardation and in those with recurrent possetting. Infants in 'near-miss' and 'events' group have similar amounts of GOR. The sibs have the lowest median value though the spread of values is wide.

Using the number of positive frames to quantitate the amount of GOR reflects the time that gastric contents were present in the oesophagus. Since a single episode might persist for a number of frames the number of positive frames overestimates the number of separate episodes of reflux ie new occurrences of GOR. Therefore, the number of new occurrences of GOR per 60 frames has been calculated for the infants in each group. Each occurrence of GOR was defined as lasting until the oesophageal area on the gamma camera was cleared of refluxed material. Where an occurrence included moderate and severe frames it was counted as a severe episode. Table 13 details the resulting picture. There is again wide variation in the number of episodes recorded within each group. The lower mean and for number of episodes / 60 frames median values confirm that

episodes of GOR usually last more than one frame. Also, for groups other than the mental retardation group the number of episodes per 60 frames is similar.

Unfortunately data on the amount of reflux that would be expected on radionuclide scans in normal infants is not available. Seibert et al (1983) have compared 1hr radionuclide scans and 24hr pH studies. They found that "if the 24hr study was used as the 'gold standard' only 1 episode of reflux was necessary on a 1hr radionuclide study for a subsequent 24 hour lower oesophageal pH study to be positive. The reflux was significant any time during the 1hr study." The minimum duration of GOR episode detectable in this study was not given. Lower oesophageal pH studies were assessed by the method of Euler and Byrne (1981).

On this basis each group in the present study had significant reflux and would have been expected to be positive on 24hr pH studies. However, these authors used a lower isotope dose than in the present radionuclide scans: 3.7MBq compared to 7-8MBq. This is likely to reduce the sensitivity but increase the specificity of GOR demonstration in Seibert et al's study.

A crude extrapolation of the data for "normal infants and children" (Table 14) from lower oesophageal pH studies can be used to derive values for the duration and frequency of GOR in the two-hour post-prandial period. An approximate comparison can then be made between these earlier studies and the current data by comparing: 1. percent time pH <4 with the number of positive frames on radionuclide scan and 2. the number of episodes of GOR on pH study with the number of episodes on

scan. When these comparisons are made the values for the frequency and duration of GOR in the present radionuclide scan studies (which all relate to the two hour post-prandial period) are similar to those obtained from the pH studies. This might suggest that the frequency and duration of GOR in the present studies is similar to that occurring in normal infants.

Since the study of Seibert et al (1983) uses similar methods it would seem more directly comparable to the current one. Comparison with the "normal" data in Table 14 utilises data obtained using a different method on different groups of infants of different ages and therefore seems less apposite than the data of Seibert et al. However, this highlights the importance of comparing circumspectly results obtained using different methods. It again emphasises the need to include suitable comparison groups wherever possible in studies of GOR.

Following Seibert et al (1983) it may be tentatively concluded that the amount of GOR noted in the various groups by radionuclide scan was abnormal.

Table 11: Summary of scan results

Group	n	GOR present		SEVERE		MODERATE	
		n	%	n	%	n	%
?Aspiration	7	5	71.4	5	71.4	0	0
Mental retardation	4	3	75.0	3	75.0	0	0
'Near-misses'	22	16	72.7	15	68.2	1	4.5
SIBS	12	11	91.7	7	58.3	4	33.3
'Events'	29	24	82.8	22	75.9	2	6.9
Recurrent possetters	8	7	87.5	6	75.0	1	12.5
Total	82	66	80.5	58	70.7	8	9.8

Table 12: GOR recorded by radionuclide scan (Frames)

		Frames showing moderate GOR: no / 60min				
Group	n	mean	sd	median	minimum	maximum
?Aspiration	7	2.2	3.0	0	0	7.3
Mental retardation	4	1.1	1.3	.9	0	2.5
'Near-misses'	22	1.0	1.5	.6	0	6.8
SIBS	12	.9	1.0	.6	0	2.7
'Events'	29	1.6	2.0	.9	0	6.1
Recurrent possetters	8	3.9	7.8	.9	0	23.0

		Frames showing severe GOR: no / 60min				
Group	n	mean	sd	median	minimum	maximum
?Aspiration	7	2.7	3.1	1.7	0	8.4
Mental retardation	4	15.1	22.5	5.4	1.0	48.5
'Near-misses'	22	2.8	3.4	1.4	0	12.5
SIBS	12	2.9	6.2	.8	0	22.0
'Events'	29	3.4	5.7	1.7	0	29.1
Recurrent possetters	8	9.0	14.2	3.4	0	42.2

Table 13: GOR recorded by radionuclide scan (Episodes)

		Moderate episodes of GOR: no / 60min				
Group	n	mean	sd	median	minimum	maximum
?Aspiration	7	1.7	2.4	0	0	6.2
Mental retardation	4	.5	.9	0	0	1.9
'Near-misses'	22	.8	1.2	.5	0	5.1
SIBS	12	.7	.9	.5	0	2.7
'Events'	29	1.0	1.5	.5	0	6
Recurrent possetters	8	.8	1.0	.5	0	2.5

		Severe episodes of GOR: no / 60min				
Group	n	mean	sd	median	minimum	maximum
?Aspiration	7	1.7	2.1	1.1	0	6.2
Mental retardation	4	3.3	2.4	2.8	1.0	6.6
'Near-misses'	22	1.9	2.0	1.2	0	5.6
SIBS	12	1.2	1.5	.8	0	4.7
'Events'	29	1.5	2.1	.9	0	10.3
Recurrent possetters	8	2.4	3.1	1.0	0	7.6

Table 14: "Normal" data for pH studies; adults, children and infants

	Groups and numbers of cases studied							
	(A) 15		(B) 20		(C) 7		(D) 11	
Reflux measure	Mean	sd *	Mean	sd	Mean	sd	Mean	sd
Total no of episodes	20.60	14.77	10.60	8.20	15.67	15.54	24.00	21.60
Time pH <=4 (%)	1.47	1.38	1.86	1.60	.85	.53	3.10	2.80
No of episodes >5min	.60	1.24	1.73	2.05	.17	.41		
Longest episode (min)	3.86	2.68	8.07	7.19	3.55	2.07	8.00	6.30

(A) Johnson and Demeester, 1974 - adults
(B) Boix-Ochoa et al, 1980 - infants and children
(C) Koch and Gass, 1981 - infants
(D) Berquist et al, 1985 - infants; acidified feeds

* mean +/-sd

Recurrent 'possetting'

The number of small vomits and possetts directly observed during the course of the scans is tabulated in Table 15.

Only 56% (61/109) vomits were associated with discernible change in oesophageal activity on the gamma camera image. This failure to detect clinically observed vomiting was felt to be due to the vomits failing to exceed a critical volume duration product (see Chapter 6 and Appendix 2).

It is very striking that of 82 scans, with GOR to the upper oesophageal level in 636 frames, vomiting was only noted on 61 frames (9.5%). Vomiting is a specific, but not a sensitive, marker of GOR.

These figures emphasise the fact that significant GOR can occur without vomiting. When vomiting is present it is likely to reflect only the tip of an "iceberg" of GOR. This is important in the situation where respiratory symptoms might be caused by GOR. The absence of clinically prominent vomiting does not preclude the possibility that respiratory symptoms are due to GOR.

Table 15: Vomiting & GOR

Scans n = 82	
883 positive frames:	636 severe GOR
	247 moderate GOR
410 episodes:	272 severe GOR
	138 moderate GOR
109 vomits:	61 visible on scan

3 When does GOR occur?

It might be anticipated that GOR would decrease with time following a feed. To assess whether this was so each scan was divided into successive thirty minute intervals timed from the end of the infant's feed. The number of frames showing GOR in each thirty minute period was computed for all 82 scans. Figures 16 and 17 display the results graphically, for moderate and severe reflux detected by scan. The amount of reflux diminished with time. This was particularly striking for reflux to oesophageal level (severe) where a five fold fall from 1st to 4th interval occurred. In contrast, there was relatively little change through the 4 time intervals for moderate reflux.

This finding is in accord with the published reports from pH studies which describe reflux occurring more commonly in the two hour post-cibal period than later (Jolley et al 1978, Sondheimer 1980). It provides additional detail in that it demonstrates that the occurrence of GOR becomes progressively less frequent as time elapses after the end of a feed. Also, as noted earlier pH studies may underestimate the amount of GOR present in the two hour post-cibal period, particularly in the immediate post-feed period; at that time radionuclide scans are more likely to give an accurate assessment of the amount of GOR. The finding that GOR diminishes with time after a feed is also in keeping with common observation and experience that infants vomit most soon after a feed.

Figure 16: Moderate reflux - time of occurrence after feed

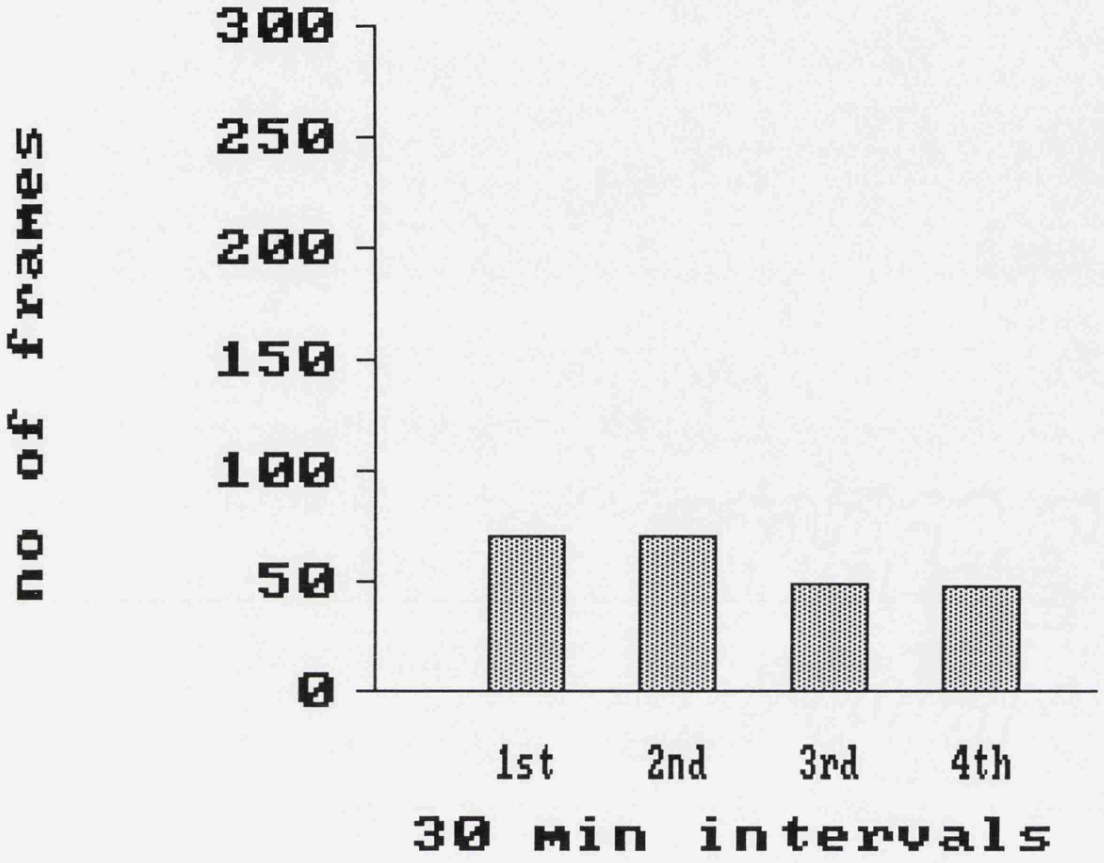
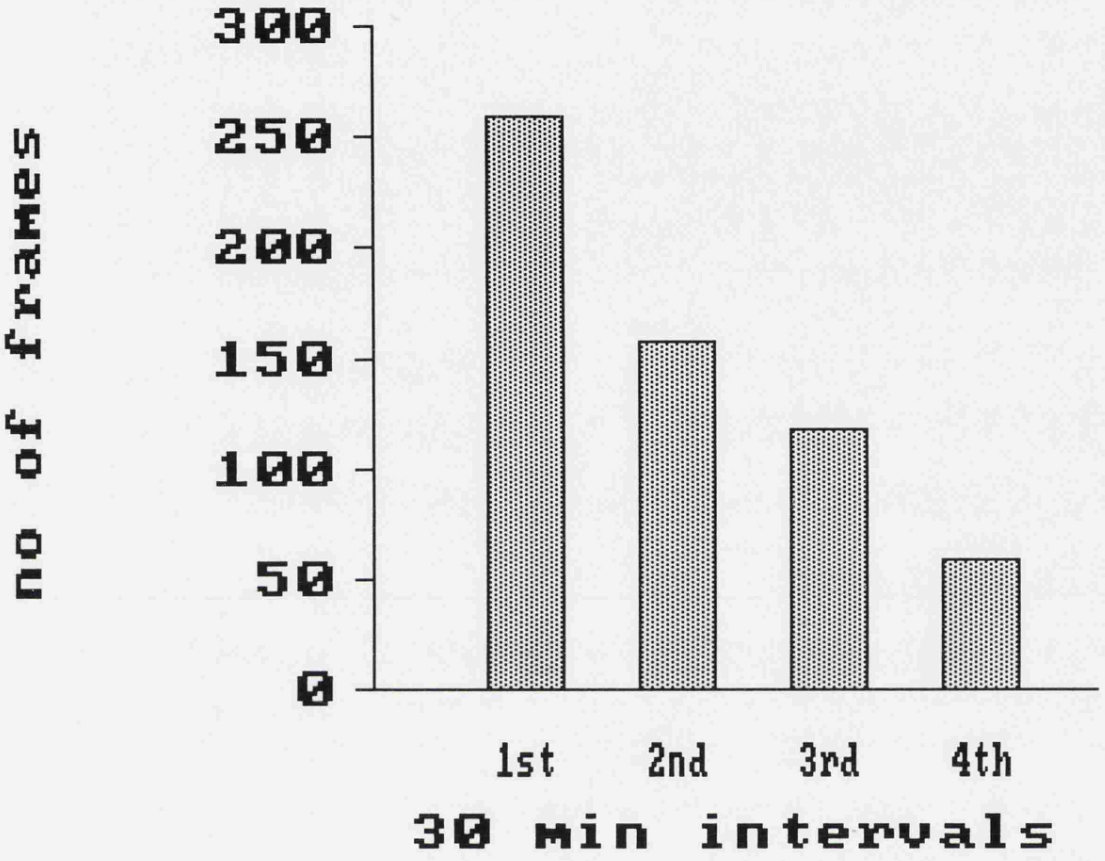


Figure 17: Severe reflux - time of occurrence after feed



4 Awake or asleep?

Table 16 summarises the findings about reflux and sleep. No attempt was made during the course of the scans to distinguish the various sleep phases. The infant was considered asleep when he was quiet with his eyes closed. The total number of positive frames, severe and moderate, and the number of vomits were computed and are presented in Table 16 for both sleep and wakefulness. The total number of frames when the infant was either asleep or awake is listed in Table 16. In 6 studies (731) frames this information was not available; accordingly, they were excluded.

It can be seen that, even allowing for the slight excess of time awake vs time asleep (1.3:1), reflux occurred more frequently when the infant was awake (2.2:1). This was also found with vomiting which rarely occurred while the infant was asleep. Detailed information on the occurrence of GOR in various sleep phases was not available from this study.

This is in agreement with the results from lower oesophageal pH studies where a constant finding has been that reflux is considerably less frequent and of shorter duration during sleep than wakefulness (Jolley et al 1978, Jeffery et al 1980).

Table 16: Number of frames showing GOR during sleep

Scans n = 82

Total no of frames = 9048
= 4695 awake, 3622 asleep, 731 sleep state not known

	Moderate	Severe	Total	Vomits scan +ve	Vomits scan -ve	Total
Awake	162	445	607	58	46	104
Asleep	85	191	276	3	2	5
Total	247	636	883	61	48	109

5 In what position does GOR occur?

During each scan the infant's position was changed after approximately 15 minutes through 4 positions:- prone, left lateral, right lateral and supine. This was then repeated until the infant had been in each position twice. The order the infant was placed in the different positions was determined haphazardly and did not follow either a random or a systematic approach.

The variation in the amount of reflux in each position was assessed by counting the number of frames showing reflux in each position. The results for the two sets of four positions are presented graphically in Figures 18 and 19.

Inspection of the graph for moderate reflux shows little variation with position during the first or second set. The same is true for the second set of positions for severe reflux. For severe reflux, however, there is marked variation with position in the first set of positions with prone emerging as the position most frequently associated with the largest number of frames with GOR.

In view of the non-random choice of position the number of times each position appeared with respect to time after the end of the feed was tabulated (Table 17). The time following completion of a feed was divided into 30min intervals. Inspection of table 16 shows that supine and prone positions were the most frequently used as starting positions. Since severe reflux diminishes with time after a feed the differences observed for severe reflux and position are probably spurious

reflecting decrease in the amount of reflux with time rather than the effect of any particular position. If there is any position effect then the graph and tally table suggest that the prone position is most likely to be associated with GOR.

Figure 18: Moderate reflux - occurrence in different positions

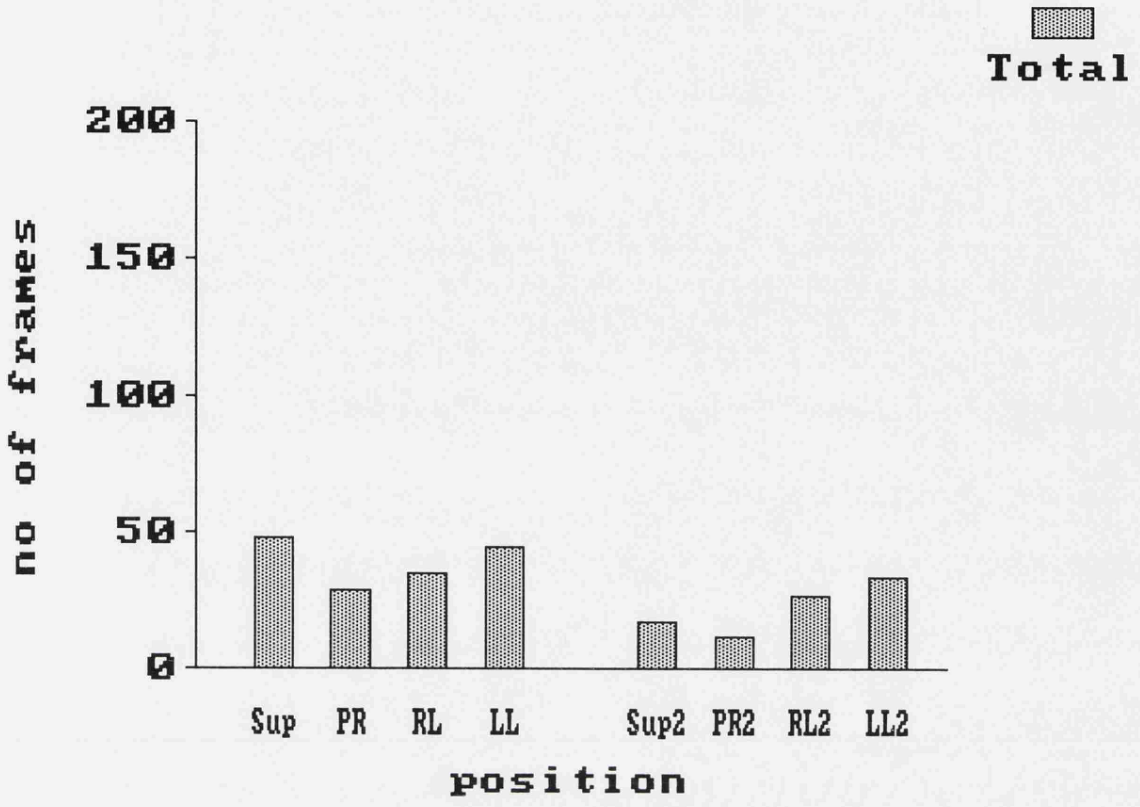


Figure 19: Severe reflux - occurrence in different positions

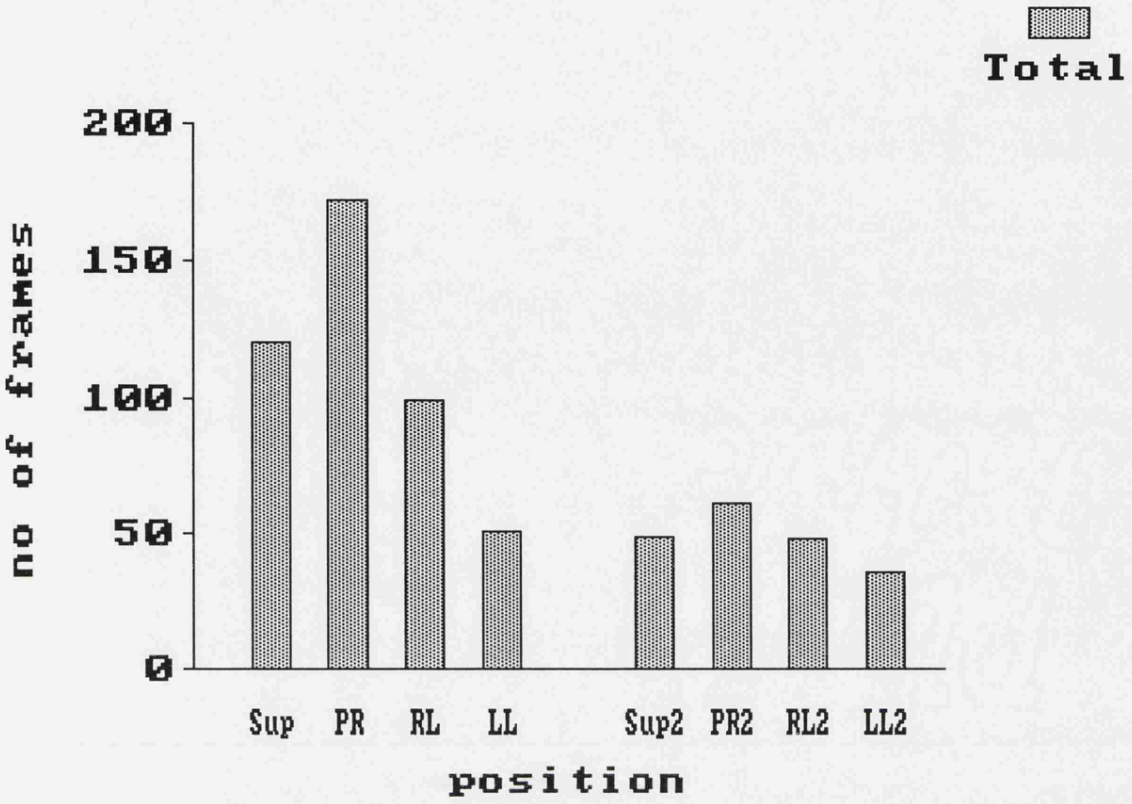


Table 17: Tally of order of positions

Positions: first set

	Interval				
	1st	2nd	3rd	4th	Total
supine	39	12	15	14	80
prone	25	11	24	21	81
R lat	7	39	17	16	79
L lat	8	17	23	28	76
	79	79	79	79	

Positions: second set

	Interval				
	5th	6th	7th	8th	Total
supine	20	15	21	24	80
prone	29	14	11	18	72
R lat	11	28	21	19	79
L lat	19	22	26	12	79
	79	79	79	73	

3 infants (nos 16, 21, 65) did not go through each position

6 Discussion

The first question posed in these studies was whether the prevalence and severity of reflux in 'near-miss' infants is different from that in 'normal' infants. The radionuclide scan studies demonstrated that GOR was present in each of the groups studied (including those thought to be at increased risk of SIDS). The amount of GOR probably exceeded that expected in normal infants of similar ages but the lack of appropriate 'normal' data, both in general and with respect to radionuclide scanning in particular, makes this conclusion tentative.

The finding that the 'near-miss' group did not have significantly more GOR than the other groups suggests that it is not differences in the frequency and extent of GOR which distinguish the various infant groups studied. This is important as it suggests that it is not merely the occurrence of GOR which leads to 'near-miss' episodes. From these studies, if GOR has any special importance in the 'near-miss' infant then it is most likely to lie in the nature of the infant's cardiorespiratory response to GOR.

A number of other interesting features of GOR were observed. Firstly, vomiting was relatively uncommon and GOR occurred to a much greater extent than would have been expected from the amount of vomiting observed. The timing of occurrence of GOR was also interesting with a marked reduction in GOR with time after a feed. By two hours, GOR was infrequent and occurred at a relatively constant rate. The frequency of GOR may be a function of the degree of gastric filling and distension. Whether such an effect is a consequence of simple

mechanical factors placing the LOS at a disadvantage or whether the effect is mediated by some more complicated neurological mechanism is unknown. Since GOR seems to occur as a result of intermittent relaxation of the LOS (Werlin et al 1980) it is more likely that the mechanism is neurally mediated.

GOR was also noted more frequently when the infant was awake than asleep. The basis for this change in occurrence with change in state is not known but could reflect some change in the neurological control of the LOS associated with the infant's state. There is some teleological satisfaction in this observation since a decrease in GOR at night, when certain other protective respiratory mechanism are depressed, seems a sensible precaution.

There was no clear evidence of a significant excess of reflux in any one position, with the possible exception of prone position which had the highest number of frames showing severe GOR. Any apparent effect was confounded by the large fall in GOR with time following the last feed.

Most studies of position in relation to GOR have concentrated on the potential therapeutic advantages of a particular position. Prone, supine and semi-upright have been studied most frequently (Jolley et al 1978, Boix-Ochoa et al 1979). The prone position is generally regarded as the position associated with least reflux (Orenstein et al 1983). However, Macfadyen et al (1983) found that GOR occurred most commonly in the left lateral position. The present work suggests that GOR

may be present in all positions and that a more important determinant than position is the time elapsed since the last feed.

The possible excess of GOR in the prone position may be associated with an effect noted by Boix-Ochoa et al (1979). These workers found that in the prone position there were fewer episodes of GOR but those which occurred took longer to clear indicating a relative failure of oesophageal clearance in this position. The present analysis of the radionuclide scan data records the number of frames showing GOR and hence reflects the time material is present in the oesophagus. The excess in the prone position might then represent slower clearance of GOR in this position.

Thus the effects of position may be quite complex, possibly reflecting a balance between occurrence of GOR, particularly in relation to time after a feed, and oesophageal clearance of reflux. The relative effects of any particular position on these two variables may differ and the resulting effects on the occurrence of GOR difficult to attribute.

7 Conclusions

Radionuclide scans demonstrated that GOR was present in each of the groups studied (including those thought to be at increased risk of SIDS). The amount of GOR may have exceeded that expected in normal infants of similar ages but the relative lack of appropriate "normal" data makes any such conclusion uncertain.

GOR occurred to a much greater extent than would have been expected from the amount of vomiting observed.

There was a marked reduction in GOR with time after a feed, and by two hours GOR was infrequent. GOR also occurred more frequently when the infant was awake than asleep.

There was no clear evidence of a significant excess of reflux in any one position, with the possible exception of prone position which had the highest number of frames showing severe GOR, any apparent effect being confounded by the large fall in GOR with time since the last feed.

The fact the 'near-miss' group did not have significantly more GOR than the other groups suggests that it is not merely the occurrence of GOR which was important in determining the occurrence of 'near-miss' episodes. From these studies, any special importance of GOR in the 'near-miss' infant is more likely to lie in the nature of the infant's response to it.

CHAPTER 6 page

A COMPARATIVE STUDY OF THE DETECTION OF GOR BY RADIONUCLIDE SCAN AND LOWER OESOPHAGEAL pH PROBE

CHAPTER 6

A COMPARATIVE STUDY OF THE DETECTION OF GOR BY RADIONUCLIDE SCAN AND LOWER OESOPHAGEAL pH PROBE

1 Vomiting and the analytical sensitivity of scanning

Vomiting, possetting or "small windy vomits" are often taken as the clinical hallmark of GOR. Studies described in Chapter 5 showed that in the great majority of cases episodes of reflux detected by radionuclide scan were not associated with vomiting. Vomiting is, therefore, in epidemiological terms a specific but insensitive marker for GOR.

However, while vomiting (usually only small amounts) was observed on 109 occasions during the course of 82 radionuclide scans it was also noted that in 61 of these GOR was not detected on the radionuclide scan (Table 15). Such false negatives had implications for the detection of reflux by radionuclide scans.

In the 61 instances where vomiting during the course of a radionuclide scan was not associated with any discernible change in oesophageal activity on the gamma camera image it seemed likely that the gamma camera had failed to detect the refluxed material because it had fallen below the limit of the camera's analytical sensitivity. This prompted the performance of an in vitro simulation experiment to assess the analytical sensitivity of the method. This simulation was performed in

collaboration with PS Cosgriff of the Department of Medical Physics, Leicester Royal Infirmary and the results were subsequently published (Paton et al 1985) (Appendix 2).

In essence, this experiment showed that the analytical sensitivity for the detection of a transient event such as GOR depended on five factors: isotope concentration in the stomach, absolute gamma camera sensitivity, absorber thickness and volume and duration of reflux. As the first three are usually fixed in the clinical situation, a critical volume-duration product must be exceeded for reflux to be detected with a given camera/computer system. Applying the results to the conditions pertaining in practice in the present studies (isotope concentration 1.0uCi/ml, camera sensitivity 6.0counts/sec per uCi) and assuming an absorber thickness of 1cm, it was estimated that the product would be 10ml.sec. This means that 1ml of GOR would have to be present in the oesophagus for 10sec or 10mls for 1sec to be detected during a radionuclide scan.

The vomits observed clinically but not detected as reflux by the gamma camera presumably failed to exceed the required volume-duration product, either because they were too small or because they moved through the oesophagus too fast, or both.

This simulation, therefore, provided an assessment of the lower limit of radionuclide scanning's ability to detect reflux.

2 Comparison of radionuclide scan and pH probe studies

2.1 Infants studied

In order to compare the two methods used in these studies to detect GOR radionuclide scans and lower oesophageal pH studies were performed simultaneously in 24 infants (Table 18).

In four patients technical problems resulted in the pH study being unsuitable for further analysis. In two infants (no. 38 & no. 54) the probe malfunctioned. In a third infant (no. 21), the probe recorded a persistently low pH and was probably positioned below the lower oesophageal sphincter or in the stomach. In the fourth case (no. 18) the presence of the probe induced marked retching and vomiting. It had to be removed and the attempt to measure oesophageal pH abandoned.

One infant (no. 41) had a technically satisfactory pH study but failed to acidify his stomach contents below pH4. This infant had persistent reflux observed on the radionuclide scan which was not detected by the pH probe. This study is not included in the comparative study but is commented on separately.

Table 18: Patients studied in combined scan and pH studies

DIAGNOSIS	Number	Mean Age (yrs)	Technically Successful
'Near-miss'	8	.25	6
Sibs	2	.08	2
'Events'	11	.19	11
Vomiters	4	.18	2
Total	25	.17	21

4 failures - 2-probe malfunctioned (38,54)
1-probe in too far (21)
1-probe induced retching and vomiting (18)

2.2 Amount of reflux detected

Table 19 summarises the results of the simultaneous radionuclide scans and pH studies in the 21 technically satisfactory studies. The mean duration of study in the 21 was 120min.

There was evidence of reflux on scan in 19 of the 21 studies. In these studies reflux was moderate in 84 frames and severe in 201. Since reflux on scan could span several frames the number of separate occurrences of reflux were counted. One study (no. 41) was excluded from this assessment because reflux on scanning was almost continuous, precluding separation into episodes. In the remaining studies, 193 frames showed 56 separate episodes of moderate GOR and 69 of severe GOR (when a prolonged episode on scan included both moderate and severe reflux then it was counted as a severe episode).

The pH of the gastric contents was checked in 18/21 studies (16 at the end of the study, 2 at the beginning before feeding and 3 both at the beginning and end). The mean, median and range of gastric pH at the end of the studies were respectively: 2.00, 1.65, and 1.02-4.1. In the 5 studies where gastric pH was checked at the beginning the values for gastric pH were: 1.68, 1.5, 1.4-2.15 (mean, median and range). In the 2 studies where gastric pH was not checked there was evidence of acid reflux during the study indicating that the infants were producing gastric acid satisfactorily.

The pH studies showed 120 drops in pH greater than 1pH unit with approximately equal numbers of spikes and episodes (59 vs 61). The number of long pH drops was small with only 2 studies having drops lasting longer than 5 minutes. The percent time with pH <4 was on average 2.28%, and the median 1.3% (range 0-10.5%).

Table 19: Details of combined scan and pH studies

			Reflux on Scans				Reflux on pH probe studies						
				Degree of reflux			pH <4	Longest	pH<4 for	pH drops >1 unit			
No	Diagnosis	Reflux	Reflux	Frames		Episodes	%	drop with	>5min	Spikes		Episodes	
		(scan)	(scan)	Mod	Sev	Mod Sev		pH<4 (min)	no/hr	no	no/hr	no	no/hr
63	'Near-miss'	N		0	0	0 0	0	0	0	1	.45	0	0
66	'Near-miss'	N		0	0	0 0	.30	.35	0	1	.52	1	.52
52	Sib	Y	MOD	1	0	1 0	1.16	1.40	0	1	.50	4	1.99
22	'Near-miss'	Y	SEV	4	4	4 3	2.10	2.40	0	0	0	4	2.15
46	'Near-miss'	Y	SEV	2	13	2 10	0	0	0	0	0	2	.97
48	'Near-miss'	Y	SEV	4	6	2 6	0	0	0	2	1.20	3	1.80
68	'Near-miss'	Y	SEV	11	9	9 5	0	0	0	1	.94	6	5.64
61	Sib	Y	SEV	5	4	2 4	.15	.20	0	2	.92	5	2.30
17	'Event'	Y	SEV	5	1	2 1	2.60	2.30	0	1	.45	2	.89
19	'Event'	Y	SEV	5	3	4 3	9.57	6	.64	12	7.66	4	2.55
20	'Event'	Y	SEV	12	8	12 4	2.56	2.90	0	5	2.65	1	.53
33	'Event'	Y	SEV	2	1	2 1	1.30	1.15	0	1	.53	4	2.11
36	'Event'	Y	SEV	2	6	1 3	3.30	3	0	2	.99	2	.99
39	'Event'	Y	SEV	1	11	1 7	2.30	1.85	0	3	1.26	2	.84
40	'Event'	Y	SEV	1	2	1 2	0	0	0	2	.87	1	.44
42	'Event'	Y	SEV	1	16	0 7	2.80	3.10	0	0	0	5	2.49
44	'Event'	Y	SEV	8	17	1 9	1.30	1	0	2	.85	3	1.27
50	'Event'	Y	SEV	6	5	7 2	8	5.20	.57	22	12.52	5	2.85
62	'Event'	Y	SEV	11	0	5 0	10.50	4.90	0	1	.49	5	2.44
27	Vomiter	Y	SEV	0	5	0 2	0	0	0	0	0	2	.97
41	Vomiter	Y	SEV	3	90		0	0	0	0	0	0	0
Total		21	18sev 1mod	84	201	56 69				59		61	
Mean				4	9.57	2.80 3.45	2.28		.06	2.81	1.56	2.90	1.61
sd				3.75	19.14	3.24 3.03	3.19		.18	5.11	3.00		
Median				3	16	2 3	1.30	1.15	0	1.15	.53	1.15	1.27
Min				0	0	0 0	0	0	0	0	3	3	3
Max				12	90	12 10	10.50	6	.64	22	12.52	6	5.64

4 technical failures - 2 probe malfunctioned (38,54)
1 probe in too far (21)
1 probe induced retching (18)

2.3 Comparison of scan and lower oesophageal pH findings

In comparing GOR detected by lower oesophageal pH studies and radionuclide scans three situations could be envisaged; that both techniques would detect an episode or one technique would detect an episode while the other did not (or vice versa).

In the initial attempts to compare the two methods of reflux detection it became apparent that matching occurrences of reflux was extremely difficult because of the different basis underlying each method of reflux detection. It was much easier to compare similar points in time and assess whether reflux was present on one, both or neither test at that point. However, before making such a comparison it was necessary to ensure that reflux detected by the two techniques was measured in the same units of time. This point had to be considered because the two methods had different units of time. In the radionuclide scan studies, the data was collected in units of 1 minute ("1 frame"). A single frame could not be subdivided into smaller intervals. In contrast, the pH data was collected in "real" ie normal time. Accordingly, the pH at any specific time could be noted and a number of short drops could occur within the space of 1 minute (1 frame). In order to give the records the same time base, in the first instance, "1 frame" was used as the common unit of time in the analysis. Then the presence or absence on scan or pH study, during the minute corresponding to a particular scan frame, was noted.

Table 20 gives the number of frames showing evidence of reflux by either method of detection. It conforms to expectations in that there are occasions when both tests are positive and also occasions when only one test detects reflux.

Table 20: "Frames" showing GOR

"Frames" showing evidence of reflux
by either method of detection

106	Both positive
107	Scan only positive
53	pH only positive

"Frames" (1 min time intervals)

1 infant (no. 41) excluded and considered separately

2.4 Both techniques positive

Table 21 examines the nature and extent of GOR detected simultaneously by both techniques.

Analysis of the scan results showed 46 frames with evidence of severe reflux and 38 frames with moderate reflux. During the performance of the scans, and later on subsequent review of the results, it was observed that on 22 occasions there was a fall in pH followed within a few minutes by the appearance of reflux on the gamma camera image. Those instances where the pH fell and there was then a phase delay before the appearance of the scan image are tabulated under "delayed positive" (the scan was negative when the pH began showing reflux but became positive). This "phase lag" was attributed to the more rapid response of the pH probe to reflux. It is explicable in terms of the earlier in vitro simulation of GOR in that detection of reflux depended on both the amount and duration of reflux. Small amounts of reflux have to be present for longer to be detected. In simple terms it takes time for the gamma camera image to "develop".

The extent of this "phase delay" is shown in table 22. In most instances the delay was one or two minutes. While a period of up to 2 minutes may be intuitively acceptable as a phase delay due to differing rates of measuring instrument responses it is unlikely that a delay of 3 or 4 minutes could be attributed to a similar mechanism. However, each of these longer delays occurred in the context of a well defined and prolonged pH drop (eg Figure 20). Hence, while the mechanism was unclear it seemed reasonable to regard the responses as

measuring the same single event of reflux. They are therefore included in the group where both radionuclide scan and pH probe results are positive.

The lowest pH during these frames is tabulated in Table 21. It can be seen that during 61 frames the lowest pH was above pH 4. Since this particular comparison includes only those frames where both techniques were showing evidence of reflux it demonstrates that there are episodes of "non-acid" reflux ie periods where the pH of the refluxing fluid is greater than pH4. It is necessary to recall that in these studies reflux was defined as a fall in pH greater than 1pH unit and was not restricted only to episodes where the pH fell below 4.

From the original definition, the pH "drop" relates the pH at the start of an episode of reflux to the lowest pH occurring during that reflux. The existence of "non-acid" reflux can be demonstrated by taking those refluxes when the scan and pH results are in agreement and scrutinising the pH changes during each episode of reflux detected by the pH probe. Accordingly, each pH drop was analysed to identify the lowest level of pH. As outlined, to be counted as GOR in a pH study a fall in pH had (by definition) to exceed 1 pH unit.

Table 23 shows that there were only some 58 falls in pH exceeding 1pH unit in the 106 frames where both the scan and the pH record were judged to show evidence of reflux. Hence, there are fewer pH drops than might be expected from the total of 106 frames where both test were judged to be positive. This might be a consequence of three contributing factors. First, it

was clearly seen that a single reflux (in pH terms) could last over a number of minutes and therefore over a number of frames. Secondly, there might have been a discrepancy between time for neutralisation of acid reflux (indicated by pH studies) and clearance of reflux (reflected in the radionuclide scan) with clearance perhaps taking longer than neutralisation. Lastly, there was the difficulty in defining general criteria for measuring episodes of reflux in pH terms which describe the reflux precisely. All these factors might lead to fewer number of "episodes" of reflux on pH than might be expected from the frame count on the radionuclide scan.

Table 23 also shows that in 21 instances the pH fell one or more pH units but the lowest pH remained above 4. This provides clear confirmation of the presence of "non-acid" episodes of reflux.

Table 21: Reflux episodes detected by scan and pH simultaneously

Reflux on scan (extent)	Positive frames (n)	Reflux by pH criteria	Positive frames (n)
Severe	46	Lowest pH>=4	61
Moderate	38		
delayed positive	22	Lowest pH<4	45
Total	106		106

* In 106 frames both tests "simultaneously" showed GOR

Table 22: Phase delay in scan detection of reflux

n = 22

Phase delay	1 min	2 min	3 min	4 min	
Number of severe frames showing delay	7	3	1	1	
Number of moderate frames showing delay	5	4	1	0	
Total	12	7	2	1	22

Figure 20: Phase delay in the detection of GOR by scan compared with pH probe

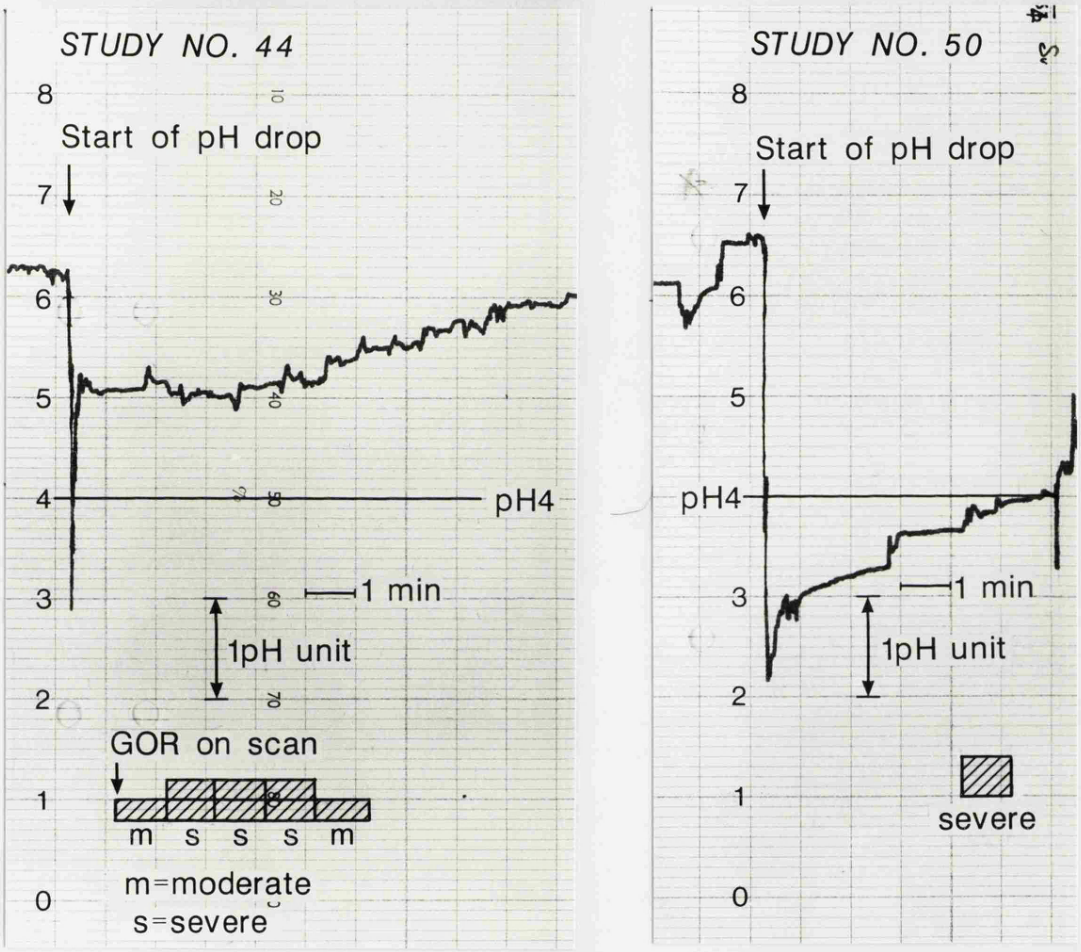


Table 23: Analysis of pH drops >=1pH unit in relation to scan +ve frames

Nature of pH drop	Lowest pH		
	>=4	<4	Total
Episode	14	24	(38)
Spike	7	13	(20)
Total	21	37	(58)

2.5 Scan only positive

There were a considerable number of frames (107, Table 24) where reflux was only detected by radionuclide scan. Why was this reflux not detected by the pH probe?

Table 24 shows that these 107 frames consisted of 64 frames with the radionuclide scan showing severe reflux and 43 showing moderate reflux. As noted for the pH studies a single episode of reflux can last over a number of frames. Accordingly, the number of "new episodes" of reflux occurring in these 107 scan only positive frames is also documented in Table 24. From this it can be seen that there were 23 single frame severe episodes and 9 multiple frame severe episodes. Similarly there were 27 moderate single frame episodes and 3 multiple frame moderate episodes. There were in addition 8 multiple episodes comprising both moderate and severe reflux on radionuclide scan. There was therefore a total of 70 separate episodes of reflux documented by scan alone. It needs to be emphasised for each of these episodes of reflux that not only was the pH above 4 but also that the pH fall was less than 1 pH unit. This provides further evidence for the occurrence of "non-acid" reflux.

Is "non-acid" reflux seen in the post-feed due to the buffering capacity of large volumes of milk neutralising the stomach's acid output? If so then most episodes of reflux detected by scan alone should occur in the immediate post-feed period. To investigate this, the occurrence of reflux on scan was tabulated at 30 minute intervals from the end of the infant's feed (Table 25). The number of episodes in each

interval is listed in the table. A number of points can be noted. First, the number of multiple frame episodes of reflux decreases rapidly with time from the end of a feed. Secondly, the number of single frame episodes also decreases with time but the decrease is very gradual. Overall, as time passes there is a change from the occurrence of both multiple and single frame severe episodes to single frame only refluxes (Figure 21). Thus, there has been a change from frequent and longer (multiple frame) refluxes in the period immediately after the feed to fewer and shorter (single frame) refluxes as time progresses further from the feed.

An overall decrease in the number of frames showing GOR occurs in the first two intervals following a feed to a lower more constant (?basal) level in the third and fourth (Table 26). The pattern is similar whether frames showing reflux on scan alone or frames showing reflux on both scan and pH are considered (Figure 22). The pattern differs for frames showing reflux only on pH with a fall over the first three intervals being followed by a rise in the fourth (Table 26).

Table 24: GOR detected by scan only: Frames & Episodes

	Scan only positive: frames and episodes			
	Severe	Moderate	Mixed	Total
Frames	64	43		107
Episodes	32	30	8	70
duration of episode				
1 frame	23	27	0	50
>1 frame	9	3	8	20

Table 25: Separate occurrences of GOR on scan

Time interval after feed	Extent of GOR on scan	Separate occurrences of GOR on radionuclide scan						
		Severe			Moderate			Mixed
	Duration (frames)	>1	=1	Total	>1	=1	Total	>1
1		6	8	14	1	7	8	5
2		3	5	8	1	7	8	1
3		0	5	5	0	7	7	2
4		0	5	5	1	6	7	0
Total		9	23	32	3	27	30	8

Total frames = 107
Total episodes = 70 ;50 single frames, 20 episodes (57 frames)
Interval = 30 minute periods from end of feed

Figure 21: Change in pattern of GOR with time after feed:
single and multiple frame occurrences

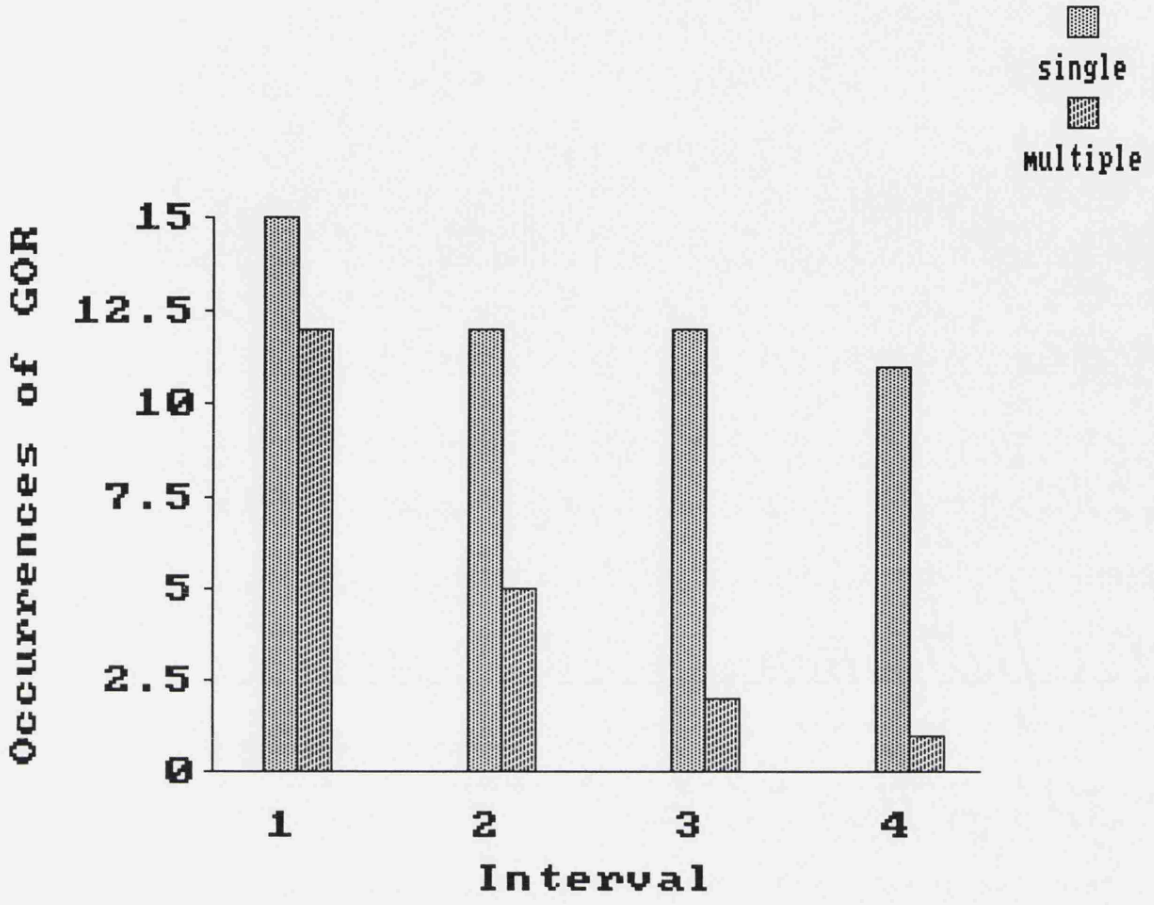


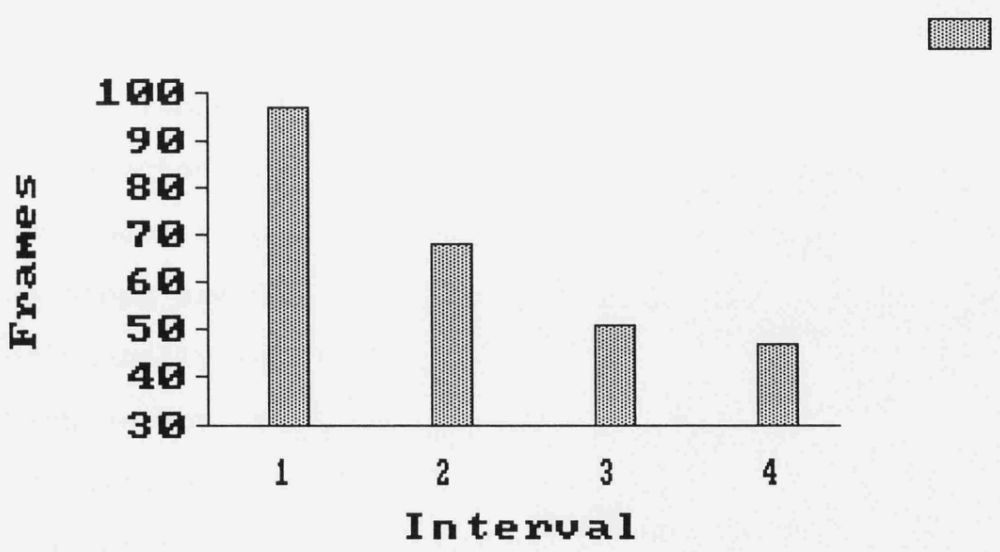
Table 26: Frames showing reflux and time from feed

	Number of frames showing reflux			
Interval	scan only (mod & sev)	both	pH only (spikes & episodes)	Total
1	47	37	13	97
2	31	25	12	68
3	16	25	10	51
4	13	19	15	47
Total	107	106	50 *	263

Interval = 30 minute periods from end of feed

*3 from interval 5 to be added giving total of 53 (cf Table 20)

Figure 22: Total frames showing reflux and time from feed



2.6 pH only positive

The observation that "non-acid" reflux is most frequent in the immediate post-feed period should have the corollary that reflux becomes more acid as time passes. If this is correct it might be expected that the refluxes detected by pH probe, either in agreement with scan or by pH alone, would be most likely to occur in the later time intervals when reflux might be more acid.

Table 27 and Figure 23 presents the results on frames showing GOR as determined by pH study, both for those frames where pH and scan were in agreement and for frames where pH alone was positive. The frames are sub-divided into those with lowest pH >=4 and those with pH <4. There is a decrease in number of frames from interval 1 to later intervals when the number stabilises. For pH <4 the number rises from interval 1 to 2 and then falls to a level similar to the non-acid drops for intervals 3 & 4.

In Table 28 the data is presented for those episodes of GOR detected by pH alone. The table shows the number of pH drops occurring in the different time intervals after a feed. The drops are divided into spikes and episodes and each is additionally subdivided into those drops below pH4 and those which do not fall below pH4. From the table, for both spikes and episodes above pH 4 the number of drops fluctuates with time and there is no definite pattern. In contrast, the number of spikes below pH 4 increases in interval 2 and then stays relatively constant as time progresses. Although the numbers are small, episodes below pH 4 show a slower but similarly

sustained increase with time. In Figure 24 the situation is shown graphically. Inspection of this suggests a broad shift from non-acid reflux early to acid reflux later. In addition, Table 28 shows that drops below pH4 became longer with time, as reflected in the increased number of episodes, appearing later in the study. There was therefore a suggestion that the pH probe detected more refluxes as time passed from the end of a feed.

The pattern emerging is of frequent GOR in the first hour after a feed but a fall thereafter to a low and fairly constant level of occurrence. In the first hour, there is a change from non-acid GOR in the first half to acid GOR in the second half. This suggests that in many infants the gastric pH has fallen below 4 by 30 minutes after the end of a feed. However, for some infants the time taken to acidify a feed is longer as non-acid GOR is still noted up to 2 hours after a feed.

This pattern has intuitive appeal. Frequent GOR occurs in the first hour when the stomach is full. With emptying of the stomach, the occurrence of GOR diminishes. Concomitantly, production of acid and digestion of feed in the stomach leads to a fall in gastric pH in the first hour after a feed. Hence GOR immediately after a feed is non-acid but becomes acid with in the first hour as digestion proceeds. Thereafter, perhaps in relation to emptying of the stomach, occurrence of reflux falls to a "background" rate.

Table 27: Lowest pH in frames showing reflux (both & pH alone) and time from feed

Interval	Frames showing reflux on pH - pH only or both				
	both	pH only (spikes & episodes)	Total	pH breakdown pH>=4	pH<4
1	37	13	50	40	10
2	25	12	37	15	22
3	25	10	35	19	16
4	19	15	34	16	18
Total	106	50 *	156	90	66 *

Interval = 30 minute periods from end of feed

*3 in interval 5 to be added giving total of 53 (cf table 20)

Figure 23: pH positive frames in relation to time

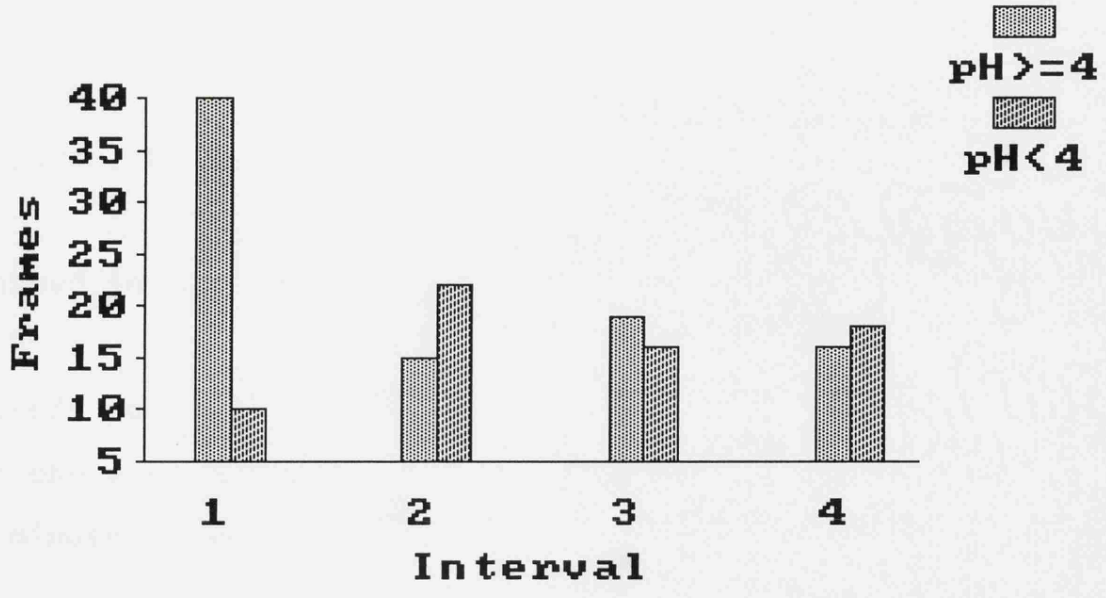


Table 28: GOR detected by pH only - pH drops and time after feed

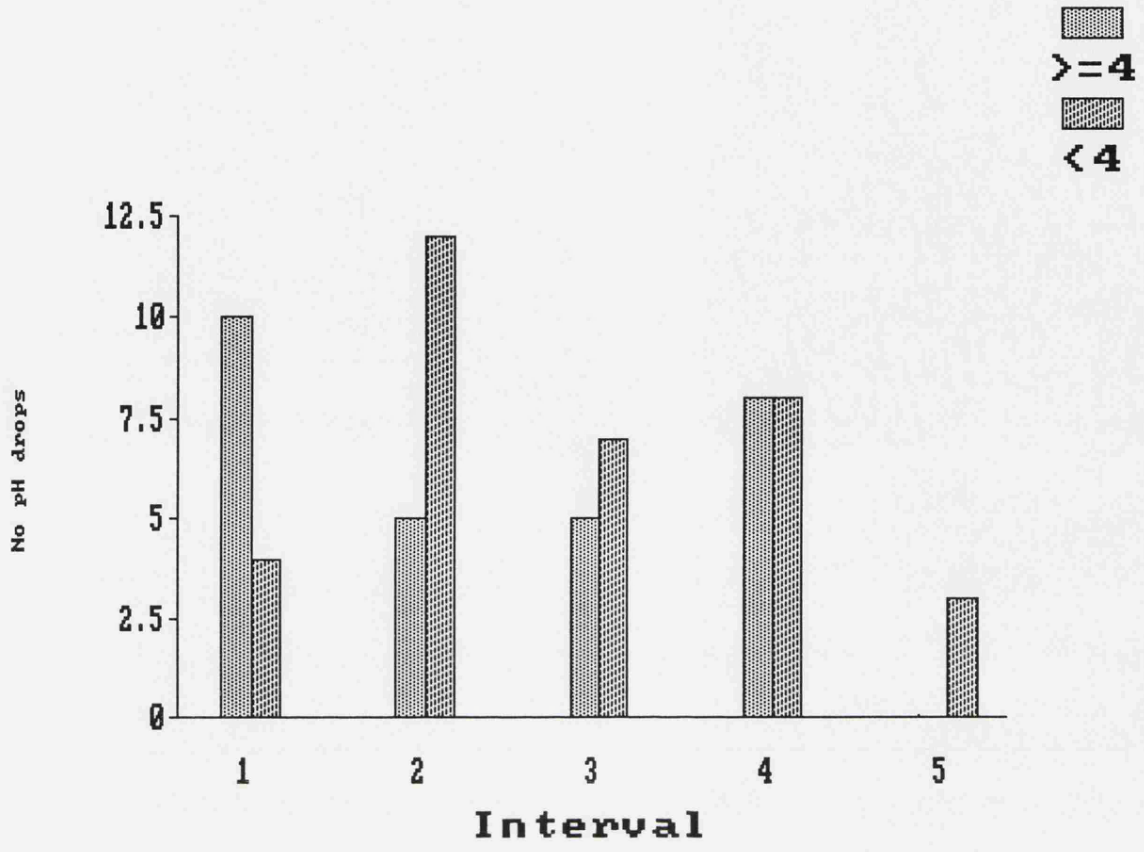
Interval	Spikes		Episodes		Total		
	pH		pH		pH		
	>=4	<4	>=4	<4	>=4	<4	
1	5	4	5	0	10	4	14
2	3	12	2	0	5	12	17
3	1	4	4	3	5	7	12
4	3	6	5	2	8	8	16
5	0	1	0	2	0	3	3
Total	12	27	16	7			62 *

39 spikes, 23 episodes

Assessed in real time rather than on frame by frame base

*Exceeds number of occurrences listed in table 4 (53) as more than one very short episode of reflux occurred within a 1 minute frame on a number of occasions.

Figure 24: pH drops and time after feed



2.7 Short duration pH drops

In previous studies only pH drops exceeding a particular duration, often 15sec, were analysed (Jolley et al 1978, Sondheimer 1980) and this duration was arbitrarily chosen as being significant. In the present studies all pH drops were analysed. Those shorter than 15sec were tabulated as "spikes" while those longer were tabulated as "episodes" How did the radionuclide scan fare in detecting these short drops?

Table 29 shows the data for all pH drops assessed on a frame by frame base divided, firstly, into spikes and episodes and then further subdivided into those with pH >=4 and pH <4. Of 59 spikes 20 were detected by scan. Of these 20 spikes 8 were closely followed by a longer period of reduction in pH. However, 12 (8sev, 4mod) spikes reflected in the radionuclide scan were not followed by longer pH drops. This represents approx 20% (8 of 58 (38 + 20) drops - see table 29) of the severe drops detected by scan. This suggests that while these pH drops are short duration they may be associated with quite extensive GOR on radionuclide scan.

In conclusion, concentrating analysis on pH drops of 15 seconds or longer may result in definite reflux, demonstrable by scan, being missed.

Table 29: pH spikes and episodes: detection by scan on a frame basis

Episodes	pH >=4	pH < 4	Total
Detected on scan	14	24	38
Not detected	16	7	23
Total	30	31	61

Spikes	pH >=4	pH < 4	Total
Detected on scan	7	13	20
Not detected	12	27	39
Total	19	40	59

2.8 Study number 41

One infant (no 41) was excluded from the above comparison between radionuclide scan and pH probe.

In this patient the pH of the stomach contents was above pH 4 at the end of the study and there had been no fall in pH to below pH 4 during the study. In addition, no drops in pH of more than 1 pH unit occurred. However, the radionuclide scan in this patient showed clear evidence of persistent reflux throughout the scan period.

The reason for the failure of production of gastric acid in this case was not discovered. This extreme example emphasises the fact that pH probe studies rely on gastric contents being acid. The reflux of acid gastric contents lowers the normally alkaline oesophageal pH and thus provides an indicator that GOR has occurred. If acid is not produced or is temporarily neutralised by feeding then a pH probe may detect no significant fall in acidity even though reflux has occurred.

3 Conclusions

These studies have demonstrated that GOR detected by radionuclide scan and GOR on pH probe studies often but not invariably coincide. Reflux where the radionuclide scan is positive and the pH study negative tended to occur immediately post-feed in the studies and was often "non-acid" ie pH drops of greater than 1pH unit but lowest pH >4. The presence of such "non-acid" reflux was directly demonstrated. Scan negative, pH positive reflux tended to occur particularly in the second half hour following a feed and then fell to a constant, possibly basal, level. These combined studies have confirmed that significant reflux can pass undetected in infants if pH 4 is the cut-off level for the diagnosis of GOR.

From the data of the simultaneous studies a general trend is apparent. On radionuclide scan immediately after a feed GOR is frequent, of longer duration and greater extent; further from a feed reflux on scan becomes less frequent, generally of shorter duration and less extensive. Reflux soon after a feed is frequently non-acid in nature and is best demonstrated by radionuclide scan. As digestion proceeds and the acidity of the stomach presumably increases, refluxing gastric contents become more acid. In this later period a pH probe becomes more efficient at detecting reflux.

While these observations have been suspected or anticipated in the literature they have not previously been directly demonstrated.

4 Discussion

These conclusions have a number of consequences both technical and general.

Firstly, in infants using pH 4 as the cutoff level for detecting GOR may tend to underestimate the occurrence of reflux. This is particularly so in the post-feed period as has been seen in these studies. Mason (1962) has also shown that it can take up to two hours post feed in normal newborn breast fed infants for the stomach pH to fall below pH 4. This increasing gastric acidity with time presumably reflects a fall in buffering capacity as a feed is digested and the stomach empties. Other workers have been aware of this potential pitfall and in published series two approaches have been used in order to circumvent the possibility of underestimating GOR in the post-feed period. One approach has been to use acid foods eg apple juice or acidified formula (Sondheimer 1980, Orenstein 1983). Alternatively, the immediate post-feed period can be analysed separately (Jolley et al 1978). The first precaution ensures that all reflux is acid while the second excludes the period when non-acid reflux is most likely to affect the overall results.

Secondly, since most studies have used a fall in pH below 4 as a marker of (acid) reflux it is implicitly assumed that acid is being produced by the subject. That this is not necessarily the case has been previously noted in the description of case 41 who failed to lower his gastric pH below pH 4. As a precaution, therefore, in any pH study the pH of the stomach contents should be checked at some point. This would

most appropriately be done at the end of a study to ensure that the gastric contents, at least at that point, have a sufficiently low pH level. If the pH is checked only at the start, just before a feed, one would never know for certain during the study that the buffering effect of any feed had been overcome and the stomach pH reduced to a suitably acid level for reflux to be detected. The present studies suggest that for most (but not all) infants the effect of milk neutralising the gastric acid is likely to be minimal within 30 minutes of the end of a feed.

Lastly, the clear demonstration of non-acid reflux is of more general significance. It is generally assumed in studies of GOR that it is the reflux of acid that is potentially damaging. It is certainly true that if any significant amount of acid is aspirated severe pulmonary consequences result (Wynne and Modell 1977). It is also possible that acid reflux may be a prerequisite of some of the other projected pathophysiological mechanisms underlying cardio-respiratory abnormalities in infants. For example, oesophageal spasm causing bradycardia may be a consequence only of reflux of acid (Fontan et al 1984). It is, however, known from experimental studies in animals that aspiration of non-acid particulate material is as damaging to the lungs as the aspiration of acid (Schwartz et al 1980). It is, therefore, perfectly conceivable that infants may be most at risk from pulmonary aspiration of refluxed material (and any cardio-respiratory consequences thereof) in that period immediately following a feed when reflux is most frequent, most extensive and most likely to be non-acid. Hence an undue emphasis on acid reflux in infants may

be unwarranted and could lead to important associations being overlooked.

5 Implications for later studies

In later parts of this research polygraphic studies were performed on infants at night during sleep. A pH probe was used to monitor for reflux. Is it likely that significant reflux episodes were being missed?

In the studies to be reported (Chapter 8) infants were fed at the start of the study immediately after the probe had been passed. No attempt was made to acidify the feed. The pH was checked, in most cases, at the end of the study and was always below 4. After the feed it usually took at least 1 hour for the infant to settle before the full polygraphic study started. In analysing the results any drop of pH in excess of 1pH unit was counted as indicating GOR. Also, pH drops of any duration were included.

From the comparative studies described above, it is likely that with these criteria there was no major underestimation of the amount of reflux occurring during sleep and that pH studies provided a sensitive indication of the occurrence of GOR. The fact that data recording commenced at least one hour after a feed made it likely that little non-acid reflux would be present.

CHAPTER 7 page

CARDIO-RESPIRATORY VARIABLES DURING SCAN STUDIES

CHAPTER 7

CARDIO-RESPIRATORY VARIABLES DURING SCAN STUDIES

1 Results

In 30 infants respiration and heart rate were monitored during radionuclide scans using the combined heart rate and respiratory monitoring system described (Methods, Chapter 4). Each study was supervised by JYP. Eight infants were subsequently excluded because of initially undetected technical problems which resulted in the tapes being unsuitable for analysis. Satisfactory tapes were obtained in 22 infants who were broadly representative of the overall population studied by radionuclide scan (Table 30). The overall mean age of the infants studied was 0.158yrs (approx 8wks) and the studies lasted on average for 124, 18.7 minutes (mean, sd).

Appendix 3 summarises the presenting clinical histories of infants in the 'near-miss', 'events' and SIBS. A number of infants within each group had a history of respiratory symptoms around the time of feeds. In other studies (Jeffery et al 1983), infants with similar symptoms have been found to have significant GOR.

Table 31 a) & b) gives details of the severity of GOR and the duration of apnea in the infants within each subgroup studied. Twenty had GOR - to pharyngeal level in 19 - whereas only two infants had central apnea exceeding 10 seconds. Table

32 gives additional details of the occurrence of moderate or severe GOR in individual infants by indicating the number of frames in each scan during which reflux was observed. A wide range (0-69 frames, median 4) was observed. Similarly, the numbers of apneas recorded (Table 32) varied considerably between infants: apneas >3-<6sec: 0-194 (median 8.5) and apneas >6sec: 0-98 (median 1). Long apneas were uncommon with only two longer than 10sec. No prolonged apnea (longer than 20sec) occurred.

One episode of bradycardia (heart rate <=80bpm for at least 10sec) was observed in one infant (no. 80) and coincided with an apneic pause of 8.5sec. GOR was not present in this infant.

These results confirm that, as anticipated, both GOR and short central apneas (>=3sec) were present in the infants studied. Hence, these infants did represent a suitable group for assessing if there was any relation between reflux and apnea.

Table 30: Infants studied by radionuclide scan and respiratory monitoring

Group	No	Mean Age (yr)	Sex (m:f)	Gestation (<=37wks)
'Near miss'	6	.174	5:1	0
Sib	5	.185	3:2	0
'Events'	8	.119	5:3	0
Vomiter	3	.188	2:1	1
Total	22	.158	15:7	1

Table 31a: Infants with gastro-oesophageal reflux

GOR on scan

	Studies (n)	Reflux on scan	Type none:mod:sev
'Near-miss'	6	5	1 : 0 : 5
Sibs	5	5	0 : 0 : 5
'Events'	8	7	1 : 1 : 6
Vomiters	3	3	0 : 0 : 3
Total	22	20	2 : 1 : 19

Table 31b: Infants with central apnea

Central apneas

	Studies (n)	Central apnea present	Nos. and duration none: >3 : >6 : >10 (sec)
'Near-miss'	6	5	1 : 5 : 3 : 1
Sibs	5	3	2 : 3 : 3 : 0
'Events'	8	6	2 : 6 : 5 : 0
Vomiters	3	3	0 : 3 : 1 : 1
Total	22	17	5 : 17 : 12 : 2

Table 32: Reflux and apnea: frames showing GOR & numbers of apnea

		Radionuclide scan				Respiration		
Diagnosis	Study no	GOR	Type	Positive frames			Apnea (sec)		Longest
				Moderate	Severe	Total	>3-<6	>=6	(sec)
'NEAR-MISS'	22	Y	SEV	4	4	8	21	7	9
'NEAR-MISS'	29	Y	SEV	1	24	25	8	1	6
'NEAR-MISS'	35	Y	SEV	3	15	18	2	0	
'NEAR-MISS'	66	N		0	0	0	50	26	11
'NEAR-MISS'	69	Y	SEV	12	9	21	3	0	
'NEAR-MISS'	70	Y	SEV	1	7	8	0	0	
SIB	12	Y	SEV	1	47	48	0	0	
SIB	26	Y	SEV	0	3	3	11	1	7
SIB	51	Y	SEV	1	1	2	36	1	7
SIB	68	Y	SEV	2	5	7	0	0	
SIB	72	Y	SEV	1	2	3	6	2	8
'EVENTS'	14	Y	SEV	2	1	3	47	6	7
'EVENTS'	15	N		0	0	0	19	3	9
'EVENTS'	19	Y	SEV	6	3	9	36	6	8
'EVENTS'	24	Y	SEV	0	1	1	1	0	
'EVENTS'	30	Y	MOD	3	0	3	120	40	8
'EVENTS'	33	Y	SEV	2	1	3	0	0	
'EVENTS'	73	Y	SEV	0	2	2	0	0	
'EVENTS'	80	Y	SEV	0	1	1	17	5	9
VOMITER	18	Y	SEV	49	20	69	194	98	14
VOMITER	27	Y	SEV	0	5	5	11	0	
VOMITER	59	Y	SEV	5	9	14	3	0	
Median					3	4	8.50	1	
Range				0-49 frames	0-47 frames	0-69 frames	0-194	0-98	

Bradycardia (<= 80/min for 10 or more seconds)

1.2 GOR and central apnea

To investigate a possible relationship between GOR and short episodes of central apnea two approaches were used.

The groups were ranked either in terms of number of frames showing reflux or in terms of number and duration of apneas and then compared using a non-parametric ranking statistic. No significant correlation was found between the amount of reflux and the numbers and duration of apneas. (Spearman's Rank Correlation test: $n = 22$, $rs = -0.371$).

In the second approach, episodes of GOR and periods of sleep were outlined on the respiratory traces at their recorded time of occurrence. The traces were then inspected visually for evidence of central apnea during periods of GOR or sleep. To make accurate comparisons between the times of occurrence of GOR and apnea and sleep the timebases used in both recordings must agree precisely.

Unfortunately, a methodological limitation of the respiratory monitoring system became apparent in making this comparison. The duration of the respiratory monitoring studies derived from the tape recording and playback system varied from the directly observed duration of radionuclide scan. The extent of the difference between the two lengths of time is listed in Table 34. This difference was due to small variations in the speed of the tape recorder and playback system (the same problem is well recognised in Hi-Fi systems and is known as wow and flutter). Although the difference between the two times was

usually less than 5% it introduced a small element of uncertainty about the precise time of occurrence of any episode of apnea during the study.

In the respiratory traces central apnea (>=3sec) occurring during periods of GOR was observed in only 4 infants (infants nos. 14, 18, 19 & 22; Figures 23, 24, 25, 26). In each infant, reflux also occurred in the absence of apnea. A temporal coincidence between the occurrence of GOR and apnea was observed in only two infants (infants nos 18 & 19; Figure 24 & 25). Detailed examination of each of these traces showed that apnea was usually more closely associated with the onset of sleep than with GOR. Fortunately, in three of the four cases where coincidence between GOR and apnea was noted the difference in timing between the scan and tape recordings was much less than 5% and hence the results on these three traces were unlikely to be affected by any timing error. However, this small uncertainty in timing precluded a precise analysis of the relation between reflux and apnea. At present, such precision is only obtainable using polygraphic techniques.

Figure 25: Respiratory tape of infant no. 14

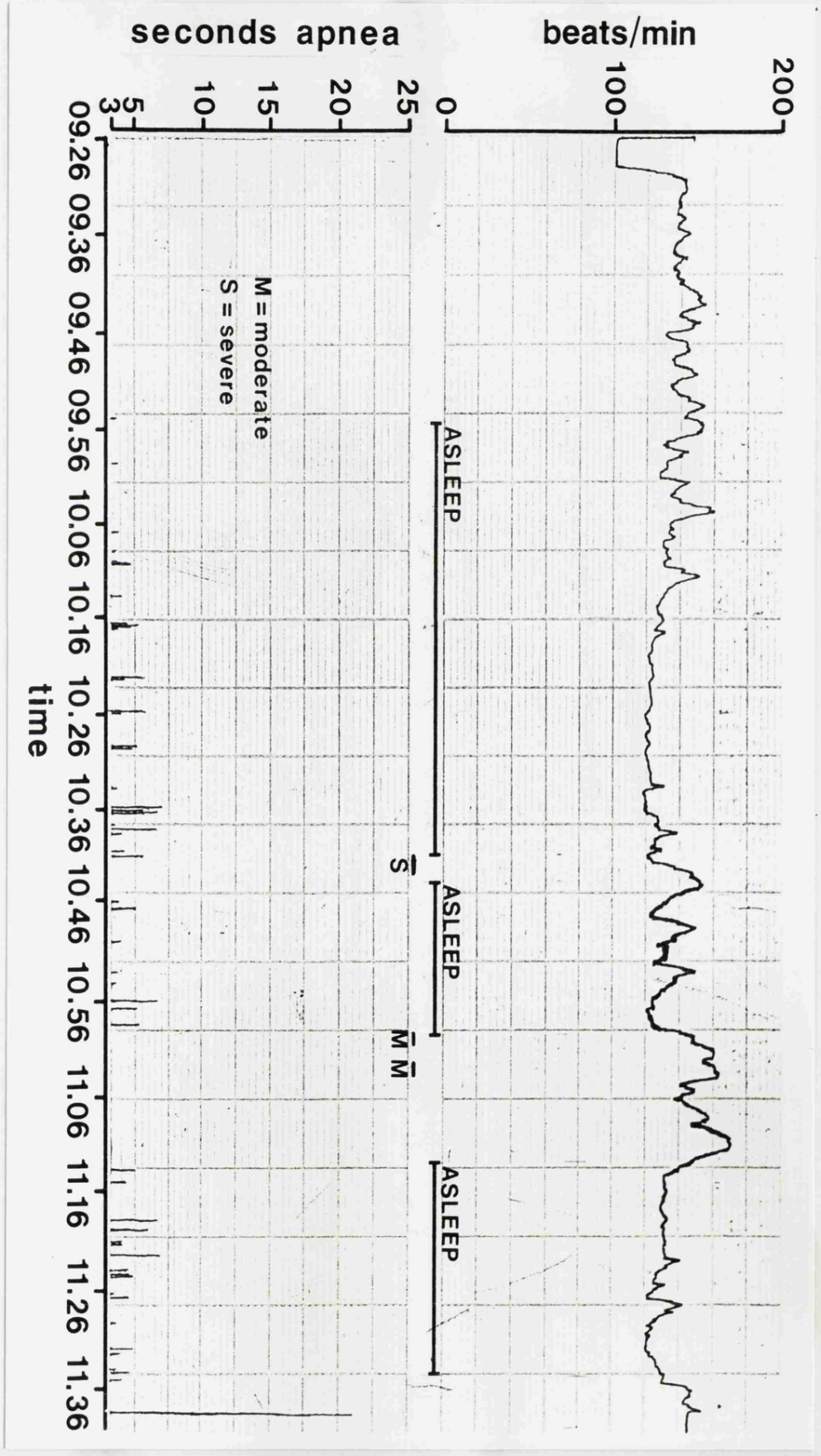


Figure 26: Respiratory tape of infant no. 18

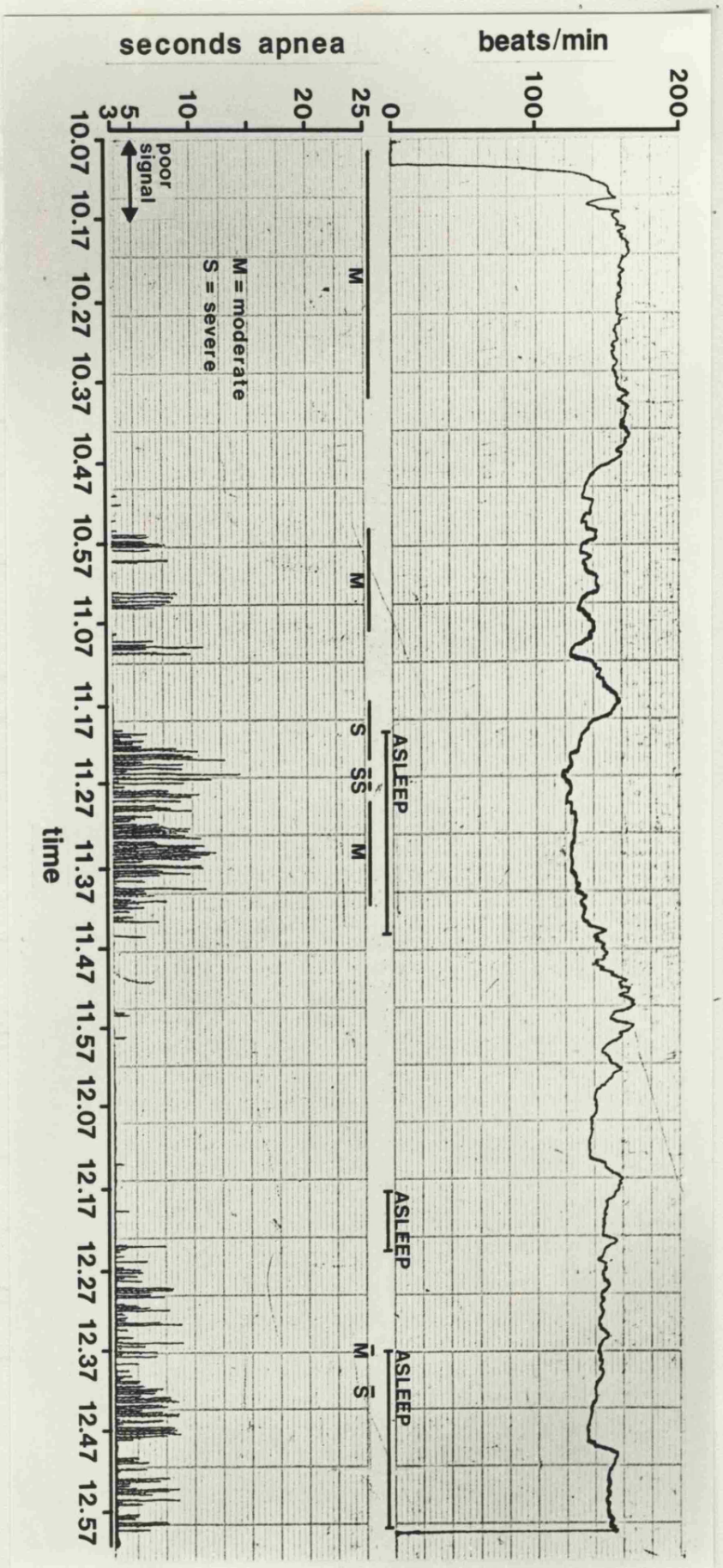


Figure 27: Respiratory tape of infant no. 19

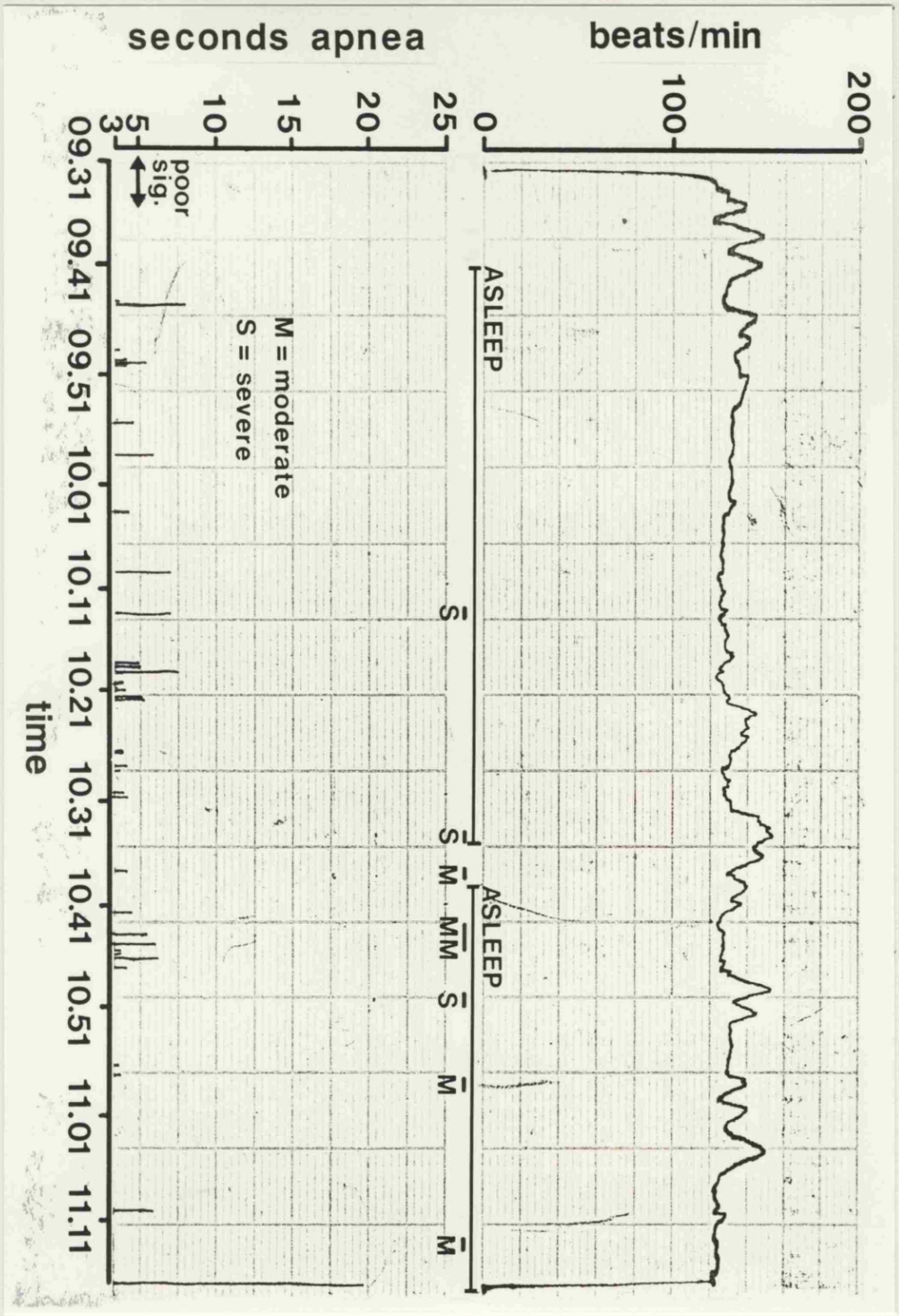


Figure 28: Respiratory tape of infant no. 22

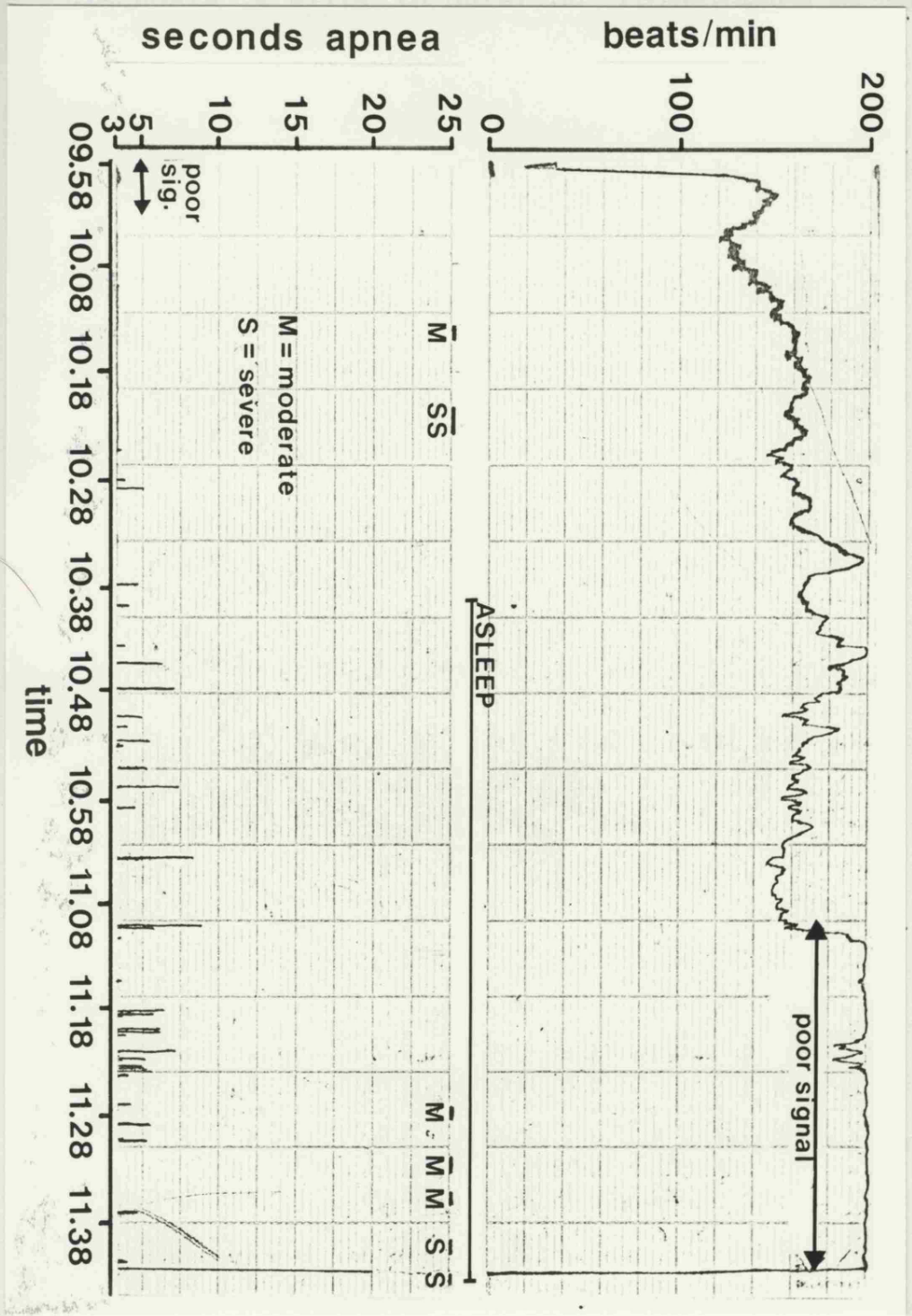


Table 33: Error in measuring study duration - and possible coincidence of apnea and GOR

No	Diagnosis	% error in duration of study*	Coincidence of reflux and apnea
22	'NEAR MISS'	-5.4	Possible
29	'NEAR MISS'	8.8	None
35	'NEAR MISS'	-2.5	None
66	'NEAR MISS'	14.0	No Reflux
69	'NEAR MISS'	5.0	None
70	'NEAR MISS'	2.8	None
12	SIB	-5.9	No Apnea
26	SIB	5.0	None
51	SIB	-1.2	None
68	SIB	-6.5	None
72	SIB	5.9	None
14	'EVENT'	.0	Possible
15	'EVENT'	.7	No Reflux
19	'EVENT'	.0	Possible
24	'EVENT'	3.3	None
30	'EVENT'	-2.3	None
33	'EVENT'	4.5	No Apnea
73	'EVENT'	-5.3	No Apnea
80	'EVENT'	1.0	None
18	VOMITER	1.2	Yes
27	VOMITER	4.1	None
59	VOMITER	.8	None

* duration of study from tape / observed duration x 100%

2 Discussion

This study of 22 infants - 14 of whom had respiratory symptoms which might have been related to GOR - does not confirm a relationship between GOR and apnea in the post-feed period.

The relation between GOR and apnea has been the subject of conflicting debate, reviewed earlier. To summarise the important relevant studies, Herbst et al (1981) and Spitzer et al (1984) have documented a close temporal association between GOR and apnea using polygraphic records. In contrast, Walsh et al compared the frequency of brief apneas during periods when GOR was detected (by lower oesophageal pH monitoring) to control periods when GOR was absent and concluded that, in general, apnea was not temporally related to the reflux of acidic gastric contents into the lower oesophagus. Walsh did find a small increase in the frequency of brief obstructive apneas during GOR. However, he pointed out as a limitation of his study that pH studies, which measure acid reflux into the lower oesophagus, may miss a significant association between GOR and apnea if apnea is related only to those episodes of GOR in which gastric contents reach laryngeal chemoreceptors. There may also be an underestimate of the importance of reflux if 'non-acid' reflux is occurring and is associated with apnea. In an attempt to overcome these criticisms, Menon et al (1985) studied the cardio-respiratory effects of episodes of GOR associated with overt regurgitation in a group of predominantly preterm infants. Such an approach ensures that GOR has reached laryngeal level and makes no assumptions about the pH of the refluxing fluid. Menon's studies showed an

increased frequency of short and long apneic spells in the 10sec interval immediately following onset of regurgitation compared with that during non-regurgitation control periods. In his view the apneas he observed were significantly longer than the brief normal 1 sec pauses in respiration associated with non-feeding swallows and speculated that this increased risk of apnea might involve failure of the laryngeal protective mechanisms allowing gastric contents to come into contact with laryngeal receptors known to be associated with apneic responses. Menon's study therefore also came down in support of an association between GOR and obstructive apnea.

In the current studies, the use of radionuclide scans to detect GOR avoided any possible confounding effects on respiration associated with the placement of pharyngeal or oesophageal probes and allowed the detection of reflux without reference to the acidity of the refluxing fluid. Scanning provided a more sensitive assessment of GOR than simple clinical observation of vomiting (see Chapter 5) and episodes of GOR reaching laryngeal level could be distinguished from those entering only the lower oesophagus. For these reasons, the techniques used in these studies provided a more physiological and sensitive assessment of GOR than the any of methods adopted in the above studies. It is therefore of interest that, using this sensitive non-invasive approach, a link between GOR and apnea was not observed.

While no clear evidence of a link between GOR and apnea was found there did appear to be a coincidence between central apneic pauses and sleep. This linkage of apneic pauses and

sleep is a pattern that has been seen frequently in traces from normal infants performed using this method of respiratory monitoring in other studies (Simpson, unpublished data).

The method of respiratory monitoring used in these studies was designed to detect absence of respiratory movements ie central apnea. It was therefore not possible to be certain that obstructive apnea (continuing and often exaggerated respiratory movement with absent airflow) did not occur. However, obstructive apnea is usually associated with the early onset of bradycardia. As stated above, bradycardia to a significant degree was only noted in one study and coincided with a respiratory pause but not GOR. It is therefore unlikely that prolonged obstructive apneas occurred in relation to GOR but brief periods of obstruction cannot be excluded.

3 Conclusion

In summary, a relation between reflux and apnea in the post-feed period in 22 infants, 14 of whom had cardio-respiratory symptoms which could have related to GOR, was not confirmed.

CHAPTER 8 page

GOR AND CARDIO-RESPIRATORY ABNORMALITIES DURING SLEEP

CHAPTER 8

GOR AND CARDIO-RESPIRATORY ABNORMALITIES DURING SLEEP

The final chapter describes the simultaneous pH and polygraphic studies performed in infants during sleep at night. These studies were designed to investigate the interrelation of GOR, cardio-respiratory abnormalities, and the sleep phase(s) during which these events occurred.

1 Patient groups

Table 34 (a, b & c) gives the clinical details of 24 infants, studied on 28 occasions. The primary group consisted of 17 infants studied on 21 occasions (Table 34a). All had been studied by radionuclide scan and in 14 severe GOR (to upper oesophageal level) had been demonstrated. Another, with a history of recurrent vomiting suggestive of GOR had only moderate GOR on scan. In the remaining 2 infants, who presented as 'near misses', GOR was not detected on scan. A further seven infants who did not have scans were also studied. They had presented as 'near misses' or with non life-threatening 'events' and were included as it seemed likely that some would have significant GOR. Tables 34b and 34c tabulates the clinical details of those with, and those without scans separately. Figure 29 shows the median age at study for each sub-group. The 'near miss' and 'events' subgroups were comparable in median age at study. The siblings of SIDS were slightly younger than

the other groups while the one infant with possible aspiration was older.

Table 34: Clinical details of infants studied at night

Table 34a

Group data

Groups	Numbers		Sex		Gestation	Age (yrs)	
	Patients	Studies	M	F	<=37wks	Median	Range
'Near miss'	9	9	6	3	1	.16	.09-.43
SIBS (i)	2	3	1	1	0	.12	.02-.17
'Events' (ii & iii)	12	15	8	4	3(2NK)	.17	.1-.42
Suspected tracheo-bronchial aspiration	1	1	1	0	0	.26	
Total	24	28	16	8	4	.16	.02-.43

2 infants (nos 61, 19) studied x2 (i&ii), 1 infant (no 20) studied x3 (iii)

Table 34b

Infants who had scans

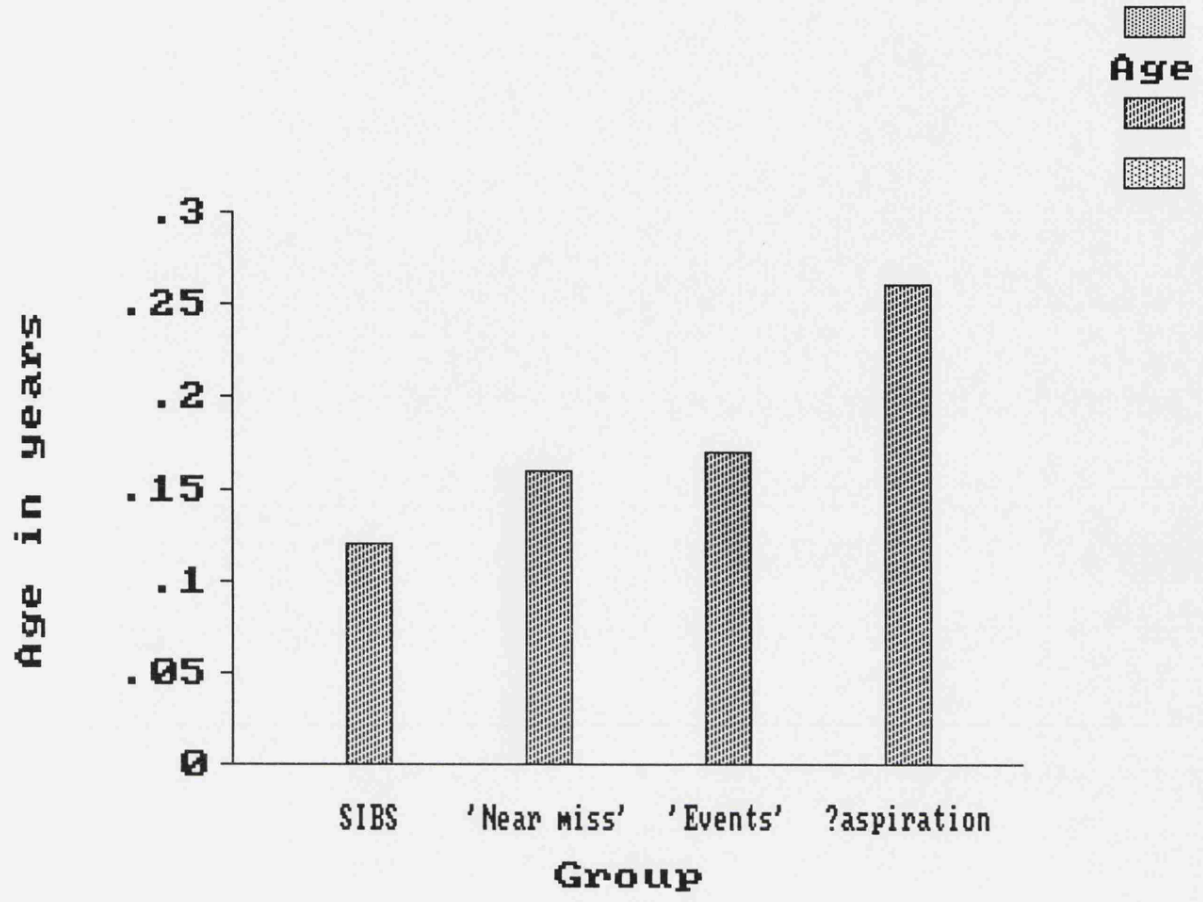
Groups	Numbers		Sex		Gestation	Age (yrs)		Scans	Reflux on scan
	Patients	Studies	M	F	<=37wks	Median	Range	7	5 SEV
'Near miss'	7	7	5	2	0	.15	.09-.29	2	1 SEV, 1 MOD
SIBS (i)	2	3	1	1	0	.12	.02-.17	7	7 SEV
'Events' (ii & iii)	7	10	5	2	1	.17	.1-.42	1	1 SEV
Suspected tracheo-bronchial aspiration	1	1	1	0	0	.26			
Total	17	21	12	5	1	.16	.02-.43	17	14 SEV, 1 MOD

Table 34c

Infants without scans

Groups	Numbers		Sex		Gestation	Age (yrs)	
	Patients	Studies	M	F	<=37wks	Median	Range
'Near miss'	2	2	1	1	1	.35	.25-.43
'Events'	5	5	3	2	3(2NK)	.25	.1-.32
Total	7	7	4	3	4	.24	.1-.43

Figure 29: Median age at night study (n=28)



2 Sleep

All studies were conducted at night during natural sleep by one observer (JP) who was present throughout. The mean overall duration of the studies was 268min (median 267, range 195-369min). The average time asleep was 200min (median 211min, range 89-261min). The difference reflected the time taken for the infant to fall asleep with all measurement transducers in place.

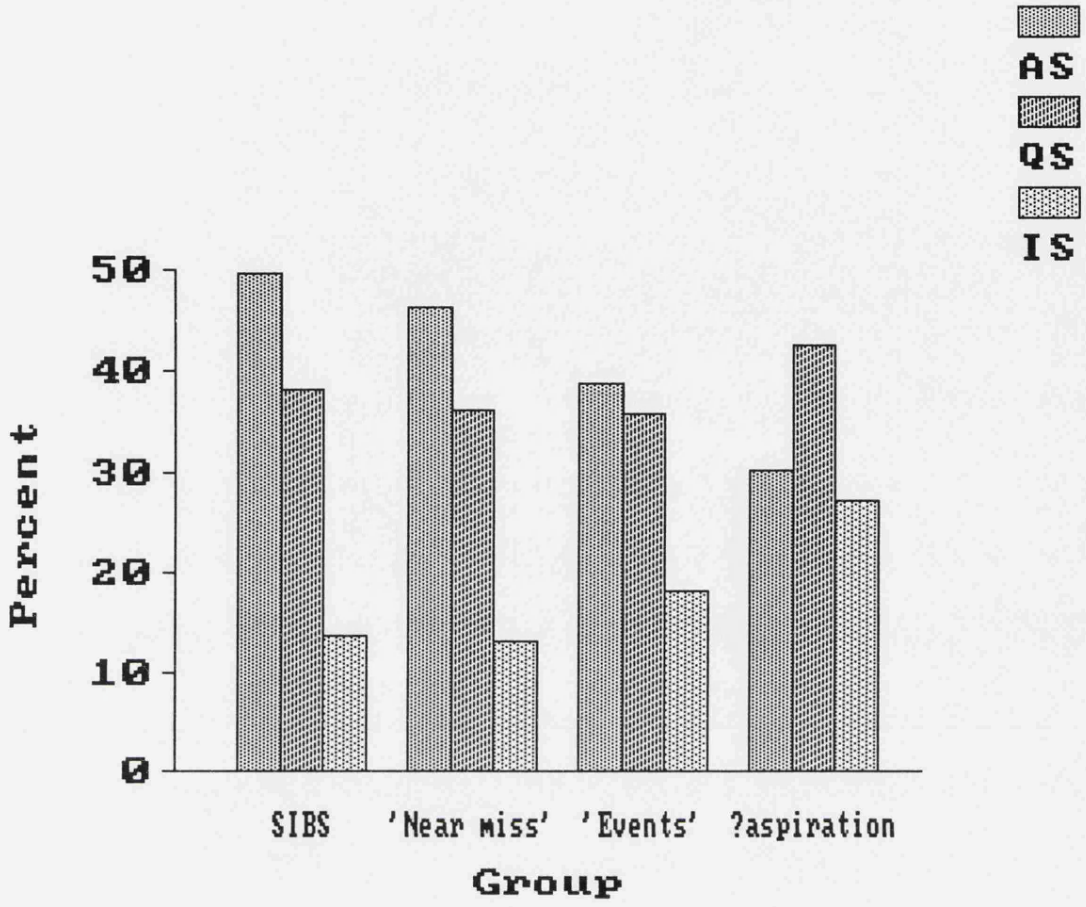
Table 35 details the percentage of time spent in each sleep phase. When compared with the median age at study for each group (see figure 29 which shows median age increasing in the order SIBS, 'near miss', 'events', ?aspiration) there was a decline in the percentage of time spent in AS as the median age increased (Figure 30).

Table 35: Percent time in each sleep phase during night studies

Studies n = 28

Group		% time in each sleep phase		
		AS	QS	IS
SIBS n = 3	Mean	50.3	35.2	14.6
	sem	1.6	3.2	3.8
	Median	49.7	38.3	13.6
	Range	47.9 - 53.2	28.7 - 38.5	8.5 - 21.6
'Near miss' n = 9	Mean	46.2	35.5	18.3
	sem	1.9	2.5	1.0
	Median	46.2	36.2	13.1
	Range	39.2 - 59.6	18.0 - 43.0	18.7 - 22.4
Non life-threatening 'events' n = 15	Mean	39.5	39.7	20.8
	sem	2.7	3.4	2.5
	Median	38.8	35.8	18.2
	Range	25.1 - 55.8	24.2 - 63.1	8.4 - 46.0
Suspected aspiration n = 1		30.2	42.6	27.2

Figure 30: Median %time in each sleep phase



3 Cardio-respiratory abnormalities

Table 36 gives the respiration and heart rate for each subgroup in AS and QS. Both were higher in AS than in QS. Mean heart rate was comparable in each subgroup for both AS and QS.

Table 37 shows the number and duration of central, mixed and obstructive apneas. 296 CAs occurred in 24 studies (21 infants). Four CAs lasted over 10sec but only one lasted longer than 15sec (18.8sec). There were no CAs longer than 20sec.

56 mixed and OAs occurred (Tables 37 & 38). Overall, obstructive or mixed apneas were identified in 12 infants (14 studies - no. 19 had OA in 2/3 studies, no. 20 had OA in 1/2 studies). Twenty seven (including 6 mixed apneas) were brief lasting >=3sec but <6sec while 26 (including 10 mixed) were prolonged lasting >=6sec. Only 7 OAs were longer than 10sec and none were longer than 15sec. All 7 longer than 10sec occurred in one infant (no. 191). All the infants with OA had at least 1 episode of GOR (>15sec) with pH below 4 on the sleep study. Four infants with no evidence of acid reflux on pH studies (nos. 196, 205, 206 & 275) had neither brief nor prolonged OA during the sleep study.

No significant bradycardias (<=80bpm for more than 10sec) were observed in any sleep study.

Table 39 gives the mean and median values for indices of CA within each subgroup. The results are broadly comparable with those obtained in 10 healthy infants at 55.5wks post-conceptional age by Abreu e Silva (1986), using identical

recording and analysis methods. Table 40, 41 list the findings for periodic breathing and gross body movements. For both periodic breathing and gross body movements the present results are again broadly similar to those obtained by Abreu e Silva in healthy infants.

With respect to the presence of OA, the infants studied differed significantly from the healthy controls described by Abreu e Silva (1986) in whom OAs were not observed. Thus the only cardio-respiratory finding which distinguished the study group from the 'normal' group described by Abreu e Silva was the presence of OA.

Table 36: Heart and respiration rates in different sleep phases

Studies n = 28

			Respiratory rate (/min)		Heart Rate (/min)	
Group			AS	QS	AS	QS
SIBS n = 3	Mean		42	35	129	124
	sem		5.2	3.8	10.5	8.5
	Median		41	37	120	116
	Range	low	33	28	117	115
		high	51	41	150	141
'Near miss' n = 9	Mean		35	33	126	123
	sem		1.3	2.3	3.5	4
	Median		33	24	128	124
	Range	low	32	46	106	99
		high	41	31	141	143
Non life-threatening 'events' n = 15	Mean		37	33	128	124
	sem		2	1.9	2.9	3.8
	Median		38	32	133	126
	Range	low	22	22	108	95
		high	50	47	147	148
Suspected aspiration n = 1			32	28	118	102

Table 37: Numbers and duration of apneas during night studies

Apnea duration (sec)	Apnea type: Central	Mixed	Obstructive	
>2 <=3	-*	0	3	
>3 <=6	-*	7	21	
>6 <=10	291	8	9	
>10 <=15	4	1	7	
>15 <=20	1	0	0	
>20	0	0	0	
Total	296	16	40	352

* central apneas less than 6sec were not counted

Table 38: Obstructive and mixed apneas during night studies

Group	Studies containing OAs (infants)	No of OAs in each sleep phase		Duration of obstructive apneas and sleep phase of occurrence		
				<3sec	>=3-<6sec	>=6sec
?Aspiration		AS	0			
n = 1		QS	0			
		IS	1	1		
	1 (1)	T	1	1		
Sibs		AS	1	1		
n = 3		QS	1			(1m)
		IS	0			
	1 (1)	T	2	1		(1m)
'Near miss'		AS	20	1	14 (5m)	5 (4m)
n = 9		QS	0			
		IS	1		1	
	5 (5)	T	21	1	15 (5m)	5 (4m)
Non life-threatening 'events'		AS	23		6	17 (5m)
		QS	0			
		IS	9		6 (1m)	3
n = 15	7 (5)	T	32		12 (1m)	20 (5m)

n = no of studies
m = mixed apnea

Table 39: Central apnea variables in various infant groups

		?aspiration	'Near miss '			Sibs			'Events'		
studies (n)		1	9			3			15		
			Mean	SEM	Median	Mean	SEM	Median	Mean	SEM	Median
Apnea Index	AS	.9	.5	.13	.6	.6	.53	.1	.9	.32	.3
	QS	.3	1.8	1.69	.1	.3	.18	.4	.4	.16	.2
	IS	.3	.8	.23	.5	.5	.18	.2	.9	.33	.3
	T	.5	1.0	.57	.6	.5	.29	.3	.7	.21	.2
Apnea attack rate	AS	.1	.1	.02	.1	.1	.08	.0	.1	.04	.1
	QS	.0	.2	.22	.0	.1	.02	.1	.1	.02	.0
	IS	.05	.1	.03	.1	.1	.02	.1	.1	.05	.0
	T	.1	.1	.07	.1	.1	.05	.0	.1	.03	.0
Episode of longest duration (sec)	AS	7.3	6.2	1.21	7.7	5.0	2.54	7.0	5.9	1.23	6.9
	QS	9.5	4.3	1.48	6.2	5.5	2.78	7.8	4.9	1.11	6.8
	IS	6.1	6.2	1.26	7.3	6.9	.80	6.2	6.4	1.32	6.3
	T	9.5	7.7	6.00	8.0	8.5	.20	8.5	6.0	1.23	7.6
Mean duration of apnea (sec)	AS	6.7	5.6	1.12	6.7	4.6	2.32	6.9	4.7	.91	6.7
	QS	9.5	3.8	1.20	6.2	4.9	2.44	7.2	4.5	1.00	6.7
	IS	6.1	5.8	1.18	6.4	6.8	.70	6.2	5.9	1.25	6.3
	T	7.2	6.2	.81	6.8	7.4	.40	6.9	6.1	.67	6.8
Apnea percent	AS	3.9	2.2	.59	2.7	2.5	2.32	.5	3.4	1.16	1.4
	QS	.2	4.7	4.34	.5	1.4	.71	1.8	1.7	.61	.8
	IS	1.4	2.7	.77	1.5	2.3	.63	2.6	3.4	1.29	1.3
	T	1.9	3.1	1.50	2.2	2.1	6.00	1.1	2.5	.77	.8
Sleep per cent	AS	30.2	46.2	1.94		50.3	1.6		39.5	2.7	
	QS	42.6	35.5	2.47		35.2	3.2		39.7	3.4	
	IS	27.2	18.3	.99		14.6	3.8		20.8	2.5	
Respiration rate	AS	32	35	1.31	33	42	5.2	41	37	2.0	38
	QS	28	33	2.29	24	35	3.8	37	33	1.9	32
Heart rate	AS	118	126	3.50	128	129	10.54	120	128	2.9	133
	QS	102	123	4.03	124	124	8.5	116	123	3.8	126

*note increased respiration rate in SIBS

Table 40: Periodic breathing and sleep phase in infant groups

		?Aspiration				'Near miss'			
		n = 1				n = 9			
Periodic breathing		Mean	Sem	Median	Range	Mean	Sem	Median	Range
Total duration	AS			4.3		1.3	.34	1.5	0 3.0
min/100min sleep	QS			.6		3.6	3.58	0	0 32.5
	IS			.8		2.6	1.10	1.6	0 10.3
	T			6		2.3	1.25	1.4	0 13.5
Number / 100min sleep	AS			10.3		2.9	.78	2.8	0 6.2
	QS			1.8		1.8	1.80	0	0 16.2
	IS			2.9		4.7	1.20	4.9	0 9.8
	T			4.7		2.9	.73	4.2	0 10.6

		Sibs					Non life-threatening 'events'				
		n = 3					n = 15				
Periodic breathing		Mean	Sem	Median	Range		Mean	Sem	Median	Range	
Total duration	AS	2.2	1.20	2.4	0	4.1	3.6	1.76	.3	0	24.2
min/100min sleep	QS	.3	.29	0	0	.9	.9	.31	0	0	2.9
	IS	.8	.42	1.2	0	1.4	1.6	.87	.5	0	12.9
	T	1.4	.68	1.5	0	1.7	2.0	.89	.5	0	10.6
Number / 100min sleep	AS	4.9	2.54	6.4	0	8.4	5.9	2.52	1.3	0	32.6
	QS	.8	.78	0	0	2.3	2.0	.75	0	0	7.9
	IS	2.4	1.25	3.2	0	4.2	3.7	1.79	1.7	0	26.7
	T	3.3	1.48	1.7	0	3.6	3.9	1.44	1.3	0	17.4

Table 41: Body movements and sleep phase in infant groups

		?Aspiration				'Near miss'			
		n = 1				n = 9			
Periodic breathing		Mean	Sem	Median	Range	Mean	Sem	Median	Range
Total duration	AS			2.5		5.3	.54	4.7	3.5 3.0
min/100min sleep	QS			.4		1.0	.29	.6	.0 32.5
	IS			18.1		18.8	2.27	18.1	8.9 10.3
	T			2.5		6.9	1.27	6.4	2.5 13.5
Number / 100min sleep	AS			30.8		27.0	3.01	27.0	9.9 38.1
	QS			3.3		5.0	1.32	5.0	.0 12.2
	IS			57.1		54.0	3.58	54.0	31.0 6.2
	T			10.3		22.0	1.89	23.0	10.3 16.2

		Sibs					Non life- threatening 'events'			
		n = 3					n = 15			
Periodic breathing		Mean	Sem	Median	Range		Mean	Sem	Median	Range
Total duration	AS	6.4	.74	6.1	5.3	7.8	6.3	1.81	4.6	.2 31.2
min/100min sleep	QS	1.1	.81	.3	.3	2.7	.8	.35	.2	.0 5.0
	IS	18.8	5.65	17.2	9.9	29.3	20.4	2.76	18.1	8.4 50.4
	T	5.4	1.27	5.2	4.7	6.4	7.9	1.58	7.3	1.5 26.6
Number / 100min sleep	AS	25.0	4.71	29.0	15.4	30.4	26.0	3.19	19.0	5.6 43.6
	QS	2.0	.94	2.0	.0	3.2	4.0	1.27	2.0	.0 15.9
	IS	59.0	3.32	58.0	53.1	64.6	55.0	5.98	47.0	22.0 102.6
	T	23.0	2.59	24.0	17.1	25.6	26.0	4.61	25.0	6.5 80.9

4 pH studies

4.1 Was GOR detected on pH studies?

Table 42 presents the pH data from 28 studies in 24 infants. 17 infants had been studied previously by radionuclide scan. In Table 43 the pH data is summarised while in Table 44 the amount and frequency of GOR is given for each subgroup studied.

Of the 17 infants who had previous radionuclide scans GOR by that method of detection was severe in 14, moderate in 1 and absent in 2. In the subsequent lower oesophageal pH study GOR was detected in 16 of these infants (20 studies) (Table 45). One infant (no. 24) with a previously positive radionuclide scan showed no evidence of reflux on pH study. On reviewing the scan, only one frame showed significant GOR. Following the scan he had been started on thickened formula feeds which he was still receiving at the time of the pH study. This could possibly have accounted for the negative pH study. Two infants (no 63, 66), without demonstrable GOR on scan, showed evidence of GOR on pH study.

Overall, therefore, there was a high degree of agreement between radionuclide scan and subsequent pH study as to whether reflux was present in each individual infant.

Table 42: Summary of pH data during night studies

Diagnosis	Reflux on scan	Study no	Duration (min)	% study pH <4	Longest episode pH <4 (min)	No drops >5min	Episodes pH <4 (no/hr)	Spikes pH <4 (no/hr)	Episodes pH >1 unit (no/hr)	Spikes pH >1 unit (no/hr)
'Event'		205	232	0	0	0	0	0	0	.5
'Event'	YES	196	271	0	0	0	0	0	0	0
'Event'		206	280.2	0	0	0	0	0	.6	0
'Near miss'	YES	275	243.6	0	0	0	0	0	.7	.2
'Event'		217	265.8	0	0	0	.2	0	.2	.5
'Near miss'		200	251.4	0	0	0	.2	0	.2	.5
'Event'		214	323.1	.2	.4	0	.7	.4	1.3	1.5
'Near miss'	YES	273	280.7	.4	1.2	0	.9	.2	1.3	.2
Sib	YES	272	288.7	.6	1.3	0	1.7	0	1.9	0
'Event'	YES	207	269.0	.8	2	0	1.3	2.5	3.1	4.2
'Near miss'	YES	215	253.9	1.0	1.4	0	1.2	.2	1.7	1.2
?Aspiration	YES	218	194.6	1.0	1.1	0	1.2	.9	1.5	2.5
'Near miss'	YES	265	261.9	1.6	2.4	0	.5	0	.5	0
'Event'	YES	208	238.8	1.6	1.3	0	1.3	1.8	1.5	3.3
'Near miss'		203	275.2	1.8	3	0	.7	0	2.2	0
'Event'	YES	201	281.7	2.5	6.5	1	.6	0	.9	.6
'Near miss'	NO	268	247	2.8	5.9	1	1.2	0	2.2	1.0
'Near miss'	NO	269	234.2	3.9	5.4	1	1.0	.3	1.5	.3
'Event'	YES	199	318.7	4.1	10.2	2	.6	0	1.5	.4
'Near miss'	YES	192	254.5	5.7	5.1	1	1.7	.2	1.9	.5
'Event'	YES	195	196.9	6.1	12	1	.3	1.2	.3	1.5
Sib	YES	270	304.6	6.9	10.2	2	1.2	.8	2.0	1.6
'Event'	YES	213	368.6	9.9	9.5	4	.8	.5	2.1	1.5
'Event'		193	281.2	14.5	22.4	3	.9	1.3	1.5	1.1
'Event'	YES	212	210.2	17.9	40.7	2	.6	3.7	.6	5.1
Sib	YES	267	299.5	22.6	45.2	3	1.6	0	1.6	.2
'Event'	YES	190	254.8	25	29.5	4	2.1	.2	2.1	.7
'Event'	YES	191	328.0	25.3	16.6	8	3.8	.7	5.3	1.1
n = 28		Median	267.4	1.7	2.7	0	.8	.2	1.5	.6
		Minimum	194.6	0	0	0	0	0	0	0
		Maximum	368.6	25.3	45.2	8	3.8	3.7	5.3	5.1
		Mean	268.2	5.6	8.3	1.2	.9		1.4	1.1
		sd	39.3	8.0	12.2	1.8	.8		1.1	

Table 43: Analysis of pH data

No Studies = 28

No patients = 24

	Length of study (min)	% study pH <4	Longest episode pH <4 (min)	No drops > 5min	Episodes pH <4 (no/hr)	Spikes pH <4 (no/hr)	Episodes >1 pH unit (no/hr)	Spikes >1 pH unit (no/hr)
Median	267.4	1.7	2.7	0	.8	.2	1.5	.6
Minimum	194.6	0	0	0	0	0	0	0
Maximum	368.6	25.3	45.2	8	3.8	3.7	5.3	5.1
Mean	268.2	5.6	8.3	1.2	.9	.6	1.4	1.1
sd	39.3	8.0	12.2	1.9	.8	.9	1.1	1.3
Infants with Scan (n = 17, studies = 21)								
Median	261.9	2.8	5.4	1	1.2	.2	1.5	.7
Minimum	194.6	0	0	0	0	0	0	0
Maximum	368.6	25.3	45.2	8	3.8	3.7	5.3	5.1
Mean	266.7	6.6	9.9	1.4	1.2	.6	1.6	1.2
sd	42.9	8.5	13.0	2.0	.8	1.0	1.1	1.4
Infants without Scan (n = 7, studies = 7)								
Median	275.2	0	.4	0	.2	0	.6	.5
Minimum	232	0	0	0	0	0	0	0
Maximum	323.1	14.5	22.4	3	.9	1.3	2.2	1.5
Mean	272.7	2.4	3.9	.4	.4	.2	.9	.6
sd	28.4	5.4	8.2	1.1	.4	.5	.8	.5

Table 44: pH studies - GOR in each group

Group		Duration min	%study pH<4	Longest episode min	No drops >5min	Episodes pH <4 (no/hr)	Spikes pH <4 (no/hr)	Episodes >1 pH unit (no/hr)	Spikes >1 pH unit (no/hr)
'Near-miss'	Median	253.9	1.6	2.4	0	0	.9	.3	1.54
n = 9	minimum	234.2	0	0	0	0	0	0	.2
	maximum	280.7	5.7	5.9	1	.3	1.7	1.2	2.2
	mean	255.8	1.9	2.9	.3	.1	.8	.4	1.4
	sd	14.8	1.9	2.1	.5	.1	.5	.4	.7
'Events'	Median	271	2.5	6.5	1	.4	.6	1.1	1.3
n = 15	minimum	196.9	0	0	0	0	0	0	0
	maximum	368.6	25.3	40.7	8	3.7	3.8	5.1	5.3
	mean	274.6	7.2	10.1	1.7	.8	.9	1.5	1.4
	sd	45.3	9.1	12.3	2.3	1.1	1.0	1.5	1.4
Sibs	Median	299.5	6.9	10.2	2	0	1.6	.2	1.9
n = 3	minimum	288.7	.6	1.3	0	0	1.2	0	1.6
	maximum	304.6	22.6	45.2	3	.8	1.7	1.6	2.0
	mean	297.6	10.1	18.9	1.7	.3	1.5	.6	1.8
	sd	8.1	11.3	23.2	1.5	.5	.3	.9	.2
?aspiration		194.6	1.0	1.1	0	.9	1.2	2.5	1.5
n = 1									

n = no of studies

Table 45: Summary of scan and pH detection of reflux

scans n = 17

	On scan *	On pH **
GOR present	15	16
GOR absent	2 (nos 63,66)	1 (no 24)

For infants with more than 1 pH study comparison is with study closest in time to scan

* reflux on scan = 1 or more frame per scan showing GOR

** reflux on pH = spikes and episodes >1 pH unit

4.2 Did the amount of reflux on pH study correlate with scans?

Although the results described above showed good agreement between the two tests on the presence of GOR was the amount and frequency of GOR detected similar for both tests?

To compare the two methods a non-parametric ranking statistic was used. The scan studies were ranked in ascending order by number of episodes GOR/hr (both moderate and severe) and also on the number of frames/hr showing GOR. Similarly, the pH studies were ranked on the number of pH drops below pH4/hr (spikes + episodes), separately on the number of pH drops >1pH/hr (spikes + episodes) and again separately on percent study pH <4. For infants, with more than one pH study the pH study closest in time to the scan study was used. The number of scan "episodes" and pH "drops" were compared (reflecting number of occurrences of GOR) and then the number of scan frames and the percent time pH<4 were compared (reflecting total duration of GOR).

For the number of episodes of GOR on radionuclide scan /hr compared to number of pH drops (both to pH<4 and by >1pH unit) there were significant correlations (Spearman's Rank correlation: 17 studies, $r = 0.54$ & $r = 0.54$, $p < 0.05$). There was no correlation, however, between percent time pH<4 and total number of frames per hour showing GOR (Spearman's Rank correlation: 17 studies, $r = 0.02$).

4.3 Did GOR occur during wakefulness or sleep?

Table 46 compares periods of sleep and wakefulness with respect to the number of pH drops >1pH unit.

pH drops were noted to occur frequently during the awake periods at the start of a study immediately after a feed and before the infant had fallen asleep. This usually represented only a short part of the study thus emphasising the frequent occurrence of reflux at this time. The data has not been normalised to a standard time because of the difficulty of determining the precise time for the infant drifting off to sleep. Hence the disparity between the two periods (wakefulness and sleep) in the occurrence of GOR is considerably understated.

Inspection of the number of pH drops after subdivision into spikes and episodes shows that the drops during waking periods contained a higher proportion of spikes (90/186) and episodes lasting less than 1min (56/186) than was observed during sleep - corresponding values 38/130 and 16/130 (Table 46). Thus, not only were drops more frequent during the awake post-feed period but they were also shorter.

Once the infant was asleep the duration of GOR and the number of pH drops falling below pH4 increased. Rather than being a specific feature of reflux during sleep the increasing acidity is more likely to be a reflection of time from the last feed.

These results are generally consistent with the earlier scan observations. Reflux was particularly common in the post-feed period and diminished with time. It will be recalled, however, that the scan studies suggested that the reflux lasted longer in the immediate post-feed period. This seems to be in conflict with the pH data. The results from the combined pH-scan studies throw light on this apparent discrepancy. In the immediate post-feed period pH falls less than 1pH unit were often observed (Figure 31 shows a typical example). Since these drops did not fulfil the criteria previously outlined they were not included in the analysis. When drops fell below pH4 they were brief. The degree and duration of pH drops were presumably limited by the neutralising effect of a recent milk feed. It seems likely that the pH study underestimated the extent of reflux present in the immediate post-feed period.

Table 46: Analysis of pH drops during asleep and awake periods

No of studies with reflux during awake periods = 26

Falls >1pH unit	Episodes	Spikes	Drops (spikes and episodes)
Number >=4	51	56	107
Number <4	45	34	79
Total	96	90	186

Episodes	
<=1min	55
>1min	41

No of studies with reflux during sleep = 20

Falls >1pH unit	Episodes	Spikes	Drops (spikes and episodes)
Number >=4	14	11	25
Number <4	78	27	105
Total	92	38	130

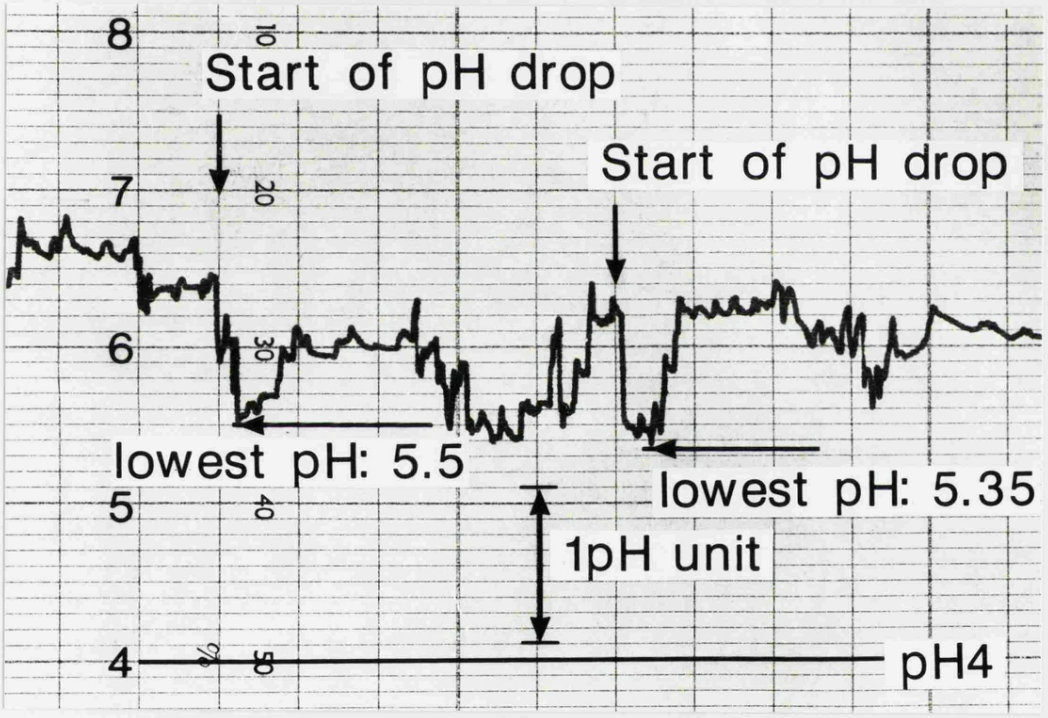
Episodes	
<=1min	16
>1min	76

Falls >1pH unit	Episodes	Spikes	Drops (spikes and episodes)
Awake	96	90	186
Asleep	92	38	130
Total	188	128	316

<pH4 = fall of pH >1pH unit to a lowest pH below 4

>=pH4 = fall of pH >1pH unit but lowest pH not below 4

Figure 31: Falls in pH <1 pH unit immediately post-feed



4.4 During which sleep phase does GOR occur?

Figure 32 shows the number of pH drops beginning in each sleep phase. Over 90% of drops started in AS or IS. When the indeterminate sleep phase was subdivided into epochs containing movement in excess of 15sec (ISM) or transitional epochs without movement (IST) it was found that reflux was largely confined to those epochs containing movement (ISM). There was a striking absence of reflux during quiet sleep, considering that for each group slightly over a third of the sleeping time was spent in this phase.

Not only did pH drops tend to occur during particular sleep phases they also tended to end in particular phases. Over 70% of pH drops lasting longer than 15sec (ie pH episodes rather than spikes) ended in AS or ISM (Figures 33 & 34). Occasionally, episodes started in one sleep phase (AS), lasted through the next phase (QS) and ended in a third (AS).

Figure 32: Sleep phase at start of pH drop

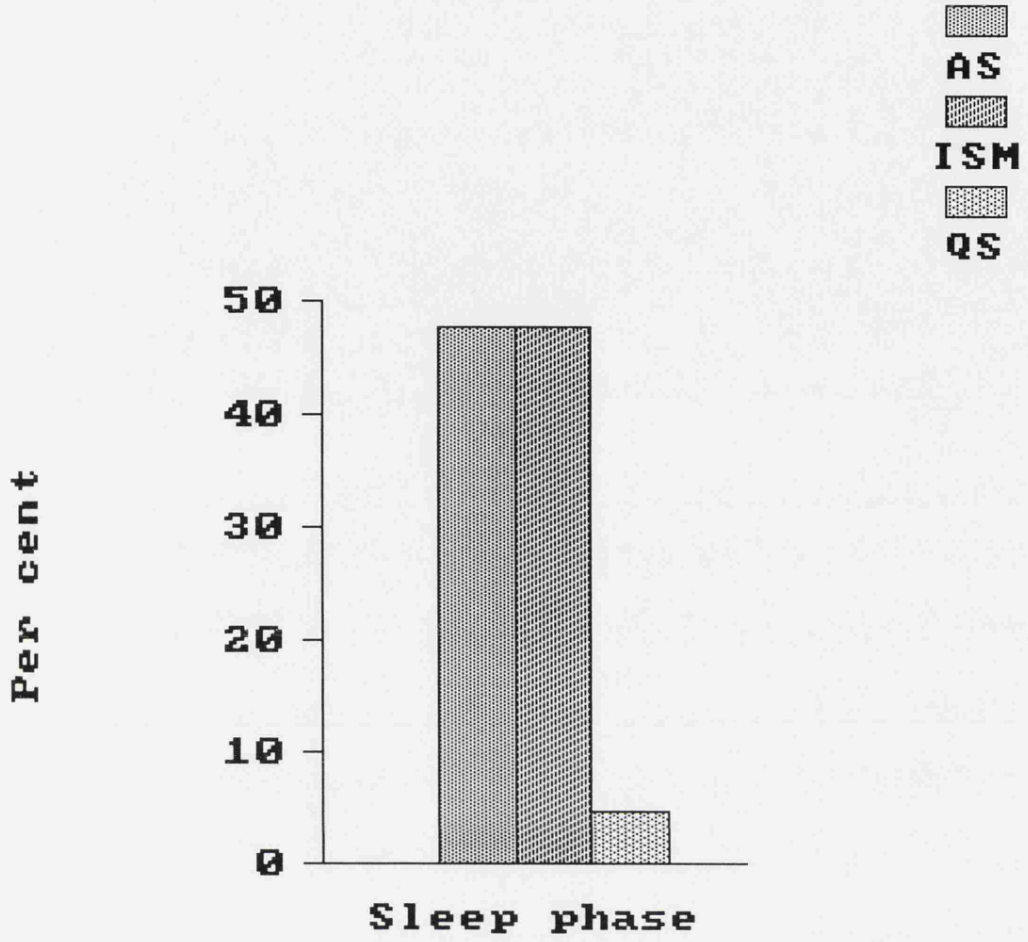


Figure 33: Sleep phase at end of pH drop (spikes & episodes)

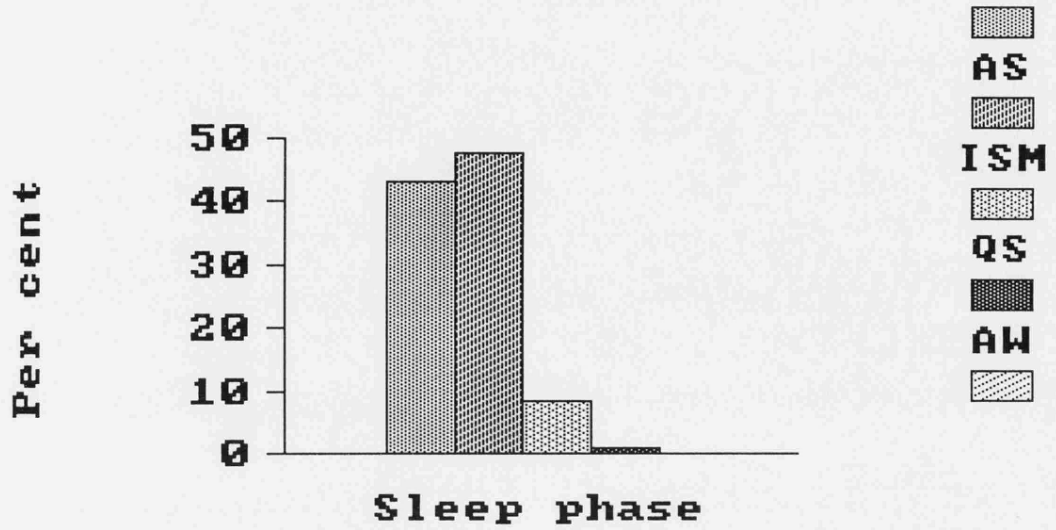
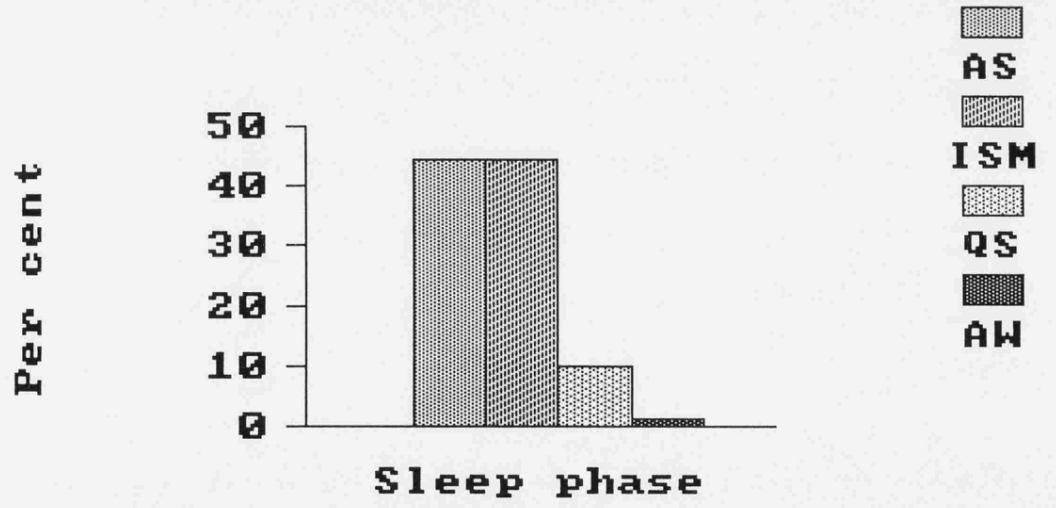


Figure 34: Sleep phase at end of pH drops (episodes alone)



4.5 Did pathological GOR occur?

Was the extent of GOR detected in the studies at night pathological? Attention has been drawn to the paucity of data from 24 hour pH studies in normal infants. For short duration studies such as those reported here control data are not available in the literature. Information on GOR from the current short duration pH studies has, therefore, been extrapolated to a 24hr period to provide a basis for comparison with the data from previous 24hr pH studies in "normal" subjects. Such extrapolation must inevitably provide only a crude estimate for comparison.

Table 47 lists data, presented and discussed earlier, from published sets of "normal" lower oesophageal pH data (Johnson and Demeester 1974, Boix-Ochoa et al 1980, Koch and Gass 1981, and Berquist and Ament 1985 Tables 4 & 5). In each study the pH probe was sited in the lower oesophagus. The data of Johnson relates to adult volunteers, that of Boix-Ochoa to infants and children of age range 2mths - 6yrs, and Koch and Gass's to infants between 6 - 30wks. Berquist and Ament also refer to an infant population (13.5 +/- 12.7wks) but in contrast to the other studies the infants were fed acidified feeds with a pH <4. This results in a greater number of episodes of GOR being observed since, as there are no non-acid episodes of GOR, all episodes are noted. Koch and Gass's studies lasted between 20 and 24hrs while the others were of twenty four hour duration.

In the same table the number of infants in the current studies whose pH indices exceeded the mean <u>plus</u> 2sd level of these earlier published studies is detailed. It can be seen

that between 9 - 13 (30 - 46%) infants under study here exceeded the 2sd level of Boix-Ochoa et al and Koch and Gass for percent time pH <4. In contrast, between 2 - 11 infants (7 - 39%) exceeded the 2sd level for number of episodes. This disparity probably reflects the observation noted earlier that there are fewer but longer episodes of GOR during sleep (when the present studies were performed). There is confirmation for this view in the larger number of the present studies exceeding the mean plus 2sd level for episodes >5min (13, 46%). The number of studies exceeding the mean plus 2sd level for any of the pH indices reported by Berquist and Ament is consistently lower. This presumably arises because Berquist and Ament are detecting more episodes of GOR because of their use of acidified feeds.

By these criteria, pathological GOR was observed in between 1/3 - 1/2 of infants in the present series. These infants were not confined to any particular sub-group such as the 'near miss' group but were representative of the overall study population.

Table 47: Numbers of present studies exceeding 2sd level of "normal data"

	Group and number cases studied			
	(A)	(B)	(C)	(D)
	15	20	7	11
Index	Mean + 2sd	Mean + 2sd	Mean + 2sd	Mean + 2sd
Time pH <=4 (%)	4.23	5.06	1.91	8.70
no of present studies >mean+2sd	9	9	13	6
Longest episode (min)	9.22	22.45	7.69	20.60
no of present studies >mean+2sd	9	3	9	4
No of episodes >5min / 24hr	3.08	5.83	.99	
no of present studies >mean+2sd	13	13	13	
No of episodes / 24hr	50.14	27	46.75	67.20
no of present studies >mean+2sd	2	11	2	1

(A) Johnson and Demeester, 1974 - adult volunteers

(B) Boix-Ochoa et al, 1980 - infants and children (2/12 - 6yrs)

(C) Koch and Gass, 1981 - infants (6 - 30wks)

(D) Berquist and Ament, 1985 - infants (13.5 +/- 12.7wks), acidified feeds

4.6 GOR and cardio-respiratory abnormalities

The relation between reflux on pH study and cardio-respiratory abnormalities was considered next.

Obstructive apnea was the only significant cardio-respiratory abnormality in the study group. Since in some studies an association between OA and GOR has been observed it was felt appropriate to compare the duration and extent of GOR detected on pH study with the number of OAs occurring over the same time period.

In the first instance, the percent time pH <4 in the sleep studies was compared with the number of OAs using a non-parametric statistic (Spearman's Rank correlation: 28 studies, $r = 0.28$). No significant correlation was found. The results were similar for the number of drops below pH 4 per hour (spikes and episodes combined). Thus neither the duration or frequency of acidic reflux was related to the frequency of OA.

While this conclusion held for the group, one infant (study no. 191), from the 'events' subgroup, was distinctly aberrant. This infant had the largest number of OAs (17) overall and all occurred when the pH was less than 4. This infant had a history of crying and excessive vomiting but had no history of 'near miss' episodes. Clinically, there was no suspicion that frequent obstructive episodes were occurring.

This finding of one infant differing markedly from the group as a whole, in terms of GOR and cardio-respiratory abnormalities, has been a feature of other studies (Walsh et al 1981, Ariagno et al 1982).

4.7 Sequence of abnormalities

The previous section detailed the lack of correlation between the duration of reflux and the frequency of OAs in these studies.

However, some studies in the literature suggest a relation between apnea and reflux with respect to the occurrence of GOR rather than to the overall amount of reflux (Walsh 1981, Spitzer 1984, Menon 1985). If correct any relation between reflux and cardio-respiratory abnormalities would be more likely to occur in the moments surrounding the occurrence of an episode of GOR. If GOR is causally related to cardio-respiratory abnormalities then it might be anticipated that specific sequences of events would be observed eg all OAs might be preceded by GOR.

In order to investigate the possibility of a relation between GOR occurrence and cardio-respiratory abnormalities, each pH drop >1pH unit and every occurrence of CA >6sec, OA >3sec, gross body movement and dips in transcutaneous oxygen >5mmHg during sleep was identified. Each of these findings was then taken in turn as the incident event and the chart recordings were analysed for the occurrence of the other events in the 60sec before and after the start of the incident event.

For example, each pH drop >1pH unit was identified and the presence of CA >6sec, OA >3sec, gross body movement and dips in transcutaneous oxygen >5mmHg in the 60sec before and after the start of the pH drop. Tables 48 - 52 summarise the findings.

From Tables 48, 49, and 50 it is apparent that there was no association between pH drops and CA or OA. Both CA and OA occurred infrequently in relation to the occurrence of GOR and were as likely to be followed as preceded by it.

The number of gross body movements far exceeded the cardio-respiratory events (Table 51). It can be seen that, as with pH, most gross body movements occurred during active or indeterminate sleep phases. There were more pH drops documented in relation to gross body movement than were recorded in relation to CA or OA. However, only a small proportion of gross body movements (<7%) was associated with a pH drop.

During the course of the studies it was not uncommonly observed that a pH drop occurred during or just after a gross body movement. This is reflected in Table 48 & 51 where an excess of movement is recorded before pH drops. The numbers confirm that the pattern, movement - pH drop, was common. This sequence, movement - pH drop - movement was the only clearly identifiable relation between any of the events studied. Figure 35 illustrates this pattern with an example taken from one trace. Table 53 details the results for each individual infant in relation to gross body movements. It can be seen that this sequence of movement preceding pH drop occurred across the range of diagnostic groups studied and was not confined to one particular subgroup.

It was also empirically observed during the studies that some CAs occurred immediately after a movement when the infant took a large breath or sigh and then had a brief respiratory pause. From Table 49 & 51 it can be seen that there was a slight excess of CA after movement in keeping with the above observation.

The number of dips in PtcO2 was small (Table 54). 85 dips greater than 5mmHg were recorded in total. Of these, there were only 6 dips more than 10mmHg, with the largest being 21mmHg. In almost every case the dip appeared to follow some "event", be it a pH drop or a cardio-respiratory abnormality or movement (Table 54). This may in part be an artefact due to the difficulty in timing the onset of a drop in PtcO2 precisely because of the 10-20sec phase delay inherent in PtcO2 monitoring. A careful attempt was made to allow for this lag during analysis and to match events as precisely as possible.

PtcO2 dips often occurred in relation to more than 1 event eg a movement and a pH drop. In Table 54 only the <u>first</u> event to occur in the minute before or after is tabulated. Dips occurred only on two occasions in relation to pH drops. Most dips appeared to be related to respiratory events. The numbers in Table 54, however, underestimate the effects of gross body movements on PtcO2. In many cases movement of the infant either dislodged the sensor or induced an artefact in the PtcO2 trace at the moment of movement. Such sections of the trace were unsuitable for analysis. Hence, the effect of movement on PtcO2 is underestimated. The susceptibility to movement artefact

represents a limitation in current techniques for PtcO2 monitoring.

Table 48: pH and cardio-respiratory abnormalities: pH as the incident event

Sleep phase	pH drops >1pH unit	Movement		Central apnea >6 sec		Obstructive apnea >3sec		PtcO2 dips >5mmHg	
		before	after	before	after	before	after	before	after
AS	62	42	28	4	4	3	3	1	6
QS	6	0	1	0	0	0	0	0	0
IS	62	66	21	4	1	0	1	0	2
Total	130	108	50	8	5	3	4	1	8

before = in 60 sec before the onset of pH drop
after = in 60 sec after onset of pH drop

Table 49: Central apnea as the incident event

Sleep phase	No of central apneas >6sec	Gross body movement		pH drop >1pH unit		pH<4*	Obstructive apnea >3sec		PtcO2 dips >5mmHg	
		before	after	before	after		before	after	before	after
AS	133	57	46	4	4	10	1	0	1	19
QS	107	3	7	0	0	8	0	0	0	1
IS	57	33	21	1	4	6	0	0	0	1
Total	297	93	74	5	8	24	1	0	1	21

before = in 60 sec before onset of central apnea
after = in 60 sec after onset of central apnea
* pH <4 at time of occurrence of central apnea

Table 50: Obstructive apnea as the incident event

Sleep phase	Obstructive apneas >3sec	Gross body movement		pH drop >1pH unit		pH<4*	Central apneas >3sec		PtcO2 dips >5mmHg	
		before	after	before	after		before	after	before	after
AS	44	16	18	3	3	17	0	1	2	15
QS	1	1	0	0	0	1	0	0	0	0
IS	11	4	3	1	0	3	0	0	0	2
Total	56	21	21	4	3	21	0	1	2	17

before = in 60 sec before onset of obstructive apnea
after = in 60 sec after onset of obstructive apnea
* pH <4 at time of occurrence of obstructive apnea

Table 51: Movement as incident event

Sleep phase	No of movements	Central apnea >6 sec		pH drop >1pH unit		Obstructive apnea >3sec		PtcO2 dips >5mmHg	
		before	after	before	after	before	after	before	after
AS	631	45	51	19	40	18	16	13	20
QS	80	7	2	1	0	0	1	0	2
IS	565	22	40	30	68	3	4	4	21
Total	1276	74	93	50	108	21	21	17	43

before = in 60 sec before onset of movement
after = in 60 sec after onset of movement

Table 52: PtcO2 dips as the incident event

Sleep phase	No of PtcO2 dips >5mmHg	Gross body movement		pH drop >1pH unit		pH<4*	Central apnea >6sec		Obstructive apnea >3sec	
		before	after	before	after		before	after	before	after
AS	63	21	14	7	1	17	19	1	16	2
QS	3	2	0	0	0	0	1	0	0	0
IS	19	20	3	1	0	1	1	0	1	0
Total	85	43	17	8	1	18	21	1	17	2

before = in 60 sec before onset of PtcO2 dip
after = in 60 sec after onset of PtcO2 dip
* pH <4 at time of occurrence of PtcO2 dip

Figure 35: Illustration of the sequence "movement - pH drop"

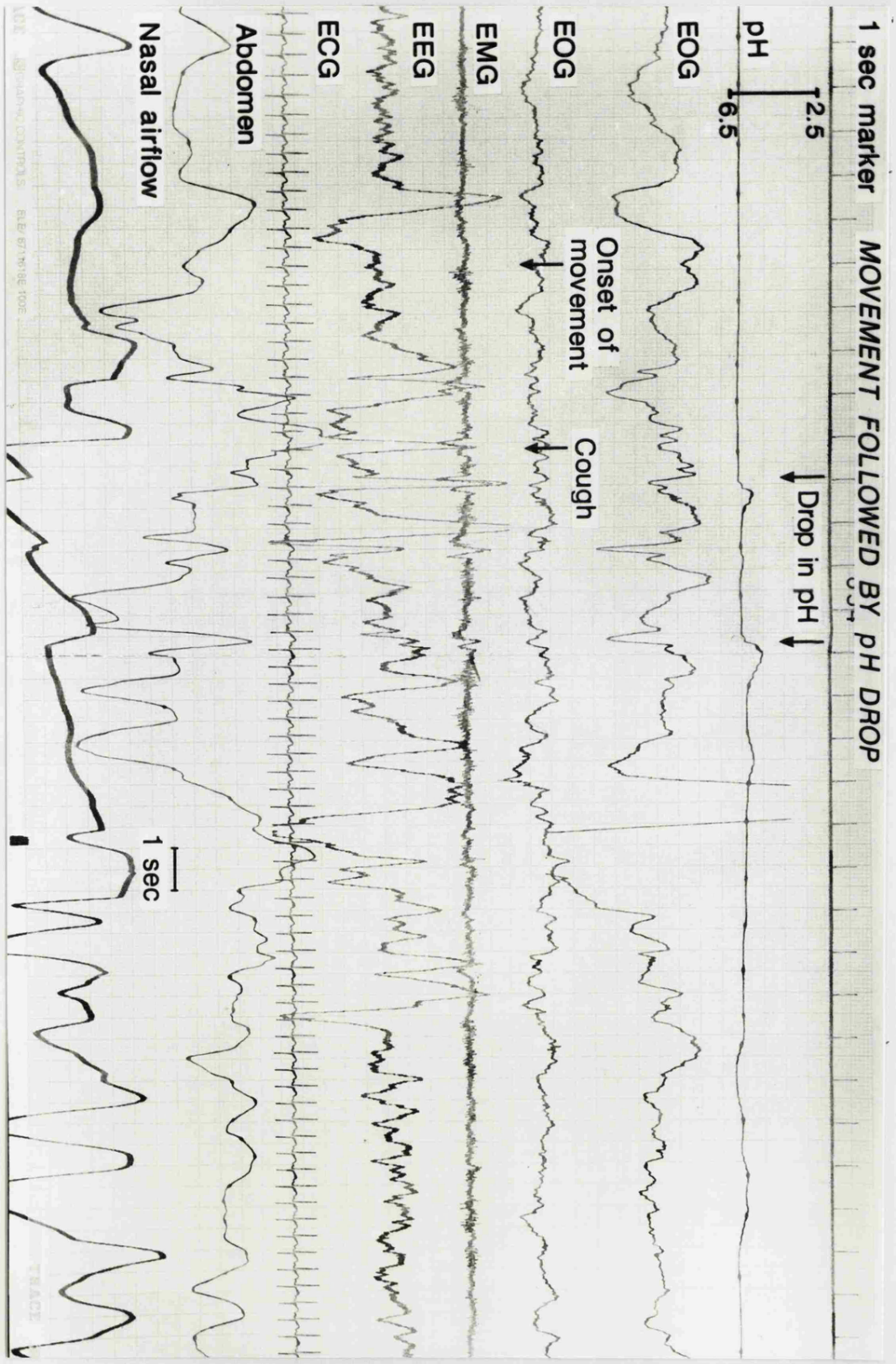


Table 53: pH & Movement - individual data for pH drops >1pH unit

		Sleep Phases							
		AS		QS		IS		Total	
Study	Diagnosis	pH drop		pH drop		pH drop		pH drop	
		before movement	after movement	before movement	after movement	before movement	after movement	before movement	after movement
218	?ASPIR	0	0	0	0	0	2	0	2
217	'EVENT'	0	0	0	0	0	0	0	0
214	'EVENT'	0	0	0	0	0	2	0	2
213	'EVENT'	2	5	0	0	5	6	7	11
212	'EVENT'	0	0	0	0	0	1	0	1
208	'EVENT'	0	0	0	0	0	1	0	1
207	'EVENT'	1	4	0	0	15	18	16	22
206	'EVENT'	0	0	0	0	0	0	0	0
205	'EVENT'	0	0	0	0	0	1	0	1
201	'EVENT'	1	1	0	0	0	0	1	1
199	'EVENT'	0	2	0	0	0	1	0	3
196	'EVENT'	0	0	0	0	0	0	0	0
195	'EVENT'	0	0	0	0	0	0	0	0
193	'EVENT'	4	6	0	0	0	3	4	9
191	'EVENT'	5	6	0	0	3	11	8	17
190	'EVENT'	1	0	0	0	0	9	1	9
275	'NEAR MISS'	0	0	0	0	0	0	0	0
273	'NEAR MISS'	0	0	0	0	0	0	0	0
269	'NEAR MISS'	1	2	0	0	0	0	1	2
268	'NEAR MISS'	0	0	0	0	1	1	1	1
265	'NEAR MISS'	0	0	0	0	0	1	0	1
215	'NEAR MISS'	0	2	0	0	0	0	0	2
203	'NEAR MISS'	0	2	0	0	2	4	2	6
200	'NEAR MISS'	0	0	0	0	0	0	0	0
192	'NEAR MISS'	2	3	1	0	1	3	4	6
272	SIB	0	0	0	0	0	0	0	0
270	SIB	1	5	0	0	2	4	3	9
267	SIB	1	2	0	0	1	0	2	2
Total		19	40	1	0	30	68	50	108

28 studies

Table 54: TcPO2 Dips >5mmHg during sleep

No of studies = 28

3 - PtcO2 not measured

3 - technical failures

22 satisfactory PtcO2 studies

Dips >5mmHg	Present	Absent	
Number of studies	15	7	
No of dips			
		>5mm - <=10mmHg	>10mm Hg
Total		79	6
Related to movement		25	
Related to cardio-respiratory events		51	6
	CA	11	
	OA	6	4
	Mixed apnea	7	
	Periodic breathing	13	
	Cough	1	2
	Not clearly defined	13	
Related to pH drop		2	
Unrelated to above		1	

5 Discussion

5.1 Sleep

The decrease with age in the amount of time in AS confirms previous observations in normal infants (eg Abreu e Silva 1985).

5.2 Cardio-respiratory variables

The respiration rate and heart rate for each different group in AS and QS show a consistent pattern with the values for AS always slightly higher than the values for QS. The small difference between active and quiet sleep is well recognised in normal infants (Carse et al 1981, Curzi-Dascalova et al 1981, Katona et al 1980). Carse et al (1981), for example, studied heart and respiration rates during the first six months of life in 10 normal infants. Their studies were carried out from 9am for a complete inter-feed nap. At three months, they reported a mean respiration rate of 36+/-2.4 in active sleep and 33+/-1.9 in quiet sleep, and a heart rate of 134+/- 3.58 in active sleep and 128+/-3.0 in quiet sleep. While not directly comparable the values obtained in the 28 studies described here are broadly similar for respiration rate but somewhat lower for heart rate. The values for both heart rate and respiration rate are, however, very similar to those of Abreu e Silva (1985) obtained on similar groups of infants during studies of sleep at night using identical technical and analytical methods.

5.3 Apnea

Appropriate control data is difficult to find for indices of apnea. The results obtained in the present studies for both CA and periodic breathing are broadly comparable to data obtained on 10 healthy infants at various ages by Abreu e Silva (1985) using identical methods of recording and analysis.

For OA, the present findings contrast with those of Abreu e Silva, for normal healthy infants. Abreu e Silva did not detect either brief (>=3sec <6sec) or prolonged (>=6sec) OAs in normal infants. In the present studies 12 infants (14 studies - no. 20 had OA in 2/3 studies, no. 19 had OA in 1/2 studies) were identified with obstructive or mixed apneas. 27 (including 6 mixed apneas) were >=3sec <6sec and 26 (including 10 mixed) were >=6sec. OAs were not confined to the 'near miss' group. Thus, the infants studied appeared to have more OA than a normal comparison group.

All infants with OA had at least one episode of GOR with pH <4 during the night studies. Conversely, 4 infants with no acid reflux in the sleep pH studies also had no evidence of OA (nos. 196, 205, 206 & 275). These observations are of interest since in some studies OA has been associated with GOR. It will be recalled that the infants studied here were selected because they had GOR or because GOR was suspected on the basis of history and that the sleep pH studies confirmed that GOR was present in most infants. This suggests that there may be some relationship between OA and GOR.

5.4 Amount of GOR

5.4.1 Scan versus pH probe

Statistical analysis showed that the number of episodes of GOR per hr demonstrable by radionuclide scan was significantly correlated with both pH drops to pH <4 and pH drops >1pH unit. There was no correlation between number of frames per hr showing GOR and %time pH <4.

The first results confirm that there is general agreement between radionuclide scans and lower oesophageal pH studies in the assessment of the occurrence of GOR. It might be expected that agreement between scan and pH study would be better for large falls in pH (>1pH unit) irrespective of the final pH because the possibility of non-acid reflux in the post feed period might prevent the pH always falling to pH 4 or below. However, there was little difference in the degree of correlation between scan findings and pH drops to pH <4 or pH drops >1 unit. The degree of agreement between radionuclide scans and lower oesophageal studies was not perfect (Spearman's Rank correlation: 17 studies, $r = 0.54$ & $r = 0.54$). This is hardly surprising since the studies were not performed simultaneously. Other factors such as sleep wake differences and/or diurnal variation in the occurrence of GOR could have accounted for the differences observed.

The lack of correlation between number of frames/hr showing GOR and %time pH <4 (Spearman's Rank correlation: 17 studies, $r = 0.02$) is at first surprising since the number of frames per hour on scan and % time pH <4 should both reflect

the duration of GOR. However, since non-acid reflux is not uncommon in the immediate postprandial period much of the GOR detected by scan will not be reflected in %time <pH4. Also, factors such as sleep wake difference are again likely to change the occurrence of GOR. Hence, this lack of correlation might have been anticipated.

Overall, the results show a satisfactory level of agreement, both in terms of the presence and amount of GOR, between the two techniques performed on different days and at different times of day on the same infants.

5.4.2 Awake vs sleep

The finding in this study that GOR occurred predominantly in AS or IS with movement can be compared those of Jeffery et al (1980) and Walsh et al (1981). Both groups of investigators report data on the occurrence of GOR during different sleep phases in infants with apnea.

Jeffery et al (1980) studied 20 'near miss' infants aged between 2 and 34 weeks. GOR - detected by lower oesophageal pH studies - was common, and seen during awake periods in 18. During sleep, GOR occurred during active sleep in 13 and was not observed during quiet sleep. The reflux episodes occurring during sleep were, overall, of longer duration than those occurring during awake periods. These findings mirror closely those in the present study.

Walsh et al (1981) documented 63 episodes of GOR during sleep. In their studies, GOR occurred during wakefulness on 39 (61.9%) occasions during quiet sleep in 18 (28.6%) occasions and during AS in 6 (9.5%). This difference from the present study and from the results of Jeffery can not be explained.

It is of interest that the amount of GOR observed by both Walsh et al (1981) and Jeffery et al (1980) was less than in the present study.

5.4.3 Pathological or physiological?

The results tabulated earlier (Table 49) showed that in the present studies pathological GOR (ie indices of GOR exceeding the +2sd level) was observed in between 1/3 - 1/2 of infants.

This would seem at variance with data from Seibert et al (1983). Their study was designed to assess the diagnostic accuracy of scintigraphy compared with 1hr pH probe monitoring. 49 infants and children suspected of GOR were studied simultaneously with radionuclide scans and lower oesophageal pH studies. 47 subsequently underwent 24 hr lower oesophageal pH studies. In the radionuclide scans the dose of Tc99m colloid was approximately half (3.7MBq) the amount used in the present studies but the volumes of feed given were comparable. GOR on scan was assessed by selecting areas of interest over the lower, mid and upper oesophagus and generating a time-activity curve for the 60min study. Reflux episodes were detected as spikes of increased activity above the background. The shortest

duration of pH drop that could be resolved was not documented. The pH probe was positioned in a position similar to the present studies ie 1/8 of the distance orad to the lower oesophageal sphincter. In the analysis of the simultaneous studies, a drop in oesophageal pH below 5 was considered significant with milk in the stomach. No justification was provided for this choice of pH 5. However, it would largely overcome the problem of non-acid reflux documented in the present studies. The subsequent 24hr lower oesophageal pH studies were judged positive according to whether the formula of Euler and Byrne (1981) was exceeded (X + 4Y >=50, where X was number of episodes of pH less than 4 and Y was number lasting more than 5min during the 24hr period). Seibert et al found a strong correlation between scintigraphy, simultaneous 1hr pH probe monitoring and later 24hr pH monitoring test in the 47 infants studied. If Euler and Byrne's recommendations for the 24hr study were accepted as the "gold standard", only one episode of GOR was necessary on 1hr scintigraphy for the 24hr pH study to be positive. Reflux occurring at any time during the 1hr monitoring was significant.

The present data, and their relation to other "normal" values from controls, suggests that scintigraphy does not correlate as well with subsequent 4-5hr pH studies as Seibert et al found for scan, 1hr pH and subsequent 24hr pH studies, and that false positives may occur on the scans. It is somewhat difficult to reconcile completely the current data with Seibert et al's findings. However, two differences should perhaps be emphasised. In the current studies the pH values were extrapolated from a short duration pH study (and not from a full 24hr study) and hence may underestimate the occurrence of

GOR as a consequence of a sampling error in a short duration study. A more important difference may be the lower dose of isotope used in Seibert et al's investigations. From the studies described earlier (Chapter 6) on the sensitivity of radionuclide scanning in detecting GOR, the lower isotope dose used by Seibert et al will have diminished the sensitivity of the radionuclide scan in detecting GOR by approximately 50% compared to the present studies. This is likely to have diminished the number of "false" positives in Seibert's study. The apparent discrepancy in the present studies in the pH results vis a vis the radionuclide scans may then be partly accounted for.

However, overall it remains difficult to reconcile all the reports completely and arrive at a definite answer to the question "is the amount and frequency of GOR physiological or pathological?" The lack of radionuclide data on normal infants, under identical experimental circumstances, for comparison makes this an unanswerable question. On balance, it would appear that in approximately 1/3 to 1/2 of the studies the GOR was of "pathological" degree by published criteria.

The difficulty in assessing whether GOR is pathological again emphasises the need to compare index groups with a group of normal infants studied using identical methods in similar circumstances. The present uncertainty reflects this lack of control data from a suitable comparison group.

It must be emphasised that while GOR may not have been of pathological degree in every infant, there was at least one episode with pH <4 in all but 4/28 sleep studies (4 infants).

This is of importance since abnormal cardio-respiratory events have been noted in relation to the occurrence of GOR (Walsh et al 1981, Spitzer et al 1982) and any relation between GOR and cardio-respiratory abnormalities may be qualitative rather than quantitative.

5.5 Sequence of abnormalities

The data from the combined pH and polygraphic sleep studies did not confirm a relationship between the occurrence of GOR and cardio-respiratory abnormalities. The only definite pattern observed was that GOR was frequently preceded by gross body movement.

The findings can be compared with those in studies where detailed investigation has been made of the temporal relation between GOR and cardio-respiratory abnormalities using polygraphic techniques (Walsh et al (1981), Ariagno et al (1982), Spitzer et al (1982), Menon et al (1985)).

Walsh et al (1981) described 14 infants (6 preterms) with pathological GOR and abnormal apnea. All infants had simultaneous pH and sleep monitoring. Each infant had between 14-16 hours of pH monitoring with the probe placed using an identical method to the present studies. An episode of GOR was defined as a pH reading less than pH 4 for a minimum of 15sec and GOR scores were calculated using the scoring system of Jolley et al (1978)'. Overall only 63 episodes of GOR were observed in the 14 infants. This seems a small number of GOR episodes for infants with supposedly pathological GOR. Sleep

was monitored for 6-9 hrs in total with continuous pH monitoring throughout the period. Respiratory pauses longer than 3sec were noted and classified as either central or OA. Walsh did not find any temporal relationship between GOR and apnea in most instances since the number of segments that contained apneas of any type were similar for segments with GOR and appropriate (non-GOR) comparison segments. It was noted that GOR onset was accompanied by OA more frequently than were similar intervals of control segments. However, OA occurred at GOR onset in only 15.9% of all recorded GOR episodes. Walsh does not specify the state of the infant when OAs occurred and, in particular, does not mention the proportion of the total which occurred during wakefulness. The increased frequency of OA in GOR segments largely reflected the data of two infants. Overall, the longest OA observed lasted 6.8sec and terminated spontaneously. These results are similar to those in the current studies; even the presence of one or two infants with larger numbers of OAs temporally related to GOR is mirrored.

In Ariagno et al's study (1982) 45 term 'near miss' infants were monitored for apnea associated with GOR using simultaneous combined lower oesophageal pH and polygraphic monitoring. In this study sleep state was not monitored either polygraphically or by observation but was interpolated by examining traces for absence of movement artefact. The monitoring lasted on average for 17hrs and the recordings were examined for occurrences of GOR in which pH was less than 4 for at least 15 seconds, for CA of 10 seconds or greater duration and for body movement and state. Airflow was not monitored, precluding comment about OAs. Particular care was taken to examine the tracings for apnea in the two minutes following a

pH drop. 341 apneas >=10sec were recorded in 46 studies; only 7 apneas >=15sec were noted. 31/341 (9%) apneas occurred when the lower oesophageal pH was less than 4. Twenty four of these 31 apneas >=10sec were seen in one infant who was the only subject to have an apneic episode within two minutes following a pH drop. No correlation was found between the number of apneas and any measure of GOR such as % time pH <4. The results from the present studies are surprisingly similar with only 8% of CAs >6sec occurring when the pH was less than pH 4.

Ariagno et al observed pH drops in all sleep states but noted that they were most frequent (73%) when the infant was awake. Similarly, 59% of drops occurred during waking periods in the present studies. When movement occurring within one minute of a precipitous pH change was analysed Ariagno et al noted that the most frequent sequence (present in 84%) was movement preceding and continuing into the period with pH <4. Only in 4% of drops was no movement noted before or after a pH drop. All pH drops, irrespective of state at moment of occurrence, were included in the analysis - most occurred when the infant was awake. In the present study 130 pH drops occurred during sleep, and movement was noted on 93 (72%) occasions in the preceding minute and in 94 (72%) in the following minute. On 74 occasions (57%) movement was present before and after a pH drop. Only in 15 of 130 drops (11%) was movement completely absent. In the detailed breakdown of the present studies it was also noted that the number of movements in the minute before the onset of GOR during sleep was much higher than in the minute after. Thus, the present findings are similar to those of Ariagno et al. A common pattern emerges of gross body movement preceding a pH drop. This interesting

observation accords with common clinical experience that movement or handling results in vomiting. The reverse sequence of a pH drop preceding movement was not commonly seen.

The studies described have concentrated on events in the lower oesophagus and their possible relation to cardio-respiratory abnormalities. The present studies differ from the previous reports in that sleep state and the presence or otherwise of nasal airflow were defined polygraphically. However, there is agreement among all three that there is no significant relation between pH drops in the lower oesophagus and cardio-respiratory abnormalities in the majority of infants in whom these events occur.

The failure to confirm an association between GOR and apnea may be a direct consequence of having focused on events in the lower oesophagus since it may be that cardio-respiratory abnormalities occur only when GOR contacts with laryngeal receptors. Stimulation of laryngeal chemoreceptors in animals has been reported to cause both apnea and swallowing (Lawson 1981). Menon et al (1985) investigated the importance of pharyngeal contact in the pathogenesis of apnea by examining the effects of episodes of regurgitation. It seemed likely that gastric contents entering the pharynx during regurgitation would also contact with and stimulate laryngeal chemoreceptors. Menon et al investigated 10 infants (9 preterms) and found that both prolonged (>20sec) and short apneas (>3sec) occurred much more frequently during regurgitation than during control periods. However, most prolonged apneic spells were not associated with regurgitation. Most short apneas and all prolonged apneas following regurgitation were mixed or

obstructive. Menon et al concluded that regurgitation was a significant predisposing factor for both short and prolonged apnea and felt that this was mediated through upper airway receptors. Menon does not comment on the state during which regurgitation occurred. As 9/10 infants were preterm the association between apnea and regurgitation may be peculiar to preterm infants.

In the present studies vomiting was very unusual during sleep. It seems likely therefore that the infants described by Menon were awake at the time of regurgitations. This is relevant to the report by Spitzer et al (1984). Spitzer pointed out that a significant number of children have apnea while awake and that different factors may be responsible for awake and asleep apnea. These authors noted that few reports had attempted to identify children with awake apnea and to determine whether this was related specifically to GOR. In this report Spitzer et al described 15 term infants who presented with apnea while awake. The clinical sequence was of a sudden startled expression, rigid posturing followed by hypotonia, absence of tonic-clonic movements and occurrence of apnea within one hour of feeding. The most common precipitant of apnea was flexion of the legs during a nappy change, or the sudden movement from lying to a seated position. These 15 infants comprised 7% of infants admitted to the hospital with apnea over an 18 month period. Polygraphic monitoring (including lower oesophageal pH and nasal thermistor monitoring of airflow) showed GOR in all 15. In 13/15 "some degree" of OA was present during periods of GOR, but was not seen in the absence of GOR. Central apnea occurred in one child and did not coincide with GOR.

What conclusions can be drawn from the present studies and previous reports? First, infants with a history of apneic episodes frequently have evidence of GOR. However, when studied in detail there does not appear to be any temporal relation between GOR detected by lower oesophageal pH studies and most central or obstructive apneic episodes during wakefulness or sleep in most infants. OAs are not uncommon in such infants whereas they are uncommon, and possibly rare, in normal infants. Most episodes of regurgitation do not result in apnea, though on certain occasions regurgitation and/or GOR may be associated with obstructive or mixed apneas. It seems likely that any relation between GOR and OA may be specific for awake reflux only.

The present studies confirm that OA during sleep is seen in infants with demonstrable GOR. During sleep there was, however, no temporal relation between GOR and apnea, either central or obstructive.

Many studies, including the present, identify occasional infants with evidence of GOR and OA. It is not clear whether this propensity to develop OA is a feature only of particular subgroups of infants, such as premature infants or Spitzer's group of term infants with awake apnea, or is a feature of all infants with GOR.

6 Conclusion

The current studies confirm that GOR was common in all 'risk' groups studied, though the extent to which this was of "pathological" importance is uncertain. In from 1/2 - 2/3 of the infants the amount and frequency of GOR was probably not "pathological" by published criteria. Whether the qualitative occurrence or the quantitative extent of GOR is more important in any putative relation of GOR with cardio-respiratory abnormalities is not known.

Cardio-respiratory abnormalities were also frequent. 296 CAs were observed in 24 studies (21 infants). Of these only 5 lasted more than 10sec with the longest being 18.8 sec; none were prolonged (more than 20sec). 56 mixed or OAs were observed in 14 studies, of which 8 only were between 10 - 15sec and none longer than 15sec.

The combined lower oesophageal pH and polygraphic studies showed that for the majority of infants during sleep there was no direct temporal relation between GOR and cardio-respiratory abnormalities such as apnea. An association between gross body movements and pH drops was confirmed with movement often preceding a pH drop.

While a direct temporal relation bewteen GOR and cardio-respiratory abnormalities was not observed, all the infants with OA had at least 1 episode (>15sec) of GOR with pH below 4 on the sleep study. Also, in the infant with the largest number and longest OAs, all OAs occurred when the pH

was less than 4. Hence an association between GOR and OA cannot be completely refuted.

CHAPTER 9 page

CONCLUSIONS

CHAPTER 9

CONCLUSIONS

These studies provide further information on the occurrence of GOR in infants at increased risk for SIDS and on the relation between GOR and cardio-respiratory abnormalities, particularly during sleep. How far do the studies reported answer the initial questions? These questions were:

1. How common is GOR?
2. Is there any relation between GOR and cardio-respiratory abnormalities?
3. How do radionuclide scan and pH probe methods of GOR detection compare?

The situation can be summarised as follows.

1 How common is reflux?

Radionuclide scans demonstrated that GOR was present in each of the groups studied (including those thought to be at increased risk of SIDS). The amount of GOR may have exceeded that expected in normal infants of similar ages but the relative lack of appropriate "normal" data made any such conclusion tentative.

The fact that the 'near miss' group did not have significantly more GOR than the other groups suggested that it was not merely the presence of GOR which was important in determining the occurrence of 'near miss' episodes. From these studies, any special importance of GOR in the 'near miss' infant is more likely to lie in the nature of the infant's response to it.

2 GOR and cardio-respiratory abnormalities - any relation?

The second question concerned the possible relation between GOR and cardio-respiratory events, especially apnea. It will be recalled that two approaches were used to study this.

2.1 During radionuclide scan

In the first approach, 22 infants (14 with cardio-respiratory symptoms possibly related to GOR) were monitored for apnea and bradycardia during the course of radionuclide scanning. Cardio-respiratory variables were monitored using a non-invasive 3 channel system for heart rate, and chest and abdominal movements. This, when combined with the radionuclide scan, allowed the assessment of the cardio-respiratory effects of reflux. With this methodology, a relation between reflux and apnea in the post-feed period in 22 infants was not confirmed.

The use of radionuclide scan in this setting offered considerable advantages in that the occurrence and extent of GOR could be detected without the use of oesophageal probes. However, the method of monitoring respiration was recognised as having some inherent limitations. In particular, the absence of an airflow sensor meant that obstructive apnea could not be detected reliably and any temporal relation between reflux and apnea was difficult to assess precisely because of certain technical features of the recording system. Another feature of the above studies was that they did not exclusively focus on sleeping infants.

2.2 During polygraphic sleep monitoring

The second approach was primarily designed to study infants with evidence of GOR on radionuclide scan during sleep at night. At the outset of this research, it was thought that any relation between GOR and apnea may be of most consequence during sleep. Hence, this was considered an important period to study and it was planned to examine this period in detail by using polygraphic monitoring of sleeping infants. This approach also overcame the technical limitations of the previous study as it allowed precise timing of the sequence of events related to episodes of reflux, and detection of obstructive apneas through the inclusion of airflow sensors.

Twenty four infants, studied on 28 occasions, took part in the detailed sleep studies. This included a group of 17 infants shown to have significant GOR on radionuclide scan. The infants were studied during sleep at night using polygraphic

techniques for monitoring sleep state, respiration and heart rate in combination with lower oesophageal pH monitoring to detect GOR.

These studies confirmed that GOR was common in all 'risk' groups studied. However, in from 1/2 - 2/3 of the infants the amount and frequency of GOR was probably not of "pathological" degree by published criteria.

Cardio-respiratory abnormalities were also frequent. 296 central apneas were observed in 24 studies (21 infants). Of these only 5 lasted more than 10sec with the longest being 18.8 sec; none was prolonged (more than 20sec). 56 mixed or obstructive apneas were observed in 14 studies, of which only 8 were between 10 - 15sec and none longer than 15sec. No significant bradycardias were observed. The information presently available suggests that obstructive apneas are rare or absent in normal healthy infants. Thus the presence of OA was a pathological finding in the study group.

The combined lower oesophageal pH and polygraphic studies showed that for the majority of infants during sleep there was no direct temporal relation between GOR and cardio-respiratory abnormalities. An association between gross body movements and pH drops was confirmed with movement often preceding a pH drop.

While a direct temporal relation between GOR and cardio-respiratory abnormalities was not observed the possibility of an association between GOR and OA could not be completely excluded.

3 How do radionuclide scanning and pH probe methods compare?

Simultaneous radionuclide scan and lower oesophageal pH studies showed that episodes detected by radionuclide scan were often, but not invariably, also detected by lower oesophageal pH probe. Episodes demonstrated on radionuclide scan alone (scan positive, pH negative) tended to occur immediately following a feed and were often "non-acid" with the lowest pH in an episode being greater than pH 4. The presence of such "non-acid" reflux was directly confirmed. There was an impression that reflux detected only by pH (scan negative, pH positive reflux) tended to occur further from a feed, possibly reflecting an increase in gastric acidity with passage of time after a feed.

4 Future directions

A. Normal infants

A recurring limitation noted throughout the course of these studies and in the studies reviewed earlier has been the paucity of information on normal infants studied under comparable circumstances. Such normal data is essential to separate pathological and physiological reflux. This criticism can be extended to the whole area of GOR and vomiting in infancy. There is, for such a common clinical problem, surprisingly little information about vomiting and GOR in normal infants and children.

There is therefore a clear need for carefully conducted, preferably longitudinal, studies of GOR in normal infants and children. GOR is best evaluated by oesophageal pH monitoring and any longitudinal studies should ideally be prolonged pH studies. The increasing miniaturisation and portability of pH monitoring equipment may make such studies both practical and ethically acceptable. Any such studies will require to take account of factors such as position of probe in the oesophagus, acidity of feeds, position of infant and method of data analysis to be adopted.

Without such information on a healthy population, important questions about GOR in childhood will remain unanswered.

B. GOR - coincidence rather than cause?

In the studies described GOR was seen frequently during radionuclide scans in both the index cases ('near miss') and in the chosen controls (non life-threatening 'events', sibs of SIDS and vomiters). Extrapolation of the available control data suggested that for a significant number of these infants GOR was of significant extent. Despite this, in subsequent detailed physiological studies there was no evidence of a causal relationship between GOR and cardio-respiratory abnormalities in the groups studied. If GOR is not a direct causal factor of such abnormalities then perhaps it is closely associated with some other causal hazard.

Adult studies (Ogilvie et al 1985) suggest one possible area for future exploration. These workers took as their starting point the known rise in lower oesophageal sphincter pressure as intra-gastric pressure is increased by abdominal compression. This response has been noted to be impaired in patients with hiatal hernia and it is also abolished by atropine and by truncal vagotomy. This suggests that it is an intrinsic vagally mediated reflex mechanism, which is responsible for normal control of the lower oesophageal sphincter. Other abnormalities including impairment of gastric secretory response to insulin-induced hypoglycaemia and impaired cardiac vagal reflexes have been described in patients with GOR. This led the authors to investigate the frequency of autonomic nervous dysfunction in patients suffering from reflux oesophagitis with and without demonstrable hiatus hernia by assessing alimentary and cardiac vagal function. Their findings suggested that impairment of afferent and efferent vagal

function were common in reflux oesophagitis. Since impairment of vagal function was not confined to the alimentary system it was unlikely to be simply a consequence of reflux oesophagitis.

Ogilvie's findings showed that the capacity of the lower oesophageal sphincter to respond to "stress" was important in protecting against GOR. Their demonstration of detectable afferent and efferent vagal damage in patients with reflux oesophagitis might account for interruption of a centrally mediated vagal reflex, normally responsible for controlling the response of the lower oesophageal sphincter to stress. In their patients, the vagal dysfunction appeared to be part of a more widespread autonomic dysfunction although the patients reported did not have any of the conditions or features normally associated with autonomic dysfunction eg bladder dysfunction or postural hypotension.

The core of their hypothesis that GOR is associated with autonomic dysfunction is important. If true in infants, then autonomic dysfunction might be a more important cause of cardio-respiratory abnormalities than GOR. Then, the presence of GOR would merely be a marker of underlying autonomic dysfunction.

There are some other suggestive hints that autonomic dysfunction might be an important line to pursue in infants. For example, Hillemeier et al (1981) demonstrated that delayed gastric emptying occurs in infants with GOR and pointed out that GOR was therefore part of a more general disturbance of intestinal motility. Recently, Kelly et al (1986) have described cardio-respiratory abnormalities in a group of

infants who later died of SIDS compared to a control group of normal age and sex matched infants. The index infants presented either as 'near miss' infants or were sibs of SIDS and were found to have significantly greater mean heart rate and periodic breathing during quiet sleep than in controls and a greater incidence of bradycardia. The authors believed that the abnormalities noted could not be explained entirely by the occurrence of clinical apnea but might reflect an underlying disturbance of autonomic function.

Thus an important future line of inquiry would be an investigation of autonomic function both in infants with GOR and in 'at risk' infants similar to the ones studied here.

C. Sleep state and other factors

These studies have concentrated on the cardio-respiratory effects of GOR during sleep and have shown no direct relation between cardio-respiratory abnormalities and GOR. However, a review of the literature has suggested that there may be an association between GOR during wakefulness and OA. Future studies should distinguish more specifically between such simple clinical features as sleep and wakefulness. The relation between GOR and wakefulness in infants 'at risk' for SIDS awaits further elucidation.

The possible impact of 'minor' illnesses on a relatively immature host was alluded to earlier. The impact of such 'stresses' has been little studied as yet. Their importance with respect to the relation between GOR and cardio-respiratory

abnormalities has not been evaluated. While detailed studies at the time of intercurrent illness will be difficult to organise and perform they might yield important information on the impact of these various factors.

5 Finale

The explorations of the last forty years have provided ample evidence that GOR in infants and children is not always a benign phenomenon. Despite an explosion of knowledge many unanswered questions about the origin and importance of GOR in childhood remain. There is every likelihood that the next fifty years will be as exciting and informative as the last.

APPENDICES page

APPENDIX 1: Brief historical details of infants studied

Study No	Group	Short clinical history
07	VOMITER	Vomiting with failure to thrive.
08	SIB	Normal infant. Frequent possetter.
09	SIB	Normal infant. Frequent possetter.
10	?ASPIR	3 episodes of 'bronchiolitis' - RSV negative.
11	'EVENT'	5-6 episodes of breathlessness followed by limpness and pallor.
12	SIB	Breast fed - occasional possets.
13	'EVENT'	Choking during feeds in first 7 weeks.
14	'EVENT'	Pale and floppy episodes during and after feeds. Possetting after feeds.
15	'EVENT'	3 episodes of pallor and limpness during feeds.
16	?ASPIR	Persistent vomiting with recurrent croupy cough.
17	'EVENT'	Episode of struggling for breath with cyanosis.
18	VOMITER	Persistent vomiting after feeds.
19	'EVENT'	2 episodes of vomiting,diarrhoea and inconsolable crying.
20	'EVENT'	Born 8 wks preterm. Recurrent episodes of bradycardia and apnea.
21	'NEAR MISS'	Episodes of apnea at 5wks and 10mth. Resuscitated with mouth to mouth breathing on both occasions.
22	'NEAR MISS'	2 episodes of choking whilst feeding. Struggled for breath, went blue and

		apneic. Responded to stimulation.
23	MENTAL RET	Preterm with birth asphyxia. Severe mental retardation. Intermittent vomiting. Recurrent chest infections.
24	'EVENT'	Episode of struggling for breath and cyanosis ater a vomit, 2hrs after a feed
25	'EVENT'	Found asleep in cot cyanosed and apneic. Responded to shaking. 3 further episodes of apnea.
26	SIB	Small windy vomits.
27	VOMITER	Persistent vomiting. 2 episodes of choking.
28	?ASPIR	Persistent vomiting with recurrent chest infections.
29	'NEAR MISS'	Apneic episode 2hrs after a feed. Pale and limp. Responded slowly to stimulation.
30	'EVENT'	Gave a strange cry. Found blue and struggling for breath. Responded to stimulation.
31	MENTAL RET	Severe mental retardation. Recurrent vomiting.
32	'EVENT'	Episode of struggling for breath just before a feed. Screamed, then became rigid and apneic.
33	'EVENT'	3 episodes of cyanosis; 2 with struggling for breath, 1 with apnea.
34	SIB	Normal breast fed infant.
35	'NEAR MISS'	2-3hr period of recurrent apnea with bradycardia and cyanosis. Responded to stimulation.

36	'EVENT'	Cyanotic attacks while supine several times a day for three or four days, always beginning with a cry.
37	VOMITER	Persisting vomiting with blood in vomit.
38	'NEAR MISS'	Found 2hrs after feed, supine neck flexed, cyanosed and apneic. Responded slowly to stimulation.
39	'EVENT'	Recurrent choking episodes.
40	'EVENT'	Coughed 1hr after feed. Found in cot choking and struggling for breath.
41	VOMITER	Persistent vomiting with failure to thrive.
42	'EVENT'	3 episodes of apnea responding to stimulation.
43	'NEAR MISS'	Found cyanosed 20min after feed. Responded to stimulation. Grand mal seizure some days later.
44	'EVENT'	Repaired TOF with near death episodes. Vomiting followed by apnea, cyanosis and loss of consciousness.
45	MENTAL RET	Severe mental retardation. Feeding problems with persistent vomiting.
46	'NEAR MISS'	Found apneic, cyanosed and cold. Started breathing after mouth to mouth resuscitation.
47	MENTAL RET	Severe mental retardation, failure to thrive with recurrent vomiting and chest infections.
48	'NEAR MISS'	Started to cry 1hr after a feed. Then became limp cyanosed and apneic. Responded to mouth to mouth

49	?ASPIR	Tracheostomy following prolonged neonatal ventilation. Milky material often noted from tracheostomy.
50	'EVENT'	Apneic episodes during feeds.
51	SIB	Normal breast fed infant.
52	SIB	Vomiting during evenings.
53	'NEAR MISS'	Episode of apnea 30min after feed. Pale and limp.
54	VOMITER	Severe feeding difficultie with vomiting and choking.
55	'NEAR MISS'	Found pale and stiff. Responded to stimulation.
56	'EVENT'	2-3 epiosdes of cyanosis during an URTI.
57	'EVENT'	Food refusal with crying and struggling after 1oz of feed.
58	'NEAR MISS'	Episode of choking followed by hypotonia and apnea. Responded to mouth to mouth resuscitation.
59	VOMITER	Frequent possetter. Pale episodes during feeds which stopped after feeds thickened.
60	'NEAR MISS'	Winded during feed. Paniced then went apneic, limp and cyanosed.
61	SIB	Details not known.
62	'EVENT'	Repaired TOF. Persistent chestiness.
63	'NEAR MISS'	Abnormal breathing following a vomit.
64	VOMITER	Persistent vomiting following a feed.
65	SIB	Persistent vomiting.
66	'NEAR MISS'	5 episode of apnea with cyanosis following a feed.
67	'NEAR MISS'	Details not known.

68	SIB	No symptoms.
69	'NEAR MISS'	Episodes of cyanosis and apnea responding to stimulation.
70	'NEAR MISS'	Found in cot cold , pale and apneic. Responded slowly to cardio-pulmonary resuscitation.
71	'EVENT'	Epsiodes of pallor and apnea.
72	SIB	Vomiting after feeds.
73	'EVENT'	Epsiode of cyanosis during feed.
74	'EVENT'	Prolonged choking episode responding to stimulation.
75	'NEAR MISS'	Found struggling for breath and cyanosed. Responded to stimulation.
76	?ASPIR	Occasional possets. URTI. Periodic respiration with pallor.
77	'EVENT'	Vomiting with choking and cyanosis. 1 episode of apnea.
78	?ASPIR	Persistent vomiting with chestiness.
79	?ASPIR	Persistent wheezing.
80	'EVENT'	Screamed 1hr after feed. Struggled for breath and became cyanosed. Responded to stimulation.
81	SIB	Normal breast fed infant.
82	'EVENT'	Recurrent chestiness.
83	'EVENT'	Episodes of nasal regurgitation with cyanosis.
84	'NEAR MISS'	Episodes of floppiness and unresponsiveness responding to mouth to mouth resuscitation.
85	'NEAR MISS'	Asleep. Coughed. Became floppy and cyanosed. Responded to mouth to mouth

			resuscitation.
IGHT	86	'NEAR MISS'	Apnea and cyanosis following a vomit. Responded to stimulation.
APMAN	87	'NEAR MISS'	Found face down apneic and cyanosed with vomit on the sheet.
NSFIEL	88	'EVENT'	Episodes of apnea and pallor during feeds.
IFFIN	217	'EVENT'	URTI. Episodes of struggling for breath.
BBS	193	'EVENT'	Choking episodes.
LL	205	'EVENT'	Persistent stridor.
GMORE	206	'EVENT'	Paroxysmal cough with apneic episodes.

APPENDIX 2: Analytical sensitivity of radionuclide scanning

Pediatr Radiol (1985) 15: 381–383

Pediatric Radiology

The analytical sensitivity of Tc99m radionuclide 'milk' scanning in the detection of gastro-oesophageal reflux

J. Y. Paton[1], P. S. Cosgriff[2] and C. S. Nanayakkara[1]

Department of [1]Child Health, University of Leicester and [2]Medical Physics Department, Leicester Royal Infirmary, Leicester, UK

Abstract. The analytical sensitivity of radionuclide 'milk' scans for detecting gastro-oesophageal reflux (GOR) has been assessed using an in vitro simulation test. Five factors were found to affect the ability to detect simulated reflux: isotope concentration, absolute gamma camera sensitivity, absorber thickness overlying the 'oesophagus' and volume and duration of reflux. We found that a critical volume-duration product must be exceeded for reflux to be detected. Radionuclide milk scanning appears to be much less sensitive in detecting transient events like GOR than might be expected from previously reported static simulation studies.

Tc99m radionuclide 'milk' scans are now widely used for the detection of gastro-oesophageal reflux (GOR) in infancy and childhood. The technique is simple and more sensitive than the barium swallow in the detection of GOR [1, 2]. Heyman et al. [3] have suggested, from a static simulation of the milk scan, that volumes of pulmonary aspiration as little as 0.025 ml may be detected.

During the course of our studies of GOR in infancy, a number of children vomited during the period of scanning. We were surprised to observe that a significant number of these vomits (23/67) were not associated with discernible change in oesophageal activity on the gamma camera image (Fig. 1). Ref-

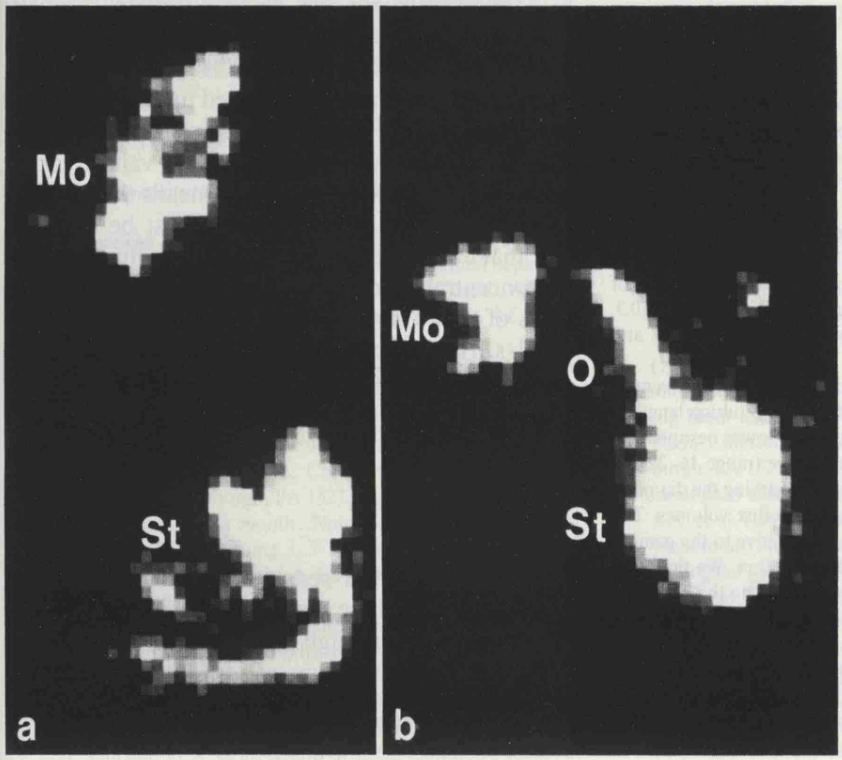


Fig. 1. 1-min images acquired during episodes of vomiting. In image (a) reflux from stomach (St) is visualised only when pooled in mouth (Mo) (false negative). By contrast, in image (b) activity is clearly seen in oesophagus (0)

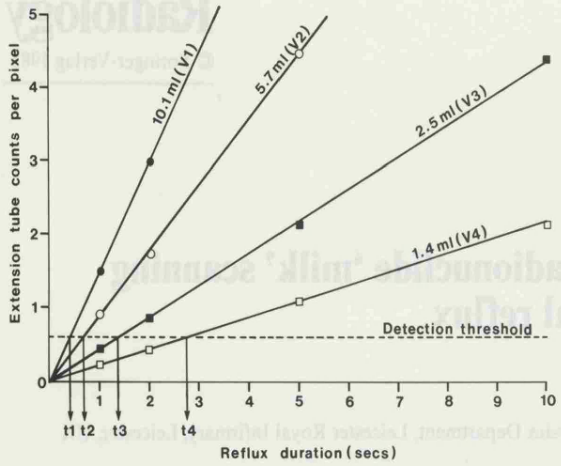


Fig. 2. Simulation study. Variation of gamma camera count density in the extension tube with volume and duration of reflux. Minimum detectable volume-duration product ($V_1t_1 \approx V_2t_2$, etc.) is approximately 4 ml/s. (Isotope concentration 1.5 μCi/ml, absorber thickness 0 cm, absolute (NEMA) camera sensitivity 6.0 counts/s per μCi)

luxed material was registered by the gamma camera only when it pooled in the mouth.

It seemed likely that the camera failed to detect the refluxed material because the event had fallen below the limits of the gamma camera's analytical sensitivity. In the absence of published information we have performed in vitro simulation tests to establish the sensitivity of 'milk scans' in detecting GOR.

Methods

A plastic wash bottle fitted with an extension tube (internal diameter 0.6 cm) and filled with 200 ml solutions of Tc99m pertechnetate (concentrations 1.2, 2.3, 5.3 μCi/ml) was positioned in front of a gamma camera with a large field of view, behind various thicknesses of perspex absorber (0, 1, 2, 3, 4, 5 cm). GOR was simulated by compressing the bottle and filling the extension tube to a level of 20 cm for varying durations (1, 2, 5, 10 s).

The experiment was repeated using a fixed concentration of isotope (1.5 μCi/ml) and different extension tube diameters (0.3, 0.4, 0.6, 0.8 cm). These gave reflux volumes of 1.4, 2.5, 5.7 and 10.1 ml.

This model approximates the situation in-vivo: the concentrations used are similar to those reported [1, 3] and tubing length is comparable to oesophageal length (mouth to lower oesophageal sphincter) in infants less than 6 months of age (range 16–22 cm) [4]. Since the oesophagus is a potential space, varying the diameter of tube allowed investigation of a range of reflux volumes. The amount of tissue overlying the oesophagus relative to the gamma camera also influences the ability to detect reflux. We therefore used absorber thicknesses up to 5 cm to investigate the effects of different thicknesses on oesophageal count density. Durations of reflux between 1 and 10 s were studied to simulate the rapid transit of materials through the oesophagus that would be anticipated in a vomit.

To assess the effect of absolute camera sensitivity the first experiment was performed with a low-energy all purpose collimator (NEMA[1] sensitivity 6.0 counts/s per μCi) while in the second a high sensitivity collimator (NEMA sensitivity 10.2 counts/s per μCi) was used.

All images were acquired in a digital 64 × 64 pixel matrix. Quantitative analysis of the images was performed by defining a region of interest around the image of the extension tube using the computer light pen. The total number of counts within the region was divided by the size of the region (number of pixels) to yield an average extension tube counts per pixel (CPP). This was used as an index of reflux.

Results

The average extension tube CPP was found to be proportional to both volume and duration of reflux (Fig. 2). Similarly, increasing the radioisotope concentration of reflux or absolute gamma camera sensitivity produced a proportional increase in extension tube CPP. The presence of increasing absorber thickness between the extension tube and the gamma camera face led to an exponential fall in extension tube CPP.

Expressed mathematically:

$$\text{ext. tube CPP} = K.V.t.\,\text{conc.}\,CS.\exp(-\mu x) \quad \ldots (1)$$

where K = constant (1/no of pixels in region of interest), V = volume of reflux (ml), t = duration of reflux (s), conc = concentration of radioisotope (μCi/ml), CS = absolute gamma camera sensitivity (counts/s/μCi), x = absorber thickness (cm) and μ = linear attenuation coefficient for 140 keV photons in perspex absorber (0.11/cm).

Empirically, for our gamma camera/computer system, it was noted that reflux was not discernible until the extension tube CPP exceeded 0.60. This figure, which could not be improved upon by computer enchancement of the image, represents a 'detection threshold' and substituting known values for K, conc, CS, μ and x in equation 1 means that an associated volume-duration product must be exceeded for that event to be detected. Figure 2 illustrates that a concentration of 1.5 μCi/ml and absorber thickness of 0 cm this product is equal to approximately 4 ml · s. Thus, a volume of 4 ml would have to be present for at least 1 s (or a 1-ml volume for 4 s) to be detectable.

Discussion

While the reported sensitivity of Tc99m labelled 'milk' scans for static events such as pulmonary aspiration may be very high [3] there is no similar infor-

[1] NEMA is the National Electrical Manufacturers Association - standards for performance specification of scintillation cameras

mation for transient events such as gastro-oesophageal reflux. Our experiments show that the analytical sensitivity for transient events depends on five factors: isotope concentration in the stomach, absolute gamma camera sensitivity, absorber thickness and volume and duration of reflux. As the first three are usually fixed, a critical volume-duration product must be exceeded for reflux to be detected with a given gamma camera/computer system. For our in vivo conditions (isotope concentration 1.0 μCi/ml, camera sensitivity 6.0 counts/s per μCi), assuming an absorber thickness of 1 cm, we estimate that this product will be approximately 10 ml · s. At 4.0 μCi/ml the product will be 2.5 ml · s. The second value is substantially larger than the value of 0.025 ml obtained by Heyman et al. [3] for static events using a similar isotope concentration. The ability to detect GOR is therefore much lower than might be expected from static simulation.

The vomits observed clinically which were not detected as reflux on the gamma camera images presumably failed to exceed the required volume-duration product. This might also explain some of the false negatives noted in other series [5, 6].

For a given camera system, once the detection threshold has been empirically determined, the above relationship (Eq. 1) can be used in two ways: firstly, when an acceptable level of absorbed radiation dose (and hence concentration) is defined, a minimum volume-duration product is automatically fixed. This determines the lower limit of detection of reflux. Alternatively, a volume-duration product may be defined clinically at the outset (for example, it might be desirable to detect refluxes as small as 1 ml lasting only 1 s). A concentration can then be chosen to achieve this.

These observations may have implications for the gamma camera detection of other transient events (such as vesico-ureteric reflux) of importance in pediatrics.

References

1. Jona JZ, Sty JR, Glicklich M (1981) Simplified radioisotope technique for assessing gastroesophageal reflux in children. J Pediatr Surg 16: 114
2. MacFadyen UM, Hendry GMA, Simpson H (1983) Gastro-oesophageal reflux in near-miss sudden death syndrome or suspected recurrent aspiration. Arch Dis Child 58: 87
3. Heyman S, Kirkpatrick JA, Winter HS, Treves S (1979) An improved radionuclide method for the diagnosis of gastroesophageal reflux and aspiration in children (milk scan). Radiology 131: 479
4. Strobel CT, Byrne WJ, Ament ME, Euler AR (1979) Correlation of esophageal length in children with height: application to Tuttle test without prior esophageal manometry. J Pediatr 94: 81
5. Rudd TG, Christie DL (1979) Demonstration of gastroesophageal reflux in children by radionuclide gastroesophagography. Radiology 131: 483
6. Gordon I (1981) Radioisotope milk scan in paediatrics. BJR 54: 705 (Abstract)

Date of acceptance: 16 January 1985

Dr. P. S. Cosgriff
Medical Physics Department
Leicester Royal Infirmary
Leicester LE1 5WW
UK

Literature in pediatric radiology (continued from p. 376)

AJDC American Journal of Diseases of Children (Chicago)

Hepatobiliary scintigraphy for cholestasis in congenital hepatic fibrosis. Stillman, A.E. et al. (Dept. of Internal Med., Arizona Health Sci. Center, 1501 N Campbell Ave., Tucson, AZ 85724, USA) **139**, 41 (1985)

Tracheal agenesis in infants with VATER association. Milstein, J.M. et al. (Div. of Neonatology, TB 193, Univ. of California at Davis, Davis, CA 95616, USA) **139**, 77 (1985)

Radiological case of the month: Pulmonary actinomycosis. Seibert, J.J. et al. (Dept. of Rad., Children's Hosp. of Pittsburgh, 125 DeSoto St., Pittsburgh, PA 15213, USA) **139**, 101 (1985)

Radiological case of the month: Nontuberculous mycobacterial infection. Lé, Ch.-T., Young, L.W. (L.W. Young, Dept. of Rad., Children's Hosp. of Pittsburgh, 125 DeSoto St., Pittsburgh, PA 15213, USA) **139**, 607 (1985)

Hypertension in children. Increased efficacy of technetium Tc99m succimer in screening for renal disease. Rosen, P.R. et al. (Div. of Nuclear Med., The Children's Hosp., 300 Longwood Ave., Boston, MA 02115, USA) **139**, 173 (1985)

Radiological case of the month: Intralobar pulmonary sequestration. Sanchez, G.R. et al. (Dept. of Rad., Children's Hosp. of Pittsburgh, 125 DeSoto St., Pittsburgh, PA 15213, USA) **139**, 207 (1985)

Congenital tuberculosis. Review and diagnostic guidelines. Nemir, R.L., O'Hare, D. (Dept. of Ped., New York Univ. Med. Center, 550 First Ave., New York, NY 10016, USA) **139**, 284 (1985)

Radiological case of the month: Pneumoretroperitoneum following blunt abdominal trauma. Weinberg, H.D. et al. (Dept. of Rad., Children's Hosp. of Pittsburgh, 125 DeSoto St., Pittsburgh, PA 15213, USA) **139**, 317 (1985)

Radiological case of the month: Amebic liver abscess. Hamdan, J.A. et al. (Dept. of Rad., Children's Hosp. of Pittsburgh, 125 DeSoto St., Pittsburgh, PA 15213, USA) **139**, 527 (1985)

Radiological case of the month: Neonatal osteomyelitis. Murray, D.L. et al. (L.W. Young (L.W. Young, Dept. of Rad., Children's Hosp. of Pittsburgh, 125 De Soto St., Pittsburgh, PA 15213, USA) **139**, 687 (1985)

Neonatal metrizamide gastrointestinal series in suspected necrotizing enterocolitis. Keller, M.S., Chawla, H.S. (Dept. of Diagn.-Rad., Hahnemann Univ. Hosp., Broad and Vine St., Philadelphia, PA 19102, USA) **139**, 713 (1985)

(continued on p. 387)

APPENDIX 3: Brief clinical details of group studied by simultaneous radionuclide scan and cardio-respiratory monitoring

No.	Diagnosis	Age (yrs)	Sex	<=37 wks	GOR extent	History
22	'NEAR MISS'	.120	M	N	SEV	2 episodes of choking whilst being fed - struggled for breath, went blue and stopped breathing. Responded to stimulation.
29	'NEAR MISS'	.189	M	N	SEV	Stop breathing episode 2hrs after a feed. Pale and floppy. Patted on back, no response, repeated, then took a deep gasp. Previous 1/2 sib died of cot death.
35	'NEAR MISS'	.266	F	N	SEV	Diarrhoea for 2 days 4-5x/day. 2-3hr period of recurrent apnea with bradycardia and cyanosis. Responded to stimulation on each occasion.
66	'NEAR MISS'	.096	M	N		1 hr after feed lying supine noted to be grey and apneic. Shaken and turned on side, colour returned. 5 further episodes soon after feeds in the next few days.
69	'NEAR MISS'	.107	M	N	SEV	3 episodes where appeared purple around lips and in face, asleep, not breathing. Shaken and breathing retuned. Lifeless after.
70	'NEAR MISS'	.370	M	N	SEV	Off colour, drowsy and not feeding well. Found prone in cot. Not breathing. White, still, limp. Felt cold. Given cardiopulmonary resuscitation. Responded after 5 min and then gradually warmed up. Repeated episodes on several occasions.
12	SIB	.192	F	N	SEV	Breast feeding well. Occasional mouthfuls of vomit noted. URTI for 2-3 days.
26	SIB	.145	F	N	SEV	Mouthfuls of vomit with wind.
51	SIB	.288	M	N	SEV	Breast fed. No problems.
68	SIB	.038	M	N	SEV	No symptoms.
72	SIB	.258	M	N	SEV	Vomiting after feeds since birth.
14	'EVENT'	.214	F	N	SEV	Pale floppy episodes during and after feeds. Posseting of milk soon after feeds, worse when upright.

15	'EVENT'	.068	M	N		3 episodes of pallor and floppiness during feeds. No vomiting. Later occasional choking during a feed.
19	'EVENT'	.140	M	N	SEV	2 episodes of vomiting, diarrhoea and inconsolable crying.
24	'EVENT'	.077	M	N	SEV	Episode of struggling for breath and cyanosis associated with a vomit 2hrs after a feed.
30	'EVENT'	.071	F	N	MOD	Strange cry. Found in cot blue and struggling for breath. Picked up and patted on back. Remained blue for 5min.
33	'EVENT'	.123	M	N	SEV	3 episodes of cyanosis; 1 associated with a stop breathing episode, 2 with struggling for breath.
73	'EVENT'	.106	M	N	SEV	Episodes of cyanosis during feeds but not apneic.
80	'EVENT'	.156	F	N	SEV	One hour after feed screamed when asleep. Found holding breath struggling. Purple in face. Patted on back and returned to normal. No vomit.
18	VOMITER	.093	M	N	SEV	Persistent vomiting of milk for several hours after a feed. Barium showed small hiatus hernia and reflux.
27	VOMITER	.195	F	N	SEV	Persistent vomiting. 2 episodes of choking 24hrs apart.
59	VOMITER	.277	M	Y	SEV	Frequent posseter. Pale episodes during feeds which stopped after introduction of Gaviscon.

APPENDIX 4: Diagnostic groups, age, sex and summary of studies undertaken on each infant

Diagnostic Group	Scan	Scan No	AGE at scan	SEX	<=37wks at birth	GOR on scan	Extent of GOR	Additional studies: Resp study	pH study	Sleep study	Sleep study no	AGE at sleep study
VOMITER	Y	07	.466	M	N	Y	MOD	N	N	N		
SIB	Y	08	.288	M	N	Y	MOD	N	N	N		
SIB	Y	09	.288	M	N	Y	MOD	N	N	N		
?ASPIR	Y	10	.512	F	N	N		N	N	N		
'EVENT'	Y	11	.025	M	N	Y	SEV	N	N	N		
SIB	Y	12	.192	F	N	Y	SEV	Y	N	N		
'EVENT'	Y	13	.164	M	N	Y	SEV	N	N	N		
'EVENT'	Y	14	.214	F	N	Y	SEV	Y	N	N		
'EVENT'	Y	15	.068	M	N	N		Y	N	N		
?ASPIR	Y	16	.989	M	N	N		N	N	N		
'EVENT'	Y	17	.074	F	N	Y	SEV	(Y)	Y	N		
VOMITER	Y	18	.093	M	N	Y	SEV	Y	Y	N		
'EVENT'	Y	19	.140	M	N	Y	SEV	Y	Y	Y	191	.153
"											207	.384
'EVENT'	Y	20	.101	M	Y	Y	SEV	(Y)	Y	Y	190	.126
"											195	.192
"											213	.392
'NEAR MISS'	Y	21	.877	M	N	N		N	N	N		
'NEAR MISS'	Y	22	.120	M	N	Y	SEV	Y	Y	N		
MENTAL RET	Y	23	1.660	M	Y	Y	SEV	N	Y	N		
'EVENT'	Y	24	.077	M	N	Y	SEV	Y	N	Y	196	.109
'EVENT'	Y	25	.496	F	N	N		N	N	N		
SIB	Y	26	.145	F	N	Y	SEV	Y	N	N		
VOMITER	Y	27	.195	F	N	Y	SEV	Y	Y	N		
?ASPIR	Y	28	.513	F	N	Y	SEV	N	N	N		
'NEAR MISS'	Y	29	.189	M	N	Y	SEV	Y	N	N		
'EVENT'	Y	30	.071	F	N	Y	MOD	Y	N	N		
MENTAL RET	Y	31	1.277	F	N	Y	SEV	N	N	N		
'EVENT'	Y	32	.284	F	Y	Y	SEV	Y	N	Y	194	.249
'EVENT'	Y	33	.123	M	N	Y	SEV	Y	Y	Y	201	.145
SIB	Y	34	.120	M	N	Y	MOD	N	N	N		
'NEAR MISS'	Y	35	.337	F	N	Y	SEV	Y	N	N		
'EVENT'	Y	36	.181	M	Y	Y	SEV	N	Y	Y	199	.172
VOMITER	Y	37	.622	M	Y	Y	SEV	N	N	N		
'NEAR MISS'	Y	38	.192	F	N	Y	SEV	N	N	Y	192	.096
'EVENT'	Y	39	.148	F	N	Y	SEV	N	Y	Y	208	.170
'EVENT'	Y	40	.170	F	N	N		N	Y	N		
VOMITER	Y	41	.142	M	N	Y	SEV	N	Y	N		
'EVENT'	Y	42	.044	M	N	Y	SEV	N	Y	N		
'NEAR MISS'	Y	43	.469	F	N	N		N	N	N		
'EVENT'	Y	44	.428	F	Y	Y	SEV	N	Y	Y	212	.422
MENTAL RET	Y	45	2.173	M	N	N		N	Y	N		
'NEAR MISS'	Y	46	.195	M	N	Y	SEV	N	Y	Y	214	.192
MENTAL RET	Y	47	2.057	M	N	Y	SEV	N	Y	N		
'NEAR MISS'	Y	48	.230	F	N	Y	SEV	(Y)	Y	N		
?ASPIR	Y	49	.274	M	N	Y	SEV	N	N	Y	218	.260
'EVENT'	Y	50	.233	M	Y	Y	SEV	(Y)	Y	N		
SIB	Y	51	.288	M	N	Y	SEV	(Y)	N	N		
SIB	Y	52	.175	F	N	Y	MOD	N	Y	Y	267	.168
'NEAR MISS'	Y	53	.490	M	N	Y	MOD	N	N	N		
VOMITER	Y	54	.287	F	N	Y	SEV	N	N	N		
'NEAR MISS'	Y	55	.156	F	N	Y	SEV	N	N	N	265	.150

Diagnostic	Scan	Scan	AGE	SEX	<=37wks	GOR	Extent	Additional studies				
'EVENT'	Y	56	.263	F	N	N		N	N	N		
'EVENT'	Y	57	.178	F	N	Y	SEV	N	N	N		
'NEAR MISS'	Y	58	.113	F	Y	Y	SEV	N	N	N		
VOMITER	Y	59	.277	M	Y	Y	SEV	Y	N	N		
'NEAR MISS'	Y	60	.189	F	N	Y	SEV	N	N	N		
SIB	Y	61	.021	M	N	Y	SEV	(Y)	N	Y	270	.019
"											272	.120
'EVENT'	Y	62	.439	M	N	Y	MOD	N	N	N		
'NEAR MISS'	Y	63	.178	F	N	N		(Y)	N	N	269	.160
VOMITER	Y	64	.619	F	Y	N		N	N	N		
SIB	Y	65	1.156	M	N	N		N	N	N		
'NEAR MISS'	Y	66	.113	M	N	N		Y	N	N	268	.090
'NEAR MISS'	Y	67	.137	M	N	Y	SEV	N	N	N		
SIB	Y	68	.038	M	N	Y	SEV	Y	N	N		
'NEAR MISS'	Y	69	.102	M	N	Y	SEV	Y	N	N		
'NEAR MISS'	Y	70	.368	M	N	Y	SEV	Y	N	N	273	.290
'EVENT'	Y	71	.154	F	N	Y	SEV	(Y)	N	N		
SIB	Y	72	.258	M	N	Y	SEV	Y	N	N		
'EVENT'	Y	73	.106	M	N	Y	SEV	Y	N	N		
'EVENT'	Y	74	.232	F	N	N		N	N	N		
'NEAR MISS'	Y	75	.167	M	N	Y	SEV	N	N	N		.150
?ASPIR	Y	76	.126	F	N	Y	SEV	(Y)	N	N		
'EVENT'	Y	77	.109	M	N	Y	SEV	N	N	N		
?ASPIR	Y	78	.817	M	Y	Y	SEV	N	N	N		
?ASPIR	Y	79	.877	M	Y	Y	SEV	N	N	N		
'EVENT'	Y	80	.156	F	N	Y	SEV	Y	N	N		
SIB	Y	81	0	F	N	Y	SEV	N	N	N		
'EVENT'	Y	82	.858	M	N	Y	SEV	N	N	N		
'EVENT'	Y	83	.145	M	Y	N		N	N	N		
'NEAR MISS'	Y	84	.611	M	N	N		N	N	N		
'NEAR MISS'	Y	85	.487	M	N	N		N	N	N		
'NEAR MISS'	Y	86	.191	M	N	Y	SEV	N	N	N		
'NEAR MISS'	Y	87	.354	M	N	Y	SEV	N	N	N		
'EVENT'	Y	88	.332	F	Y	Y	SEV	N	N	N		
'EVENT'	N			M	N			N	N	Y	193	.096
'EVENT'	N			M	N			N	N	Y	205	.145
'EVENT'	N			M	N			N	N	Y	217	.318
'NEAR MISS'	N			M	N			N	N	Y	203	.246
'EVENT'	N			F	N			N	N	Y	214	.148
'NEAR MISS'	N			F	Y			N	N	Y	200	.425
'EVENT'	N			F	N			N	N	Y	206	.238

REFERENCES

REFERENCES

1. ABREU E SILVA FA, BREZINOVA V, SIMPSON H

Sleep apnoea in acute bronchiolitis.

Arch Dis Childh 1982; 57: 467-472

2. ABREU E SILVA FA, MACFADYEN UM, WILLIAMS A, SIMPSON H

Sleep apnoea in infancy.

J R Soc Med 1985; 78: 1005-1008

3. ALLEN CJ, NEWHOUSE MT

Gastroesophageal reflux and chronic respiratory disease.

Am Rev Respir Dis 1984; 129: 645-647

4. ANDERS T, EMDE R, PARMALEE A

A manual for standardised terminology and criteria for scoring of states of sleep and wakefulness in newborn infants.

Los Angeles: UCLA Brain Information Service,

BRI publications Office, 1971.

5. ARASU TS, WYLLIE R, FITZGERALD JF, FRANKEN EA, SIDDIQUI AS,

ET AL

Gastroesophageal reflux in infants and children - comparative accuracy of diagnostic methods.

J Pediatr 1980; 96: 798-803

6. ARIAGNO RL, GUILLEMINAULT C, BALDWIN R, OWEN-BOEDDIKER M

Movement and gastroesophageal reflux in awake term infants with "near miss" SIDS, unrelated to apnea.

J Pediatr 1982; 100: 894-897

7. ASK P, EDWALL G, JOHANSSON K-E, TIBBLING L

On the use of monocrystalline antimony pH electrodes in gastro-oesophageal functional disorders.

Med & Biol Eng & Comput 1982; 20: 383-389

8. ASTLEY R, CARRE IJ

Gastro-oesophageal incompetence in children.

Radiology 1954; 62: 351-361

9. BALISTRERI WF, FARREL MK

Gastroesophageal reflux in infants.

N Engl J Med 1983; 309: 790-792

10. BARTLETT Jr. D

Ventilatory and protective mechanisms of the infant larynx.

Am Rev Respir Dis 1985; 131: S49-S50

11. BEARDSMORE CS, HELMS P, STOCKS J, HATCH DJ, SILVERMAN M

Improved esophageal balloon technique for use in infants.

J Appl Physiol 1980; 49: 735-742

12. BELSEY R

The pulmonary complications of oesophageal disease.

Br J Dis Chest 1960; 54: 342-348

13. BERENBERG W, NEUHAUSER EBD

Cardio-esophageal relaxation (chalasia) as a cause of vomiting in infants.

Pediatrics 1950; 5: 414-420

14. BERQUIST WE, AKHANJEE N, AMENT ME

Increased gastroesophageal reflux by prolonged pH monitoring in infants with severe apnea and cyanosis.

Clin Res 1984; 32: 96A

15. BERQUIST WE, RACHELEFSKY GS, KADDEN M, SIEGEL SC,

KARE RM, ET AL

Effect of theophylline on gastroesophageal reflux in normal adults.

J Allerg Clin Immunol 1981; 67: 407-411

16. BERQUIST WE, RACHELEFSKY GS, KADDEN M, SIEGEL SC, KATZ RM,

ET AL

Gastroesophageal reflux-associated recuurrent pneumonia and chronic asthma in children.

Pediatrics 1981; 68: 29-35

17. BIANCANI P, WALSH JH, BEHAR J

Vasoactive intestinal peptide: a neurotransmitter for lower esophageal sphincter relaxation.

J Clin Invest 1984; 73: 963-967

18. BLANK L, PEW WL

Cardio-esophageal relaxation (chalasia) studies on the normal infant.

Am J Roentol 1956; 76: 540-550

19. BOGGS DF, BARTLETT JR. D

Chemical specificity of a laryngeal apneic reflex in puppies.

J Appl Physiol 1982; 53: 455-462

20. BOIX-OCHOA J, LAFUENTE JM, GIL-VERNET JM

Twenty-four hour esophageal pH monitoring in gastroesophageal reflux.

J Pediatr Surg 1980; 15: 74-78

21. BOWES G, WOOLF GM, SULLIVAN CE, PHILLIPSON EA

Effect of sleep fragmentation on ventilatory and arousal responses of sleeping dogs to respiratory fragmentation.

Am Rev Respir Dis 1980; 122: 899-908

22. BOYLE JT, TUCHMAN DN, ALTSHULER SM, NIXON TE, PACK AI

Mechanisms for the association of gastroesophageal reflux and bronchospasm.

Am Rev Respir Dis 1985; 131: S16-S20

23. BRADY JP, DONOVAN M, DUMPIT FM

Absence of abnormal control of ventilation in infants with aborted sudden infant death syndrome (SIDS).

Clin Res 1980; 28: 128A

24. CARPENTER RG, GARDNER A, MCWEENY PM, EMERY JL

Multistage scoring system for indentifying infants at risk of unexpected death.

Arch Dis Childh 1977; 52: 606-612

25. CARRE IJ

Pulmonary infections in children with a partial thoracic stomach ('hiatus hernia').

Arch Dis Childh 1960; 35: 481-483

26. CARRE IJ

The natural history of the partial thoracic stomach (hiatus hernia) in children.

Arch Dis Childh 1959; 34: 344-353

27. CARSE EA, WILKINSON AR, WHYTE PL, HENDERSON-SMART DJ,

JOHNSON P

Oxygen and carbon dioxide tensions, breathing and heart rate in normal infants during the first six months of life.

J Dev Physiol 1981; 3: 85-100

28. CHRISTIE DL, O'GRADY LR, MACK DV

Incompetent lower esphageal sphincter and gastroesophageal reflux in recurrent acute pulmonary disease of infancy and children.

J Pediatr 1978; 93: 23-27

29. CHRISTIE DL

Pulmonary complicatons of oesophageal disease.

Paed Clin N A 1984; 31: 835-849

30. COHEN S, HARRIS LD

Does hiatus hernia affect competence of the gastro-esophageal sphincter?

N Engl J Med 1971; 284: 1053-1056

31. COHEN S

Swallowing and upper gastrointestinal function: specific gastrointestinal aspects.

Am Rev Respir Dis 1985; 131: S61

32. COOK RCM, BUSH GH

Tracheal compression as a cause of respiratory symptoms after repair of oesophageal atresia.

Arch Dis Childh 1978; 53: 246-248

33. COONS S, GUILLEMINAULT C

Motility and arousal in near miss sudden infant death syndrome.

J Pediatr 1985; 107: 728-732

34. CURZI-DASCALOVA L, GAUDEBOUT C, DREFYUS-BRISAC C

Respiratory frequencies of sleeping infants during the first months of life: correlations between values in different sleep states.

Early Hum Dev 1981; 5: 39-54

35. DANUS O, CASAR C, LARRAIN A, POPE CE

Esophageal reflux - an unrecognised cause of recurrent obstructive bronchitis in children.

J Pediatr 1976; 89: 220-224

36. DARLING DB, FISHER JH, GELLIS SS

Hiatal hernia and gastroesophageal reflux in infants and children: analysis of the incidence in North American children.

Pediatrics 1974; 54: 450-455

37. DARLING DB, MCCAULEY RGK, LEONIDAS JC, SCHWARTZ AM

Gastroesophageal reflux in infants and children: correlation of radiological severity and pulmonary pathology.

Radiology 1978; 127: 735-740

38. DE ABREU E SILVA FA

Clinical studies of breathing during sleep and the sudden infant death syndrome.

Ph D Thesis, University of Edinburgh 1985

39. DEMEESTER TR, WANG C-I, WERNLY JA, PELLIGRINI CA,

LITTLE AG, ET AL

Technique, indication and clinical use of 24hr esophageal pH monitoring.

J Thorac Cardiovasc Surg 1980; 79: 656-670

40. DENT J, DODDS WJ, FRIEDMANN RH, SEKIGUCHI T, HOGAN WJ,

ET AL

Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects.

J Clin Invest 1980; 65: 256-267

41. DEVEY ME, ANDERSON KJ, COOMBS RRA, HENSCHEL MJ, COATES ME

The modified anaphylaxis hypothesis for cot death. Anaphylactic sensitisation in guinea pigs fed cow's milk.

Clin Exp Immunol 1976; 26: 542-548

42. DIAMANT NE

Development of esophageal function.

Am Rev Respir Dis 1985; 131: S29-S32

43. DODDS WJ, DENT J, HOGAN WJ, HAUSER R, PATEL CK,

Mechanisms of gastroesophageal reflux in patients with reflux oesophagitis.

N Engl J Med 1982; 307: 1547-52

44. DOWNING SE, LEE JC

Laryngeal chemosensitivity: a possible mechanism for sudden infant death.

Pediatrics 1975; 55: 640-649

45. EULER AR, AMENT ME

Value of esophageal manometric studies in the gastro-esophageal reflux of infancy.

Pediatrics 1977; 59: 58-61

46. EULER AR, AMENT ME

Detection of gastroesophageal reflux in the pediatric-age patient by esophageal intraluminal pH probe measurement (Tuttle Test).

Pediatrics 1977; 60: 65-68

47. EULER AR, BYRNE J

Twenty-four esophageal intraluminal pH probe testing: a comparative analysis.

Gastroenterology 1981; 80: 957-961

48. EULER AR, BYRNE WJ, AMENT ME, FONKALSRUND EW, STROBEL CT, ET AL

Recurrent pulmonary disease in children: a complication of gastroesophageal reflux.

Pediatrics 1979; 63: 47-51

49. EULER AR

Use of Bethanecol for the treatment of gastroesophageal reflux.

J Pediatr 1980; 96: 321-324

50. FILLER RM, ROSSELLO PJ, LEBOWITZ RL

Life-threatening anoxic spells caused by tracheal compression after repair of esophageal atresia: correction by surgery.

J Pediatr Surg 1976; 11: 739-748

51. FONTAN JP, HELDT GP, HEYMAN MB, MARIN MS, TOOLEY WH

Esophageal spasm associated with apnea and bradycardia in an infant.

Pediatrics 1984; 73: 52-55

52. FORSHALL I

The cardio-oesophageal syndrome in childhood.

Arch Dis Childh 1955; 30: 46-54

53. FROGGAT P, LYNAS MA, MACKENZIE G

Epidemiology of sudden unexpected death in infants ('cot death') in Northern Ireland.

Br J Prev Soc Med 1971; 25: 119-134

54. FRY DL

Physiologic recording by modern instruments with particular reference to pressure recording.

Physiol Review 1960; 40: 753-788

55. GHAED N, STEIN MR

Assessment of a technique for scintigraphic monitoring of pulmonary aspiration of gastric contents in asthmatics with gastroesophageal reflux.

Ann Allergy 1979; 42: 306-308

56. GUILLEMINAULT C, ARIAGNO R, KOROBKIN R, NAGEL L,

BALDWIN R, ET AL

Mixed and obstructive sleep apnea and near miss for sudden infant death syndrome: 2. Comparison of near miss and normal control infants by age.

Pediatrics 1979; 64: 882-891

57. GUTTMAN FM

On the incidence of hiatal hernias in infants.

Pediatrics 1972; 50: 325-328

58. HADDAD CG, LEISTNER HL, EPSTEIN RA, EPSTEIN MAF,

MELNIKOFF B,

Abnormal breathing pattern and increased ventilatory response to CO2 in aborted SIDS infants during sleep.

Am Rev Respir Dis 1979; 119: 269A

59. HERBST JJ, BOOK LS, BRAY PF

Gastroesophageal reflux in the "near miss" sudden infant death syndrome.

J Pediatr 1978; 92: 73-75

60. HERBST JJ, MINTON SD, BOOK LS

Gastroesophageal reflux causing respiratory distress and apnea in newborn infants.

J Pediatr 1979; 95: 763-768

61. HERBST JJ

Gastroesophageal reflux and pulmonary disease.

Pediatrics 1981; 68: 132-134

62. HERBST JJ

Gastroesophageal reflux.

J Pediatr 1981; 98: 859-870

63. HEYMAN S, KIRKPATRICK JA, WINTER HS, TREVES S

An improved radionuclide method for the diagnosis of gastroesophageal reflux and aspiration in children (Milk scan).

Radiology 1979; 131: 479-482

64. HILLEMEIER AC, BIANCANI P

Antireflux mechanisms.

Am Rev Respir Dis 1985; 131: S24-S25

65. HILLEMEIER AC, LANGE R, MCCALLUM R, SEASHORE J, GRYBOSKI J

Delayed gastric emptying in infants with gastroesophageal reflux.

J Pediatr 1981; 98: 190-193

66. HOPPER AO, KWONG LK, STEVENSON DK, SHAHIN SM,

D'HARLINGUE A, ET AL

Detection of gastric contents in tracheal fluid of infants by lactose assay.

J Pediatr 1983; 102: 415-418

67. HOYOUX C, FORGET P, LAMBRECHTS L, GEUBELLE F

Chronic bronchopulmonary disease and gastroesophageal reflux in children.

Pediatr Pulmonl 1985; 1: 149-153

68. JEFFERY HE, RAHILLY P, READ DJC

Multiple causes of asphyxia in infants at high risk for sudden infant death.

Arch Dis Childh 1983; 58: 92-100

69. JEFFERY HE, REID I, RAHILLY P, READ DJC

Gastro-esophageal reflux in "near-miss" sudden infant death infants in active but not quiet sleep.

Sleep 1980; 3: 393-399

70. JOHNSON LF, DEMEESTER TR

Twenty-four-hour pH monitoring of the distal osophagus, a quantitative measure of gastroesophageal reflux.

Am J Gastroenterol 1974; 62: 325-332

71. JOLLEY SG, HERBST JJ, JOHNSON DG, MATLAK ME, BOOK LS,

Postcibal gastroesophageal reflux in children.

J Pediatr Surg 1981; 16: 487-490

72. JOLLEY SG, HERBST JJ, JOHNSON DG, MATLAK ME, BOOK LS

Esophageal pH monitoring during sleep identifies children with respiratory symptons from gastroesophageal reflux.

Gastroenterology 1981; 80: 1501-1506

73. JOLLEY SG, HERBST JJ, JOHNSTON DG

Surgery in children with gastroesophageal reflux and respiratory symptoms.

J Pediatr 1980; 96: 194-198

74. JOLLEY SG, JOHNSON DG, HERBST JJ, PENA R A, GARNIER C R

ET AL

An assessment of gastroesophageal reflux in children by extended pH monitoring of the distal esophagus.

Surgery 1978; 84: 16-24

75. KATONA PG, FRASZ A, EGBERT J

Maturation of cardiac control in full term and preterm infants during sleep.

Early Hum Dev 1980; 4: 145-159

76. KELLY DH, GOLUB H, CARLEY D, SHANNON DC

Pneumograms in infants who subsequently died of sudden infant death syndrome.

J Pediatr 1986; 109: 249-254

77. KELLY DH , SHANNON DC, O'CONNELL K

Care of infants with near-miss sudden infant death syndrome.

Pediatrics 1978; 61: 511-514

78. KOCH A, GASS R

Continuous 20-24 hr esophageal pH-monitoring in infancy.

J Pediatr Surg 1981; 16: 109-113

79. LAWSON EE

Prolonged central respiratory inhibition following reflex-induced apnea.

J Appl Physiol 1981; 50: 874-879

80. LEAPE LL, HOLDER TM, FRANKLIN JD, AMOURY RA, ASHCRAFT KW

Respiratory arrest in infants secondary to gastroesophageal reflux.

Pediatrics 1977; 60: 924-928

81. LILLY J, RANDOLPH J

Hiatal hernia and gastroesophageal reflux in infants and children.

J Thorac Cardiovasc Surg 1968; 55: 42-54

82. MACFADYEN U, HENDRY GMA, SIMPSON H

Gastro-oesophageal reflux in near-miss sudden infant death syndrome or suspected recurrent aspiration.

Arch Dis Childh 1983; 58: 87-91

83. MALMUD LS, FISHER RS

Gastroesophageal scintigraphy.

Gastrointest Radiol 1980; 5: 195-204

84. MALMUD LS, FISHER RS

Radionuclide studies of esophageal transit and gastro-esophageal reflux.

Seminars in Nuclear Medicine 1982; 12: 104-115

85. MANSFIELD LE, STEIN MR

Gastroesophageal reflux and asthma: a possible reflex mechanism.

Ann Allergy 1978; 41: 224-226

86. MASON S

Some aspects of gastric function in the newborn.

Arch Dis Childh 1962; 37: 387-391

87. MCCAULEY RGK, DARLING DB, LEONIDAS JC,SCHWARTZ AM

Gastro-oesophageal reflux in infants and children: a useful classification and reliable physiologic technique for its demonstration.

Am J Roentgenol 1978; 130: 47-50

88. MENDELSON CL

The aspiration of stomach contents into the lungs during obstetric anaesthesia.

Am J Obstet Gynaecol 1946; 52: 191-204

89. MENON AP, SCHEFFT GL, THACH BT

Apnea asscociated with regurgitation in infants.

J Pediatr 1985; 106: 625-629

90. MILLER RA

Gastric acidity during the first of life.

Arch Dis Childh 1942; 17: 198-209

91. MORAN TJ

Pulmonary edema produced by intratracheal injection of milk, feeding mixtures, and sugars.

Am J Dis Child 1953; 86: 45-50

92. MOROZ SP, ESPINOZA J, CUMMING WA, DIAMANT NE

Lower esophageal sphincter function in children with and without gastroesophageal reflux.

Gastroenterology 1976; 71: 236-241

93. MULLER W, RIEGER CHL, von der HARDT H

Increased concentrations of milk antibodies in recurrent pulmonary aspiration in infants and young children.

Acta Paediatr Scand 1985; 74: 660-663

94. NEUHAUSER EBD, BERENBERG W

Cardio-esophageal relaxation as a cause of vomiting in infants.

Radiology 1947; 48: 480-483

95. NIELSON DW

Gastroesophageal reflux as a risk factor for recurrent apnea in infants.

Paediatr Res 1983; 17: 386A

96. OGILVIE AL, JAMES PD, ATKINSON M

Impairment of vagal function in reflux oesophagitis.

Quart J Med 1985; 54: 61-74

97. ORENSTEIN SR, WHITINGTON PF, ORENSTEIN DM

The infant seat as treatment for gastroesophageal reflux.

N Engl J Med 1983; 309: 760-764

98. PARKER AF, CHRISTIE DL, CAHILL JL

Incidence and significance of gastroesophageal reflux following repair of esophageal atresia and tracheoesophageal fistula and the need for anti-reflux procedures.

J Pediatr Surg 1979; 14: 5-8

99. PARMALEE AH, STERN E, HARRIS MA

Maturation of respiration in premature and young infants.

Neuropadiatrie 1972; 3: 294-304

100. PATRICK FG

Investigation of gastroesophageal reflux in various positions with a two-lumen pH electrode.

Gut 1970; 11: 659-667

101. PELLEGRINI CA, DEMEESTER TR, WERNLY JA, JOHNSON JA,

SKINNER DB

Alkaline gastroesophageal reflux.

Am J Surg 1978; 135: 177-184

102. PERKETT EA, VAUGHAN RL

Evidence for a laryngeal chemoreflex in some human preterm infants.

Acta Paediatr Scand 1982; 71: 969-972

103. PERLMAN MA

Gastroesophageal reflux (GER): a potential life-threatening cause of apnea.

Paediatr Res 1983; 17: 387A

104. PETERSON DR, CHINN NM, FISHER LD

The sudden infant death syndrome: repetitions in families.

J Pediatr 1980; 97: 265-267

105. PHILLIPSON EA

Control of breathing during sleep.

Am Rev Respir Dis 1978; 118: 909-939

106. PLAXICO DT, LOUGHLIN GM

Nasopharyngeal reflux and neonatal apnea.

Am J Dis Child 1981; 135: 793-794

107. RAMENOFSKY ML, LEAPE LL

Continuous upper pH monitoring in infants and children with gastroesophageal reflux, pneumonia, and apneic spells.

J Pediatr Surg 1981; 16: 374-378

108. RECHTSCHAFFEN A, KALES A

A manual of standard terminology, techniques, and scoring system for states of human subjects.

Washington: National Institute of Health, 1968 (No 204).

109. REID LM

Developmental anatomy, embryology of the foregut.

Am Rev Respir Dis 1985; 131: S60-S61

110. ROSEN CL, FROST JD, HARRISON GH

Infant apnea: polygraphic studies and follow-up monitoring.

Pediatrics 1983; 71: 731-736

111. ROVELSTAD RA, OWEN JR. CA, MAGATH TB

Factors influencing the continuous recording of in situ pH of gastric and duodenal contents.

Gastroenterology 1952; 20: 609-624

112. SCHEY WL, REPLOGLE R, CAMPBELL C, MEUS P, LEVINSKY RA

Esophageal dysmotility and the sudden infant death syndrome.

Radiology 1981; 140: 67-71

113. SCHWARTZ DJ, WYNNE JW, GIBBS CP, HOOD CI, KUCK EJ

The pulmonary consequences of aspiration of gastric contents at pH values greater than 2.5.

Am Rev Respir Dis 1980; 121: 119-126

114. SEIBERT JJ, BYRNE WJ, EULER AR, LATTURE T, LEACH M,

Gastroesophageal reflux - the acid test: scintigraphy or the pH probe.

AJR 1983; 140: 1087-1090

115. SHANNON DC, KELLY D

Abnormal ventilatory response to CO2 during quiet sleep in aborted SIDS.

Chest 1979; 73: 301

116. SHANNON DC, KELLY DH, O'CONNEL K

Abnormal regulation of ventilation in infants at risk for sudden-infant-death.

N Engl J Med 1977; 297: 747-750

117. SHANNON DC, KELLY DH

Impaired Regulation of Alveolar Ventilation and the Sudden Infant Death Syndrome.

Science 1977; 197: 367-368

118. SIMPSON H, MACFADYEN U

Near-miss for sudden infant death syndrome: a clinical approach.

Recent Adv Paed 1986; 8: 201-216

119. SONDHEIMER JM, MORRIS BA

Gastroesophageal reflux among severely retarded children.

J Pediatr 1979; 94: 710-714

120. SONDHEIMER JM

Continuous monitoring of distal esophageal pH: a diagnostic test for gastroesophageal reflux in infants.

J Pediatr 1980; 96: 804-807

121. SPITZER AR, BOYLE JT, TUCKMAN DN, FOX WW

Awake apnea associated with gastroesophageal reflux: specific clinical syndrome.

J Pediatr 1984; 104: 200-205

122. STANTON AH, DOWNHAM MAPS, OAKLEY JR, EMERY JL, KNOWELDEN J

Terminal symptoms in chidren dying suddenly and unepectedly at home.

BMJ 1978; 2: 1249-1251

123. STANTON AN, OAKLEY JR

Pattern of illnesses before cot deaths.

Arch Dis Childh 1983; 58: 878-881

124. STEINSCHNEIDER A, RABUZZI DD

Apnea and airway obstruction during feeding and sleep.

Laryngoscope 1976; 86: 1359-1366

125. STEINSCHNEIDER A

Prolonged apnea and the sudden infant death syndrome: clinical and laboratory observations.

Pediatrics 1972; 50: 646-654

126. STEINSCHNEIDER A

Nasopharyngitis and prolonged sleep apnea.

Pediatrics 1975; 56: 967-971

127. STEINSCHNEIDER A

Nasopharyngitis and the sudden infant death syndrome.

Pediatrics 1977; 60: 531-533

128. STROBEL CT, BYRNE WJ, AMENT ME, EULER AR

Correlation of esophageal lengths in children with height: Application to the Tuttle test without prior esophageal manometry.

J Pediatr 1979; 94: 81-84

129. STY JR, STARSHAK RJ

The role of radionuclide studies in pediatric gastro-intestinal disorders.

Seminars in Nuclear Medicine 1982; 12: 156-172

130. THACH BT, MENON A

Pulmonary protective mechanisms in human infants.

Am Rev Respir Dis 1985; 131: S55-S58

131. TONKIN SL, PARTRIDGE J, BEACH D, WHITENEY S

The pharyngeal effect of partial nasal obstruction.

Pediatrics 1979; 63: 261-267

132. TUCHMAN DN, BOYLE JT, PACK AI, SCWARTZJ, KOKONOS M, ET AL

Comparison of airway responses following tracheal or oesophageal acidification in the cat.

Gastroenterology 1984; 87: 872-881

133. TUTTLE SG, RUFIN F, BETTARELLO A

The physiology of heartburn.

Ann Intern Med 1961; 55: 292-300

134. VAN SOMEREN V, STOTHERS JK

A critical dissection of obstructive apnea in the human infant.

Pediatrics 1983; 71: 721-725

135. WAGENER JS, TAUSSIG LM

Chronic aspiration pneumonitis.

Ariz Med 1976; 37: 220-

136. WAILOO MP, EMERY JL

The trachea in children with tracheo-oesophageal fistula.

Histopathology 1979; 3: 329-338

137. WALSH JK, FARREL MK, KEENAN WJ, LUCAS M, KRAMER M

Gastroesophageal reflux in infants: Relation to apnea.

J Pediatr 1981; 99: 197-201

138. WERLIN SL, DODDS WJ, HOGAN WJ, ARNDORFER RC

Mechanisms of gastroesophageal reflux in children.

J Pediatr 1980; 97: 244-249

139. WERNE J

Post mortem evidence of acute infection in unexpected death in infancy .

Am J Pathol 1942; 18: 759-761

140. WILKINSON JD, DUDGEON DL, SONDHEIMER JM

A comparison of medical and surgical treatment of gastroesophageal reflux in severely retarded children.

J Pediatr 1981; 99: 202-205

141. WILLIAMS AL
Tracheobronchitis and sudden infant death syndrome.
Pathology 1980; 12: 73-78

142. WINTER HS, GRAND RJ
Gastroesophageal reflux.
Pediatrics 1981; 68: 134-135

143. WOLFE JE, BONE RC, RUTH WE
Diagnosis of gastric aspiration by fiberoptic bronchoscopy.
Chest 1976; 70: 458-459

144. WYNNE JW, MODELL JH
Respiratory aspiration of stomach contents.
Ann Intern Med 1977; 87: 466-474

145. WYNNE JW, RAMPHAL R, HOOD CI
Tracheal mucosal damage after aspiration.
Am Rev Respir Dis 1981; 124: 728-732

ABSTRACT

TITLE: GASTRO-OESOPHAGEAL REFLUX AND THE SUDDEN INFANT DEATH SYNDROME

AUTHOR: JAMES Y PATON

Gastro-oesophageal reflux (GOR) has been reported in infants presenting as 'near miss' for the sudden infant death syndrome (SIDS). This study investigated the occurrence of GOR in infants at increased risk for SIDS and examined the relation between GOR and cardio-respiratory abnormalities, particularly during sleep.

82 infants were studied by radionuclide scan: suspected tracheo-bronchial aspiration (7), sibs of SIDS victims (12), persistent possetters (8), mentally retarded (4), minor cardio-respiratory 'events' eg choking (29) and 'near miss' for SIDS (22). In 22 children respiration and heart rate were recorded simultaneously. To assess the relationship between GOR and cardio-respiratory events during sleep 24 infants, including 17 with significant GOR on scan, were monitored polygraphically during sleep at night with simultaneous lower oesophageal pH monitoring to detect acid GOR.

Radionuclide scan images were collected for two hours following a labelled milk feed. Severe GOR (to the upper oesophageal/pharyngeal level) was observed in 58 (70%), from each of the groups studied. 7/22 infants had both severe GOR and respiratory pauses >6sec but no clear relation between GOR and such pauses was observed.

The night studies confirmed that GOR was frequent in all 'at risk' groups. Cardio-respiratory abnormalities were also frequent but only 5 central apneas lasted longer than 10sec and no significant bradycardia (<80 bpm for >=10sec) was observed. A pathological finding was the presence of 56 mixed and obstructive apneas. No direct temporal relation was observed between the occurrence of GOR and cardio-respiratory abnormalities. An association between gross body movements and pH drops was noted with movement often preceding a pH drop.

These studies confirm that GOR is common in 'near miss' SIDS infants but demonstrate that it is also found frequently in other 'at risk' groups. Despite its frequent occurrence, GOR did not precipitate respiratory pauses or bradycardia.