ASPECTS OF PAEDIATRIC GASTRO OESOPHAGEAL SCINTIGRAPHY

by

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For my mother and wife,

in partial thanks for so much that is owed to you

CONTENTS

ABSTRACT

This work is concerned with the application of scintigraphy in studies of foregut motility in paediatric patients; notably oesophageal transit during swallowing, gastro oesophageal reflux (GOR) and stomach emptying as measured by the gastric contents 30 and 120 minutes after deglutition of liquid. Relevant anatomy, physiology, pathophysiology and non radioisotopic methods of gastro oesophageal examination are outlined. The extremely important question of dose deposited by ionising radiation in paediatric patients is also considered. Because currently available estimations of absorbed dose after swallowing non absorbable radionuclides are unsatisfactory and often contradictory, a new model was derived. It is based on more physiological principles than previous models, with a continuously varying exponential passage between four compartments in the gastrointestinal tract.

From a review of previous work and our experience, a standard method of examination was developed. There is emphasis on normal physiological manoeuvres. The broad extent of useful information available in the study stems from the positions in which the patient is investigated, the quantity of labelled fluid swallowed, its physiological nature and observations of oesophageal transit, GOR, gastric emptying and pulmonary aspiration after two hours.

The wide range of paediatric problems amenable to investigation by this means is described, including those of a life threatening nature. Also the importance of using this examination to determine the likelihood of successful surgical intervention in the gastro oesophageal region is explained. By using the observations made during swallows in neonates, the closure of the lower oesophageal sphincter (LOS) was observed during a short series of rapid

deglutitions. This extends previous knowledge of the function of the neonatal LOS. These findings were very clearly demonstrated by the condensed image technique.

A comparison between the abilities of radiology and scintigraphy to detect GOR in paediatric patients, with and without oesophagitis, gives unequivocal results in favour of scintigraphy. Two independent clear correlations between oesophageal transit time and the severity of GOR and age are demonstrated by variance and correlation analysis. The mean duration of GOR, maximum height of a GOR, gastric contents 30 and 120 min after deglutition, the effect of the nature of liquid swallowed and age are also examined and their relations are described. The application of the method to assess drug response is illustrated by the paediatric use of cisapride, an experimental drug which increases acetylcholinesterase release.

The deductions from this work include values of the radiation dose deposited in paediatric patients of various ages, after swallowing non absorbed Tc-99m compounds. Other contributions are a scintigraphic means to allow recognition of the importance of oesophageal dysmotility in paediatrics, especially in the absence of GOR and its relevance to the efficacy of surgery in cases of apparent GOR. Also this gastro oesophageal scintigraphic study provided information on the paediatric use of cisapride, the relevance of GOR to repeated respiratory problems and the recognition of a new paediatric syndrome analagous to the diffuse oesophageal spasm syndrome of adulthood. It has been demonstrated that a routine, uncomplicated, paediatric scintigraphic examination, useful for investigating a wide range of problems in both a first and third world setting is possible for a nuclear medicine practitioner with normally available radiopharmaceuticals, equipment and radiographical expertise.

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"Who is wise? He who learns from all men."
Ben Zoma; Ethics of the Fathers, Chap 4.

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ABBREVIATIONS

All abbreviations which may not be standard symbols for units etc are defined when first introduced into the text in addition to being included in the following list if used more than once.

al	Alii or alius
Ba	Barium
CNS	Central nervous system
CSIR	Council for Scientific and Industrial Research
CT	Computed tomography
d	day(s)
DMSA	Dimercapto succinic acid
DTPA	Diethylene triamine pentacetic acid
Eqn	Equation
F	Female
GAST 30	Gastric contents 30 minutes after deglutition as % of swallowed activity
GAST 120	As GAST 30, but after 120 minutes
GIT	Gastro intestinal tract
GOR	Gastro oesophageal reflux(es)
IMP	N-isopropyl I-123 iodoamphetamine
In	Indium
LET	Linear energy transfer
Kr	Krypton
LOS	Lower oesophageal sphincter
LOSP	LOS pressure
LI	Large intestine
LLI	Distal LI
M	Male
min	Minute(s)
mo	Month(s)
ms	Millisecond(s)
N	Normal
No	Number
OTT	Oesophageal transit time
Ref	Reference
ROI(s)	Region(s) of interest
s	seconds(s)
SD	Standard deviation
SI	Small intestine
SIDS	Sudden infant death syndrome
Tc	Technetium
TOF	Tracheo oesophageal fistula
ULI	Proximal LI
u	Micro
y	year(s)

CHAPTER 1: INTRODUCTION: SOME CHARACTERISTICS OF NUCLEAR MEDICINE AND ITS RELATION TO PAEDIATRICS

> "Every art and every scientific inquiry, and similarly every action and purpose may be said to aim at some good.... As there are various actions, arts, and sciences, it follows that the ends are various, thus health is the end of medical art.... It often happens that a number of such arts or sciences combine for a single purpose."
> Aristotle, Ethics, Book 1.

Nuclear medicine has two main advantages over most other in vivo imaging diagnostic methods. These are the functional information that it can supply and its non invasive character. This is relevant to both paediatrics and adult medicine. Radioisotopic techniques can be applied to many organs, systems and regions and with the advent of dedicated computer systems and advances in the acquisition and processing of dynamic images, applications have increased manyfold in their variety and in the amount of diagnostic information which can be provided.

As paediatrics is not the medicine of very small sized adults, so paediatric nuclear medicine is not a diagnostic modality providing miniature images of the corresponding studies in adults. Apart from the different range of diseases and disorders which affect children, the radiation burden experienced by them has a different significance from that of adults. Some Xray studies which are practised on children, such as an upper gastro intestinal series or a search for vesico ureteric reflux, have in their scintigraphic counterpart a more sensitive investigation with a significantly lower radiation dose (Guillet et al 1983). Yet many writers appear to pay little attention to this aspect and clinical review articles still can ignore the information which can be supplied by nuclear medicine (Watson 1987, Katz et al 1987, Bowen et al 1987). This attitude can extend to Institutions. Recently the establishment of a large multidisciplinary centre to study swallowing at the Johns Hopkins University included ten medical and two

paramedical specialities and dentistry but no nuclear medicine (Ravich et al 1985).

The use of a gamma camera to image radiopharmaceuticals labelled with Tc-99m has probably resulted in the greatest advances in scintigraphy. In general the spatial resolution available from scintigraphy is less than that of Xray images, being sometimes almost an order of magnitude lower. However an analysis of a series of dynamic images of a radiotracer often provides information concerning function. This ability has greatly increased in recent years with the availability of dedicated computer systems. The integrated distribution of activity in successive images, which may be recorded at required time intervals, can allow analysis of the passage of the radionuclide or the medium which carries the radioisotope. There is frequent exploitation of this technique in studies of different systems and organs. An assumption that is usually justified, supposes thorough mixing of the radiotracer with the medium whose motion is under study, for this principle can be used to measure movement of blood, inspired gases, lymph, cerebro spinal fluid, urine, tears and other fluids. Other dynamic radionuclide examinations, for example with the observed passage of swallowed radiotracers, allow the function of hollow muscular organs to be studied.

The diagnostic use of radioisotopes in clinical paediatrics has increased steadily in the last few years and at most paediatric hospitals in large centres there is access to nuclear medicine facilities. The introduction of conveniently produced radionuclides with favourable radiation characteristics has further increased the use of nuclear medicine techniques in paediatrics (Conway 1972). The detected radiation should preferably be a pure gamma emission and, in terms of physical and biological properties, the marked compound's half life should be short enough to avoid excess irradiation of the

patient, but long enough to allow sufficient counts to be recorded in an appropriate time and for the study to be completed.

There are various reasons for requiring a diagnostic nuclear medicine investigation. Usually scintigraphic investigations are safer, simpler and cheaper than those using other modalities of special investigation, so they are useful for screening, particularly when a sensitive but non specific test is appropriate. Hence it is often useful as the first of several possible investigations. In this vein it should be stressed that since the data provided by nuclear medicine results from a mechanism which usually is different from that of alternative investigations, it is best considered as a complementary or supplementary study with respect to the other investigations. Where functional information is required it is frequently the only practical method for obtaining such information. Examples are the investigations of pulmonary ventilation and perfusion, cerebral uptake of amine and other lipophilic compounds, parathyroid visualisation, quantitation of various refluxed liquids and differential renal function. Monitoring the progress in a patient is best with a safe, simple, inexpensive procedure. This is often characteristic of nuclear medicine as exemplified by following up the effect of appropriate drugs and thickened feeds for a neonate with gastro oesophageal reflux (GOR), or the radionuclide cystogram after treatment for vesico-ureteric reflux. Even though nuclear medicine is not primarily used for identifying anatomical abnormalities, it can do so, but often by measuring an aspect of function. But using single photon scintigraphy it can be difficult to detect a lesion which affects radiotracer distribution in a volume with greatest dimension less than about 1 cm.

The nature of the patient and his problems are as relevant to scintigraphy as the techniques themselves. Paediatric diseases, responses and problems differ radically from those of adults. Yet, because of experience

obtained initially from nuclear medicine studies in adults, some ideas of the resulting possible clinical advantages and safety is gained. Although the resulting data cannot be directly extrapolated to paediatric patients, much that is of use can be deduced, for example an evaluation of a new diagnostic method.

The radiation absorbed by a child can have a different significance from that experienced by an adult in part because of subsequent growth and development. Although comparable radiation risks are found in adults, the greatly increased life expectancy for a child makes it more likely that stochastic effects, such as induced malignancy and genetic damage, will be expressed. For example, since a child of age 10 years may have a life expectancy of over 60 years, irradiation of paediatric bone marrow from diagnostic investigations is more likely to cause leukaemia than even huge doses in an elderly person (Parker 1986). Also paediatric gonadal dose should be minimised since children's germinal epithelium is particularly sensitive to ionising radiation (Kereiakes et al 1980) and children still have their reproductive years before them. Further, at different paediatric ages anatomical proportions and separations vary, hence absorbed doses differ. The crucial question of irradiation by the relevant diagnostic radionuclides and its effects will be considered in detail in Chapters 8 and 9.

Although the applications of nuclear medicine may seem at first sight sophisticated, expensive and suitable only for highly developed countries, in fact there are facilities established almost everywhere, including third world countries such as Niger (Syrota 1986), Zambia (Mulaisho et al 1981), the Phillipines (Felizardo 1982), Malaysia (Rasid et al 1986), Thailand, Tunisia, Gambia, Sri Lanka and Nigeria (Ajdukiewicz et al 1985). The nuclear technologist can work efficiently in such countries, for appropriate isotopes can be made available on a world wide basis. Modern gamma cameras are

reliable and able to function effectively far from the nearest service facilities (Romsai Suwanik 1984).

The range of existing nuclear medicine examinations is very broad and covers most systems and organs. In this work we illustrate the breadth of its application by describing a study of aspects of function of oesophagus, stomach and small gut. It was rapidly developed into a routine study providing a wide variety of information so permitting over 600 paediatric patients to be studied in the first 2 years. The resulting information provided diagnoses of greatly differing conditions (including the life threatening sudden infant death syndrome or SIDS) and decisions to be made concerning management or follow up in appropriate situations. The gamma camera, computer and radiopharmaceutical (Tc-99m sulphur colloid) required for the gastro oesophageal studies are all standard and this allows the routine procedure developed to be widely practised.

The evolution of the examination, its results and their significance are described in the following chapters.

CHAPTER 2: RELEVANT ANATOMY, PHYSIOLOGY AND PATHOPHYSIOLOGY

> "The ends of the master arts or sciences, whatever they may be, are more desirable than those of subordinate arts or sciences, as it is for the sake of the former that the latter are pursued."
> Aristotle; Ethics, Book 1.

Normal anatomy and physiology of relevant parts of the foregut will be discussed together where this is appropriate. The sources of standard material for this chapter have included "Gray's Anatomy" (Williams et al 1980), Guyton's "Physiology" (Guyton 1986) and other more specialised works (Baron et al 1981, Godfrey et al 1979).

2.1 Embryology

The embryology of the gastro intestinal system has been clearly described (Patten 1976, Moore 1983). The primitive gut is walled in by the splanchnopleure at about sixteen days and two or so days later the primitive foregut and hindgut are distinguished as parts of the intra embryonic portion of the gut. In the caudal part of the foregut a fusiform swelling, which will become the stomach, becomes distinguishable by the end of the first month. Approximately simultaneously with the formation of the primitive stomach, a median ventral swelling grows from the laryngotracheal groove at the level of the fourth pharyngeal pouch. Although this will provide larynx, trachea, bronchi and lungs it is usually called the lung bud. Incomplete division of the foregut into its digestive and respiratory parts will result in various forms of tracheo oesophageal fistula (TOF) and other well known anomalies of this region.

The oesophagus proper is a uniform tube forming the foregut between pharynx and stomach. Its smooth muscle arises from splanchnic mesenchyme and initially the organ is proportionally short. But as the stomach moves caudally the oesophageal relative length increases. Part of the oesophageal

dorsal mesentery becomes the median portion of the diaphragm and part of the crura. The stomach is formed parallel to the principal axis of the embryo and attains its final position by two main movements. Firstly at about five weeks there is a counterclockwise rotation, as viewed from the caudal end, about an axis in a sagittal plane parallel to the longitudinal axis of the embryo. Then there is a further clockwise rotation about an orthogonal axis in the same sagittal plane, as viewed from a ventral standpoint. The mesenteries are taken with the stomach on its rotations. The duodenum, which arises from caudal foregut and cranial midgut, grows rapidly into a C shaped loop which projects ventrally while the stomach rotates.

The intestines commence to elongate at the same time as the development of stomach and duodenum. Firstly there is narrowing of diameter and lengthening as the gut moves in the form of a loop into the umbilical coelom. Just beyond the loop's apex the gut communicates with the yolk stalk. The caecum develops as a small swelling just caudal to this communication. The small intestine results from the part of the gut situated cephalic to the caecal enlargement.

2.2 Anatomy

The oesophagus proper is a hollow muscular organ, flattened in the anterior posterior direction, except during deglutition. It extends from the cricopharyngeal muscle superiorly, to the lower oesophageal sphincter (LOS). As elsewhere in the gastro intestinal tract (GIT) there are inner circular and outer longitudinal muscular fibres. It is lined with a mucosa of stratified squamous epithelium and is susceptible to damage by acid and alkali, because it is non keratinised and has no other protection. Striated muscle is found proximally and its fibres gradually interdigitate with fibres of smooth muscle near to the level of the aortic arch so that the inferior oesophagus is composed virtually only of smooth muscle. The anatomical relations, blood

supply etc of the oesophagus are well known (Williams et al 1980, Romanes 1981) and essentially the same lymphatic drainage scheme had been taught by anatomists whether they published in 1901 (Gray 1901) or the early 1980s (Williams et al 1980, Romanes 1981). However the lymphatic drainage has recently been shown by scintigraphic means (Baba et al 1985, Kato et al 1985, Szilvási et al 1986) to be much more variable than that traditionally described by accepted authorities on the subject.

The proximal part of oesophagus is the upper oesophageal sphincter, mainly composed of the cricopharyngeus. Unlike the LOS it is a distinctly muscular entity. The LOS is a functional sphincter rather than a distinct and recognisable anatomical entity, although a thickened muscular segment has been described (Lieberman et al 1979). In effect it is the distal portion of the oesophageal wall which responds to stimuli in a different manner from the rest of the muscle so providing a sphincteric action. Both these sphincters have a high resting tone compared to adjacent parts of the gastro intestinal tract. They relax after receiving an appropriate stimulus to allow passage of a swallowed bolus in a distal direction and then contract to prevent back flow.

2.3 Physiology

Deglutition starts with coordinated voluntary musculature action as the tongue and buccal muscles propel a bolus towards the pharynx. Then appropriate muscular action guides the bolus through the oesophagus with the LOS opening to allow passage through to the stomach. Deglutition is classically described in three sequential stages; buccal, pharyngeal and oesophageal. In terms of a mechanical description the tongue acts as a piston within a cylinder (the pharynx) with two valves. These two uni-directional valves in the pharynx are the soft palate, which prevents the bolus moving superiorly, and the cricopharyngeal muscle which opens to allow the bolus to

be projected distally into the oesophagus. The body of the oesophagus and the LOS are like a propulsive pump with a peristaltic action and a distal exit valve, the LOS. Successful deglutition depends on appropriate action from all these components and it is a totally reflex action after initiation. Chewed food is formed into a lubricated bolus mixed with saliva in the mouth and when ready to be swallowed it is propelled back into the oropharynx by the tongue. Simultaneously the soft palate and posterior pharyngeal wall close the passage between buccal cavity and nasopharynx. The oropharynx moves so the bolus enters the hypopharynx with the laryngeal entrance closed. Then the cricopharyngeus opens and the bolus enters the oesophagus. This is the start of the third and last stage (oesophageal) of swallowing, which follows the pharyngeal stage. For satisfactory function of the upper oesophageal sphincter there are narrow limits on the relative timing of the successive contractions of inferior pharyngeus and cricopharyngeus. Uncoordinated timing of contraction and relaxation and muscle weakness or paresis (Ekberg 1986) are causes of abnormal peristalsis in this region, as elsewhere.

During the pharyngeal stage of swallowing, the hypopharyngeal pressure rises sharply to about 45 mmHg in the adult. Since this is much greater than the mid oesophageal (i.e. intrathoracic) pressure of about 6 mmHg below atmospheric pressure, the bolus passes rapidly into the oesophagus. Recently the pharyngeal phase of a normal swallow has been shown to be one of two distinct types (Curtis et al 1984). One is akin to the sucking swallow of a bottle fed infant whose oropharynx is cleared of air before the bolus enters it. A continuous peristaltic wave from the buccal cavity sweeps the bolus through the pharynx to the oesophagus. In the other type the oro and hypopharynx are filled with air so the bolus drops towards the oesophagus. The pharyngeal contraction starts later in this case than with the sucking swallow. As the bolus leaves the hypopharynx the upper oesophageal sphincter closes and this sets off a peristaltic wave which moves distally.

In the upper oesophagus the component of the force directed radially inwards exerted by the contracting muscle exerts a maximum pressure, which is about half of the homologous pressure exerted by the cricopharyngeus. In this way the bolus can only be displaced distally. The upper oesophageal sphincter probably has several functions which include the prevention of retrograde motion of a swallowed bolus, so reducing the chances of pulmonary aspiration. It also closes the oesophagus during respiration, thus restricting the amount of air that is swallowed. Oesophago pharyngeal reflux has been observed in adults with reduced upper oesophageal resting pressure (Gerhardt et al 1980) but not in infants. In infants upper oesophageal resting pressure, pharyngeal contraction amplitude, duration and velocity are not related to the presence or absence of gastro oesophageal reflux (GOR) (Sondheimer 1983).

As the peristaltic wave moves along the oesophagus, the upper sphincter relaxes slightly to take up its normal resting tone. Such a wave, initiated by the action of swallowing, with or without a bolus, is primary peristalsis. When such a primary peristaltic wave (the (n-1)st) is in progress and another swallow (the nth) is initiated, it has been shown that in normal adults the nth swallow sometimes causes its predecessor's peristalsis to stop. In such a series only the last swallow continues to the LOS. These findings have not been previously described for paediatric patients, but are observed in this work. For adults they have been reported after studies using cinēradiology (Sodeman 1974), manometry (Ask et al 1980) and nuclear medicine (Ham et al 1985b). Using the latter it has been shown that transit time may depend on body posture or volume of bolus swallowed (Ham et al 1984).

Primary peristalsis results in much movement of the oesophageal wall as the longitudinal muscle contracts and the bolus descends. The LOS, normally at or just below the oesophageal hiatus can move proximally into the thorax during a normal swallow. Following passage of the bolus into the stomach, the

LOS regains its normal resting position. The absence of such restoration of position suggests a hiatal hernia.

Control of oesophageal function depends on nerves, muscles and hormones. Propagation and amplitude of the orderly, progressive primary and secondary peristaltic waves are very similar although they depend on different neural mechanisms. Primary peristalsis is a response to swallowing and secondary peristalsis results from distension of the oesophagus. Both forms of peristalsis have increasing amplitude and decreasing velocity of the peristaltic wave as it travels distally. Secondary peristalsis is probably independent of vagal activity. This is unlike primary peristalsis, which is initiated by means of a swallowing centre in the reticular formation of the medulla and then followed by a motor response in the vagus nerves. Primary and secondary peristaltic waves move smoothly along the oesophagus probably because the different portions of involuntary muscle have increasing latencies for onset of excitation by efferent signals. Nerves within the oesophagus may contain this mechanism of variable latent period and can be excited by efferent vagal pathways (primary peristalsis) or directly by stretch receptors (secondary peristalsis). An alternative explanation is that the swallowing centre determines the oesophageal muscle firing pattern. External pressures acting on the oesophagus can slow transit of a swallowed bolus at a localised site, for example the effect of the left atrium in patients with mitral valve disease (Channer et al 1984). Isolated or segmented contractions that do not progress distally may occur at one or several sites simultaneously, in isolation, or superimposed on otherwise normal primary or secondary waves. Such contractions are abnormal and are termed tertiary contractions. Aperistalsis may occur with severe motor abnormalities secondary to nerve transmission malfunction, but an oesophagus described as aperistaltic may have tertiary contractions present.

The interactions between circulating compounds and the oesophagus are varied. Cholinergic stimulation, histamine and alpha adrenergic drugs increase the peristaltic amplitude, while anticholinergic substances decrease this amplitude. They have no effect on the steady distal movement of the peristaltic wave.

The oesophago gastric junction has been much studied because of the complexity and importance of its action and some of its properties will now be discussed. There is no distinctive anatomical LOS, but microscopic dissection does show certain characteristics. In three species (opossum, cat and rhesus monkey) there is physiological specialisation of tissue from this region in terms of innervation and mechanical properties of the circular muscle in comparison with neighbouring stomach and oesophagus (Christensen et al 1973). Although this is also likely to be true for humans, ethical considerations prevent similar investigations, as they would involve experiments on the isolated oesophagus and stomach. The LOS separates the positive pressure region of the abdomen, and hence stomach, from the negative pressure of the intra thoracic region and oesophageal body (De Meester et al 1979). Its normal action therefore prevents GOR.

However the normal and abnormal function of the LOS is not fully understood. For example, even the effect on the lower oesophageal sphincter pressure (LOSP) of as direct and well defined a physical influence as intra abdominal pressure is unclear. There is also considerable confusion as evidenced by lack of consensus on the following points. Studies of the effects of respiration still remain to be fully elucidated for they have given contradictory results (Boyle et al 1984). The threshold of response of the LOS to circulating factors is usually lower than that of the oesophagus and the effects of very many neural transmitters, hormones and other active compounds on the LOS have been studied, but their importance is not clear.

Some, (for example acetylcholine, serotonin, prostaglandin F2 alpha, motilin, substance P, histamine and pancreatic polypeptide) increase the LOSP and others (such as secretin, cholecystokinin, vasoactive intestinal peptide, dopamine, prostaglandins E1 and E2, cyclic nucleotides, glucagon and many common drugs) decrease it (Brock-Utne et al 1986). Serum gastrin levels are probably related to LOS function in adults yet for healthy neonates aged 1 and 4 days, LOSP is neither correlated with age nor serum gastrin levels although there was some relation to eating and composition of the food (Dent et al 1983). It seems that for neonates serum gastrin levels are not concerned with maintaining resting LOSP values (Moroz et al 1981), but may control small gut uptake of galactose and glycine (Schwartz et al 1986).

In the very young, possetting is a well known phenomenon and it may be associated with a reduction of LOSP. It seems likely that in humans and other animals the LOS matures after birth (Bilistreri et al 1983). To investigate this possibility LOS function was studied in normal infants and children. In one centre the following changes in LOSP were observed. By the age of 2 weeks the LOSP was well developed and its value (43,3 $\pm$ 2,4 mmHg) remained at this level till age about 1 year and then decreased to a value of (30,6 $\pm$ 2,3 mmHg) in children aged over 1 year (Moroz et al 1976). Another report described the results of 4 000 manometric determinations in 680 healthy infants aged between 1 day (d) and 6 months (mo). By the age of 6 to 7 weeks there was sufficient LOSP to prevent significant reflux. The most important factor in LOS maturation was stated to be neither birthweight nor gestational age, but postnatal age (Boix-Ochoa et al 1976).

Abnormal anatomy of the gastro oesophageal region can also be important. The hiatal hernia, a well recognised entity, is frequently asymptomatic. The majority are sliding and more likely to be associated with GOR, but the rolling variety is more prone to mechanical complications such as

strangulation or gastric volvulus. Mixed sliding and rolling hiatal herniae are liable to suffer the complications of each type, including oesophagitis (Berstad 1986), stenosis, frank or occult haemorrhage and respiratory problems (Gosselin 1982).

In essence, the anatomy and physiology of the oesophagus are concerned with its main functions. The first is the transport of a swallowed bolus to the LOS in an orderly fashion by sequential muscle contractions. The second is the intrinsic resting tone of the LOS to prevent reflux and the third a mechanism for its relaxation to allow passage of the swallowed bolus. Each function has its part to play in oesophageal emptying (Phaosawasdi et al 1981, Helm et al 1980, Meyer et al 1981). The LOS has been most intensively studied in the paediatric population and all its actions can malfunction independently or together (Cohen 1979).

The main functions of the stomach are fourfold; storage, liquefaction, digestion and controlled transfer to the small bowel. Food is stored temporarily and its movement distally is controlled, so that the time during which the food is presented to the small gut is spread out. Humans can eat in haste and digest at leisure. Gastric mucosa produces HCl, pepsin, gastrin, intrinsic factor etc which can assist in digestion. Ingested food is liquefied, mixed with these additions and passed on as chyme in small metered amounts most suitable for subsequent small gut function. A further property of the stomach is to reduce the risk of swallowed noxious substances entering the distal GIT.

The muscle circular and longitudinal layers of the oesophagus continue into the stomach. In the proximal stomach there is also an oblique layer between the circular layer and a thin layer in the mucosa. Parasympathetic innervation is from the vagi and sympathetic from the coeliac plexus. The

latter are postganglionic. As already noted there is no distinctive anatomical sphincter comprising the LOS, but the LOS and cardia musculature are functionally related (Lieberman-Meffert et al 1979). The deduction that distal oesophagus and proximal stomach act together is supported by measurements which show that LOSP and gastric muscle tone increase and decrease simultaneously (Lind et al 1961). Thus there is evidence that the LOS is a functional sphincter which can be defined in terms of its physiology. Stomach wall motion results in mixing and propulsion of gastric contents. Peristaltic waves originating in the body of the stomach and which first appear at the age of several weeks (Tornwall et al 1958), travel towards the pylorus. There is an autonomous rhythm which can be modified by the vagi. Weaker waves originate in the upper half of the stomach and mix gastric secretions with the gastric contents forming chyme which is transferred into the pyloric antrum. The action of the fundus has been described as of primary importance for the gastric emptying of liquids (Dozois et al 1971). Unlike the LOS, the pylorus is normally relaxed and peristaltic waves moving distally towards it allow a small metered spurt of chyme to pass from the stomach to the duodenum. The pylorus closes as the peristaltic wave passes over it. Antral peristalsis contributes to mixing, as each wave arriving at the pylorus also displaces significant amounts of chyme proximally.

The control of gastric emptying is complex, depending on many factors including the volume and composition of gastric contents. By analogy with ECG signals, gastric muscle action is accompanied by electric activity which "in infancy does not have the orderly pattern of that of adults" (Hinder 1986). Stomach wall distension increases frequency of different vagal nerve impulses, the stomach contracts and duodenal peristalsis is reduced, so allowing chyme to move distally. Osmolality, pH, digestion products of fat (medium chain triglycerides empty faster than long chain equivalents for premature infants (Siegel et al 1985)), carbohydrate and protein in chyme all contribute to

gastric emptying. Many other factors are also relevant, ranging from duodenal distension, psychiatric status (e.g. anorexia nervosa (McCallum et al 1985)) and emotion, to concentrations of hormones (Kleibeuker et al 1985) and other circulating compounds and the direction of gravity, but neither local arterial blood flow (Qamar et al 1986) nor exercise (Ollerenshaw et al 1987). The interplay of all these influences is most complex (Rees 1985) and not fully understood (Jolley et al 1979). A fuller discussion is not justified here, but it has recently been shown that for a large variety of liquids and semi liquids gastric emptying remains consistent over 15 days (Thouvenot et al 1986).

2.4 Pathophysiology

In terms of understanding gastro oesophageal pathophysiology the mechanical model is useful. All the components (piston, cylinder with two directional valves and peristaltic pump with exit valve) function adequately in normal subjects. The stomach is considered further below. It is clearest to describe malfunction initially in some well recognised syndromes "for the cause of motor abnormalities of the esophagus in unknown" (Gelfand et al 1987). One authority describing oesophageal motility disorders lists 43 causes, excluding those associated with the upper sphincter (Dodds et al 1973). It is inappropriate to go into such detail here, but some rare conditions merit discussion because they can illustrate useful points.

Achalasia is characterised by absent peristaltic pump action, insufficient exit valve (LOS) opening and high closing pressure. Its onset is slow and increasingly painful dysphagia which is usually the presenting feature, although repeated respiratory problems are also possible (Patrick et al 1983). Achalasia is uncommon in children with an occurrence rate of 1 in 10^5 and most rare in infants (only 12 cases having been reported in the English language literature (Starinsky et al 1984)). It is associated with

neurological lesions, central, vagal and oesophageal (but not sphincteric (Csendes et al 1985)). The aetiology is unknown though a neutrotropic virus has been postulated.

Diffuse oesophageal spasm is well known in adults and although it has not been described in paediatric patients it is likely that a similar condition has been observed in this work. Primary peristalsis continues to the mid or distal oesophagus where the wave progression disappears and tertiary contractions take its place. In adults this condition is often associated with chest pain and dysphagia. Valve function is rarely affected. Its aetiology is unknown but it can evolve into achalasia and there are similar lesions in the oesophageal branches of the vagi.

Abnormal oesophageal motility is known to be able to accompany all of the connective tissue disorders (Rohrmann et al 1984) in particular dermatomyositis and scleroderma. (In the latter, using a hepatobiliary radiopharmaceutical; duodeno gastro oesophageal reflux has recently also been demonstrated (Sawaf et al 1987)). The primary peristaltic wave descends, falters, then vanishes at a region where there is muscle atrophy, typically in smooth muscle with the latter and in both types of muscle in the former disorder. The LOS is often involved, with resulting chalasia.

Systemic neurological and primary muscle diseases can also cause abnormalities of peristalsis in particular muscular regions of the oesophagus. Oesophageal dysmotility has been investigated in adults as a possible accompaniment of oesophagitis, Barrett's oesophagus (Karvelis et al 1987), hiatal hernia and achalasia (Singh et al 1985). Only in the latter and in diabetes mellitus (Keshavarzian et al 1987) were there clear associations. Upper oesophageal sphincter spasm can rarely result from central nervous system (CNS) defects, causing dysphagia and aspiration. In infancy

regurgitation is common and the chalasia of infancy (Stewart 1981) is frequently associated with a slowly maturing LOS. Such a LOS usually responds normally to cholinergic drugs which therefore can be used as a temporary form of treatment. Considerable attention has been paid to GOR in considering paediatric foregut disorders, for it has been described as "the most important disorder of the esophagus and the lower esophageal sphincter in early childhood" (Höllwarth et al 1985). The simplest mechanical explanation for GOR is that the resting LOSP is too low, so allowing retrograde motion of gastric contents, but measurements of LOSP have shown this theory to be too simplistic. Similarly initial observations of frequent coincidence of hiatal hernia with GOR suggested a cause and effect relation between them. Also as long ago as 1955 two types of associated LOS incompetence were described; a sub diaphragmatic LOS and one associated with a sliding hiatus hernia (Forshall 1955). More recently the non equivalence of GOR and presence of a hiatus hernia have been emphasised (Colin 1982). The latter is anatomical and the former is of physiological significance. After experimental and clinical observations the location of the LOS was shown to bear no relation to the LOSP, for example in children (Moroz et al 1976), although some circumstantial evidence suggested otherwise (Edwards 1973). Also hiatal hernias are frequently discovered in symptom free patients, (Cohen 1976). This does not negate the necessity of surgical correction if GOR and hiatal hernia coexist, with an additional complication (Vansant 1978).

Conversely, reduced LOSP is apparently not the sole cause of GOR (Fisher et al 1977, Weihrauch 1985) for LOSP values in normals and refluxers overlap. However LOSP can vary with time, position, many circulating factors, gastric contents (Davis et al 1986a) and pressure. It has been shown to suffer transient relaxations with gastric distension (Holloway et al 1985). Thus LOS incompetence may be the most probable cause of GOR with other factors playing a part, even if a direct association remains unproven in all cases.

Further factors which are thought to play an important role in the pathogenesis of GOR are the gastro oesophageal angle (or angle of His), the mucosal folds in the region of the LOS and the intra abdominal oesophagus. Experiments with dogs have shown as the angle of His tends to zero the intra gastric pressure necessary to cause GOR monotonically increases (Boix-Ochoa 1986). Mucosal folds can act as a choke on flow through the LOS (Chrispin et al 1967) and finally pressure within the abdomen also acts on the intra abdominal segment of the oesophagus and thus counteracts the extra gastric component of the same pressure acting on the stomach and tending to force stomach contents through the LOS (Edwards 1973). For those patients with an incompetent LOS, inadequate response to stretch of the circular muscle is seen (Biancani et al 1975). Since this is a mechanical problem, it is reasonable that there is improvement after surgical correction of the reflux. Yet the resulting surgical procedure must be chosen with care, for the Stamm gastrostomy, sometimes used for children with a neurological impairment, causes or increases pre-existing GOR. The length of the LOS and pressure exerted by it have recently been shown to decrease after the operation and this is believed to be the mechanism explaining the procedure's lack of success (Canal et al 1987).

The pathogenesis of reflux oesophagitis is associated with gastric or gastro duodenal contents in the oesophagus. Dysmotility of the oesophagus can prevent the resolution of such inflammatory lesions, by delaying the emptying of acid from the inferior oesophagus (Stanciu et al 1974, Szilivasi et al 1986, Little et al 1980). Thus the severity of the oesophagitis depends on the duration of contact of the oesophageal mucosa with refluxate and also on the nature and concentration of compounds in it, such as HCl, pepsin, bile salts and possibly pancreatic enzymes. When there is duodeno gastric reflux and all these compounds are present, the resulting cocktail has been described as "explosive" (Boix-Ochoa 1986). A positive correlation has also been

suggested with hiatal hernia (Kaul et al 1986). The relation between oesophagitis and GOR is not fully understood, although some find a positive correlation (Collins et al 1986). A scintigraphic index of quantification of GOR described by the Brussels group is unable to predict the existence of oesophagitis (Piepsz et al 1981). Although from studies in adults gastric emptying was found to be unassociated with reflux oesophagitis, a correlation with reduced antral motility was seen (Behar et al 1978, Csendes et al 1978). The latter is a recently described syndrome which presents with excess vomiting, but which so far has only been described in terms of Xray findings. A funnel shaped antral region is seen, without recognised contraction (Byrne et al 1981).

The degree of oesophageal dysmotility needed to cause oesophagitis is controversial, LOSP inadequacy being considered the sole cause by some (Cozzariari et al 1978), but others state an associated abnormal oesophageal transit pattern coexists with oesophagitis (Espinola et al 1983, Roland et al 1985). A vicious cycle has been clearly described in which oesophagitis causes vagal paresis and then delayed gastric emptying. Another part of the cycle is a two way relation between oesophagitis, impaired oesophageal clearance and delayed gastric emptying. Thus the prevention of oesophagitis and breaking of the cycle are crucial parts of effective treatment (Boix-Ochoa 1986). The histological reaction in the mucosa is very similar to that found in adults (Wurnig et al 1985) and is initially either a cellular infiltrate (Seefeld et al 1977) or basal cell hyperplasia and elongation of the papillae (Ismail-Begi et al 1974).

Studies of the possible mechanism of GOR indicate that the situation is complicated. In a similar way the relation between gastric emptying rate and GOR is not straightforward. Again a simplistic approach suggests delayed gastric emptying would predispose a patient to increased GOR, for the longer

food remains in the stomach, the greater the chances of its regurgitation into the oesophagus. In fact clinical results have allowed diametrically opposed deductions concerning correlations between delayed gastric emptying and GOR both for paediatric patients (Hillemeier et al 1981, Baulieu et al 1984, Rosen et al 1984, Seibert et al 1983) and adults (Behar et al 1978, McCallum et al 1981, Jolley et al 1979). These results will be discussed more fully below in Chapter 6. A connection between delayed gastric emptying and GOR at first sight seems logical, in spite of possibly contradictory evidence. The complexity of the situation becomes further apparent when a cause for the delay is postulated. Insufficient pyloric relaxation with or without antral hypomotility, GOR of the radiotracer and duodeno gastric reflux are all possible mechanisms. It seems likely that reflux does not contribute greatly to the protracted stomach clearing if one considers the amounts of regurgitant stomach contents measured in this work, which rarely exceed 2%. Observations of the distal oesophagus during gastric emptying studies failed to find any relation between tardy stomach clearing and increased counts in the oesophagus (McCallum et al 1981). Similarly, in another study, increased intra abdominal pressure was necessary to show GOR (Fisher et al 1976). The difference in observed emptying rates of solids and liquids from the stomach, with the former increased, implies that reflux does not contribute significantly to gastric hold up (Ippoliti et al 1976). Antral dysmotility and pyloric malfunction are likely to be the main contributory factors to delayed stomach emptying, although there is no reason why the various other mechanisms mentioned cannot coexist.

The conclusion which can be drawn from these various apparently contradictory observations concerning different aspects of gastro oesophageal function is that there is no simple connection between action or malfunction of the different mechanical components associated with swallowing and gastric emptying and observed clinical problems. They can occur in isolation or

together. Particular significance is often given to GOR however (Leisner et al 1984). Our results using both correlation and variance analysis confirm the independence of different types of foregut malfunction. This is discussed below in Chapter 9.

CHAPTER 3: NON RADIOISOTOPE METHODS FOR OESOPHAGEAL INVESTIGATIONS

"Bid him recount before-recited practices; whereof we cannot feel too little, hear too much." William Shakespeare; Henry VIII, Act 1, Sc 2.

A number of important methods for study of the paediatric oesophagus predate the use of radiotracers and scintigraphy. Several are still in common use and their relevance to nuclear medicine must be considered. The best known and oldest are Xray studies with a contrast medium. Others include measurements of the pH in the oesophageal lumen, pressure determinations at various locations in the oesophagus, oesophagoscopy, with or without biopsy and ultrasonography. More exotic and much less commonly practised methods not discussed in detail in this work include oesophageal electromyography (Clark et al 1976), staining of an intraluminal cotton thread (Girardi et al 1978), ratio of papillary length to epithelial thickness in oesophageal mucosa (De Meester et al 1976), mucosal electrical potential measurements (Clark et al 1976) and elastance determination (Kunath et al 1979). The existence of such a variety of investigation methods, each enthusiastically described by different groups of authors, suggests at least two things. Firstly in specific centres there is expertise developed with the use of a particular technique and its proponents are happy with their results. Secondly the existence of a variety of methods, all claimed as reasonably effective, implies that no single one is best and that each can supply some useful information. This situation is well known in therapeutic medicine. If a large number of different drugs exists and they are often prescribed, all nominally to treat similar disease states, then no one drug is likely to be much more efficacious than the others. Writing in the Journal of Pediatric Surgery in 1980, Boix-Ochoa et al begin an article with the striking words,

"The more we have investigated gastro esophageal reflux in children, the more we have doubted our means of accurate diagnosis" (Boix-Ochoa et al 1980).

The report goes on to compare a variety of invasive methods and contrast medium studies. Hence to have an effective non invasive method, which demonstrates the oesophageal motility and stomach emptying of the particular child being investigated, seems necessary.

3.1 Radiology

Radiological examinations of stomach and oesophagus, to examine transit and reflux, are relatively easy to perform but virtually all authors agree that other methods of study are better, especially when infants are being investigated (Leonidas 1984, Willich 1986). The principle involved is to swallow a contrast medium, most commonly an insoluble barium compound with relative density 1,5 to 2 (Tolin et al 1979), and to observe its transit through the oesophagus with fluoroscopy, or less frequently cinéradiology, and/or the occurrence of subsequent gastro oesophageal refluxes etc. Sometimes the contrast medium is instilled directly into the stomach (McCauley et al 1978) which demonstrates stomach emptying of the particular child being investigated. A scoring system for radiological GOR studies in infants and children has been reported involving five grades of severity for the GOR, although in an individual child the severity can vary considerably between any two examinations. Even though it is "designed to be as physiologic as possible", the following manoeuvre is described;" the gastro oesophageal junction is carefully examined while turning the baby gently from side to side in a supine position or occasionally rolling him 360°" (McCauley et al 1978). Often non physiological manoeuvres are performed as part of a radiological study to detect GOR. These can include use of the Trendelenburg position, leg raising, the Valsalva and Mueller manoeuvres, rotation through 360° about a horizontal axis, externally applied abdominal pressure and bending at the waist. Both the presence of a barium compound, which has been described as an irritant in the paediatric oesophagus (Sheiner 1975, Heyman 1984), and these movements are not typical of normal feeding.

A further non physiological attempt to improve sensitivity of radiological detection of gastro oesophageal reflux is the water siphon test. Here the stomach is distended with a barium sulphate suspension and the supine patient then placed in the left posterior 25°-oblique supine position on the table. In this way the fundus is filled with Ba and the gastro oesophageal junction covered. Between 30 and 120 ml of water is instilled into the stomach, the volume depending on the child or infant size. A positive result is a reflux observed soon after the water administration, which reaches at least to the mid-thoracic region. However, many false positives and few false negatives result (Blumhagen et al 1979). In spite of its invasive and non physiological nature, one enthusiast has performed the test on several thousand infants and children (Blumhagen et al 1979) as a primary screening procedure. Another advocates its use before scintigraphy (Willich 1986).

The radiological studies performed to detect GOR with the patients described in this work did not include any of the non physiological measures already mentioned. Typically there was rapid interval screening for about 5 min. This could of course fail to visualise some cases of GOR. During the study the infant patient was comfortable and warm and neither crying nor struggling, which made GOR less likely, probably by increasing the LOSP. If GOR was observed radiologically, possible association with a gastric outlet obstruction was always considered and eliminated.

Morphological detail for anatomical changes and mucosal lesions is excellent, but dosimetric considerations in general limit the number of exposures which can be made, (especially with computed tomography (CT) (McCullough et al 1978, Fearon et al 1985)). Radiographic reflux is not considered as a reliable sign of gastro oesophageal reflux although the use of Xrays was important in showing that the incidence of hiatal hernia was far commoner than previously suspected in the USA paediatric population

(Darling et al 1974). In contrast these hernias are rare in patients seen at the Red Cross War Memorial Children's Hospital (Fisher 1987).

Real time ultrasound has recently been shown to detect paediatric GOR about as well as barium studies, although it has little ability to recognise morphological details (Naik et al 1984, Naik et al 1985). This method shows promise but it requires much experience before it can be considered reliable. Technical factors are very important to ensure success of the study and in spite of its advantages over the use of Xrays, notably the absence of ionising radiation, it is much less easy to perform (Fisher 1987). However the need to compare ultrasonographic detection of GOR with a more sensitive modality is the next step in its evaluation (Euler 1986).

When studies have been reported which compare radiological methods with others, such manometry and endoscopy, with or without biopsy, in children with symptoms of gastro oesophageal reflux (Euler et al 1978), or recurrent chest disease (Euler et al 1979), the results of Xrays are the least sensitive and least significant. A liquid bolus of a barium compound is often unable to demonstrate abnormalities of oesophageal motility (Stewart 1981). In an attempt to improve this situation, it was concluded after radiological studies of the oesophagus in 500 patients (mainly adults) that, "Thorough evaluation should consist of a minimal multiphasic approach involving double and single contrast radiography, fluoroscopic studies of motility and a mucosal relief study" (Maglinte et al 1983). Yet oesophagitis associated with GOR is rarely seen with a barium examination even if it is obvious with oesophagoscopy (Fisher 1987). One standardised fluoroscopic approach searches for reflux for 15-20s during a total time of 5 min (Cleveland et al 1983). This time interval is very short when compared with some non radiological methods which extend over much longer periods. The radiation dose with Xrays is high and limits the duration of studies. This is especially significant if a fast

framing rate is needed. When the pharyngeal stage of swallowing is investigated in adults, 50 to 100 frames per second are used. (Ekberg et al 1982a, Ekberg et al 1982b). Finally a rare, but potentially serious, complication of Ba studies in infants must not be forgotten, that of tracheobronchial aspiration. Three such fatalities have recently been reported (McAlister et al 1984). Two GIT contrast media, not containing Ba (3:5-diiodo-4-pyridone and sodium with meglumine diatrizoate), have also been shown to cause reaction in the lungs after experiments in rats, but three others (meglumine with sodium ioxaglate, 3:5-diiodo-4-oxopyridin-1-ylacetate and metrimazide) seemed safe (Ginai et al 1984). However one opinion states "Barium sulphate suspension is normally used; water soluble contrast material is indicated only in cases of suspected perforation" (Willich 1986), although others advocate a more conservative approach (Fisher 1987).

3.2 Oesophagoscopy

Oesophagoscopy has benefitted from the introduction of flexible fibre optic instruments, but even so the rigid device has some advantages when there is a stricture and a "feel" of the region is required (Cooper et al 1981). Another advantage is that dilation is possible. Experience is required to recognise and grade the different degrees of oesophagitis (Jaeger 1985) although in its early stages it is difficult to recognise with oesophagoscopy alone. The diagnosis is usually made on the basis of friability, ulceration, or both (Euler et al 1979). Biopsy too is possible and the appearance of the lower oesophageal sphincter can provide important information for the surgeon (Hiebert 1977). However, in the words of Shub et al (Shub et al 1985) "histologic esophagitis is more common in infants with clinically significant gastro esophageal reflux than previously appreciated and more likely to be moderate to severe after the first 6 months of life". The 33 infants studied by them had GOR, as determined by non scintigraphic means. Histological evidence of oesophagitis was seen in 61% but "gross endoscopic evidence of

esophagitis was found in 18%" (Shub et al 1985). Thus oesophagoscopy without biopsy has been shown to be less reliable than was previously believed. Suction biopsy is preferable to pinch biopsy (Knuff et al 1984). However the examination is invasive, requires sedation (Euler 1979) and the risk of perforation is not trivial, being about ½%. For the detection of stenoses fibre optic oesophagoscopy was recently shown to be somewhat inferior to barium studies using marshmallows (Somers et al 1986), a neglected technique although first described in 1961 (Kelly 1961).

3.3 pHmetry

In 1958 Tuttle and Grossman described the use of an intra luminal pH electrode (Tuttle et al 1958) to detect acid reflux in the oesophagus. In the same year Bernstein et al (Bernstein et al 1958) reported an acid perfusion test to reproduce pain resulting from gastro oesophageal acid reflux. Saline or 0,1 M hydrochloric acid was infused into the distal oesophagus. The test was considered positive if the acid infusion produced pain and saline relieved it. Each liquid was infused in turn for 15-30 minutes. Some workers replaced the saline by viscous xylocaine (Hiebert 1977). Many variations on the combination or refinement of these two techniques have been described subsequently.

The basic principle is for the electrode to monitor the pH of its environment. A decrease in recorded pH is taken as indicating a reflux of stomach contents. This procedure is frequently used for children and microelectrodes of diameter 1,6 mm (Berquist et al 1981) are available. Normalising buffers and a reference pH are also required. The latter is usually obtained from a skin electrode. Signals are typically recorded on a pen chart recorder and are conducted along leads in the electrode tube, which is often introduced through the nares. Continuous radio telemetric recording of the pH has also been described for infants (Urbano et al 1978) and others,

but the equipment is expensive, complicated and rarely used. Recently a very sophisticated version has been described with four channels allowing pH measurements to be made at four sites in the oesophagus of infants and children with two stage transmission, one being via satellite (Haase et al 1987). In this way data can be acquired a long way from the centre where data is recorded and reduced.

The electrode is usually placed 2 to 5cm proximal to the lower oesophageal sphincter. The common criterion, which defines reflux, is for the distal oesophageal pH to fall to 4,0 for at least 15s. However normal feeds can buffer gastric acid, so making it difficult to detect their reflux by this method immediately after feeding. Tuttle's original procedure was to withdraw the electrode from the stomach and to note a sharp rise in pH within 2 cm of the gastro oesophageal junction, located by manometry, in a normal situation. A gradual pH decrease extending over a larger distance was presumed evidence of reflux.

Another variation in the technique is the standard acid test of Skinner et al (Kantrowitz et al 1969). After instillation of 0,1 M HCl into the stomach, the volume being determined by a formula depending on the patient's surface area (Euler et al 1977), oesophageal pH recordings allow detection of reflux. This is usually performed in conjunction with a selection of the non physiological manoeuvres mentioned previously, to increase the likelihood of detecting a reflux. The acid clearing test is often performed immediately after this standard acid study in adults. A bolus of 0,1 M HCl is instilled into the oesophagus proximal to the electrode and the subsequent variation of pH is recorded, with and without swallowing, (Galmiche 1982). An excessive time taken for the oesophageal pH to increase to a value above 5 is associated with the presence of oesophagitis.

In 1974 the superiority of continuous 24 hour pH monitoring was demonstrated (Johnson et al 1974) and it was soon applied to paediatric use with success (Jolley 1978). The choice of most workers, who use a fall of oesophageal pH to 4 to define an acid reflux, results from Tuttle's observations that reduction of pH to 4 corresponds to a subjective onset of pyrosis and to the onset of peptic activity (Johnson 1981c). However at least one group uses a value of pH=3 to define reflux (Euler et al 1977).

Various scoring systems for 24 hour pH studies have been described to aid diagnosis of GOR and the following is adopted by several authors describing work with children and infants (Jolley et al 1978, Hill et al 1977, Koch et al 1981, Carghill et al 1982, Seibert et al 1983). Appropriate weighting (Jolley et al 1978) is given to

(i) the total number of refluxes,

(ii) those of length greater than 5 min,

(iii) the duration of the longest reflux,

(iv) percentage of time the pH is below 4,

(v) fractional time of reflux in each of a variety of positions

and (vi) a clearance time during which the pH value returns to the pre-reflux value or 6.

In each centre a selection is made from this list of factors when scoring a study. Some authors studying infants feed them apple juice, with pH=3 to 4, before the extended oesophageal pH study (Jolley et al 1979) rather than their normal feed, because unlike milk feeds it does not buffer gastric acid and regurgitation is more readily detected. The initial work with pH probes was done with adults but it was quickly adapted to paediatric use. Adult experience proved useful but an important difference concerns the patient's position. A child's reflux depends less on position than an adult's, with the important exception of the prone position, where refluxes in children are much longer in duration although usually less numerous (Boix-Ochoa et al 1980).

The 24 hour pH monitoring with a scoring system is considered the best way of using the intra oesophageal electrode by some (Erbelding et al 1985), although 8 hours may be adequate if there are no respiratory symptoms (Jolley et al 1978). However apart from the non physiological presence of the electrode, the patient must be hospitalised and medicated if under 5 years of age (Euler et al 1977). Some workers (Koch et al 1981) splint the arms of all infants over the age of 3 months. Fluids with pH above 6 (Hill et al 1977) or food and liquid with pH above 5 (Berquist et al 1981) are administered. The frequency of reflux in a given infant has been shown to depend on the nature of the fluid administered (Jolley et al 1978) (whether it was clear or not and on its pH). These initial conclusions suggest that whatever the merits of 24 hour oesophageal pH measurements, and some consider their prognostic value is poor in infants (Koch et al 1985), they can never become a reliable, routine, easily repeated investigation in the investigation of GOR.

3.4 Pressure and other measurements

A study of the pressure exerted during the oesophageal muscle's peristalsis and by the lower oesophageal sphincter bears obvious relevance to problems of swallowing and reflux of stomach contents. Fyke et al first reported intraluminal pressure recordings in the inferior oesophagus (Fyke et al 1956) and in 1959 Ingelfinger described the functional LOS (Ingelfinger 1959). It is a physiological concept, not an anatomical entity. The pressure at various sites in the oesophagus is measured for further understanding of peristaltic pressure waves which follow deglutition. In the normal situation relaxation of the upper oesophageal sphincter and primary peristalsis are set in motion by swallowing. The contraction wave takes with it the bolus and there is passive opening of the LOS as the bolus approaches it. After complete oesophageal emptying the LOS regains its usual resting tone. A secondary identical peristalsis can be initiated by oesophageal distention, a further bolus, remnants of the first bolus, or reflux. Tertiary or non

peristaltic contractions have also been described above and are due to incoordinated oesophageal muscular activity. They are usually isolated or segmental and may appear simultaneously at one or more sites during or after primary or secondary peristalsis (Cooper et al 1981). Also they are most frequently associated with diffuse oesophageal spasm reported radiologically (Richter et al 1984) and in adults scintigraphically (Wynchank et al 1986).

The continuing presence of the pressure measuring device in the oesophagus is obviously a non physiological situation. Hence its diameter has been reduced to as small a value as possible. Intraluminal pressure transducers exist, but they are not in common use, being very fragile and expensive (Clark et al 1976) and the usual method of measuring pressure is to use a modified manometric technique. Individual tubes can have an external diameter 3 mm and usually three or more are attached in parallel. They have holes in the lateral wall of diameter 1,5 to 2 mm (Berquist et al 1981) spaced up to 5 cm apart. The manometer is normally infused continuously, at a low flow rate, typically 0,8 mℓ/min (Euler 1977), so that when the lumen is unobstructed no pressure rise is recorded. A common procedure is to pass the catheter into the stomach like a nasogastric tube and then to withdraw it in increments and to record the pressure at the different sites. In this way the pressures of the LOS and within the oesophageal lumen are recorded. Sedation is often required for infants (Koch et al 1981) and children (Euler et al 1978).

The interpretation of these results is often subjective and allowance must be made for respiration and sometimes heart beats (Clark et al 1976). Also isolated pressure measurements are of little value especially if the LOS is being examined. Euler et al have made the categorical statement that for manometry studies in children performed in conjunction with other investigations; "Caution should be exercised in establishing the diagnosis of

gastro esophageal reflux on the basis of a single positive study" (Euler et al 1978). It is well known that LOS pressure values in paediatric patients with GOR overlap the normal range for such pressures (Moroz 1976, Blumhagen et al 1979).

There are also inherent inaccuracies in the manometric method of measuring pressure. The manometer or transducer reacts to the component of force perpendicular to the oesophageal axis. However the force propelling a solid bolus of necessity has an important vector element acting parallel to this axis. This remains undetected. A typical oesophageal contraction must also apply a centripetal radial force which tends to block the manometer outlet. Hence such components whether from peristaltic or sphincteric contraction tend to be recorded inaccurately with inconsistently low values. This can be overcome in part by increasing the liquid flow rate through the catheter. However rapid pressure changes, again typical of peristaltic action, reduce the effective perfusion rate because of the system's compliance. The "system" for this purpose comprises not only of the catheter but also the infusion pumping mechanism. Although these can be reduced by variations in the design, they cannot be totally eliminated. To consider these problems further is inappropriate here.

In spite of these limitations manometry is useful to detect gross abnormalities of peristalsis, especially aperistalsis. It is also the only method for detecting a high LOSP which has been associated with a discontinuous type of GOR (Jolley et al 1979). Few authors rely on pressure measurements alone in children but perform them in conjunction with one or more other methods. These range from Xray (Fotter et al 1985) and pH studies (Blumhagen et al 1979, Jolley et al 1979) to electromyography and pH (Carghill et al 1982). Intraoperative oesophageal manometry has been used by various authors (Hill 1978, Cooper et al 1977). For children (Christie et al 1978) a

poor correlation was found between LOS tone intra and post operatively. It seems likely that for all patients (Orringer et al 1980) this procedure is of little value.

In an attempt to improve the results of routine oesophageal manometry a direct reflux measurement has been performed immediately after pressure measurements. The catheter system is placed to measure simultaneously pressures in stomach, LOS and oesophagus. Through the gastric orifice a solution of phenol red in isotonic saline is instilled and later aspiration through the oesophageal opening detects the presence or absence of phenol red (Malmud et al 1982).

Hence in conclusion, although manometry has its enthusiasts, it "is expensive, requires close supervision to obtain technically good recordings, is clearly invasive and has poor patient acceptance" (Datz 1984). In addition there remains the necessity for some form of correlation with other investigations and the other difficulties already mentioned.

Although there are several non radionuclide examinations available for study of gastro oesophageal problems they all suffer from the disadvantages of often requiring hospitalisation, being invasive and complicated and making measurements in a non physiological situation. One of the important advantages of the present scintigraphic method, which we describe later, is the absence of any non physiological manoeuvre. Hence a radionuclide method "promises to displace the other techniques" (Anon 1982).

CHAPTER 4: NUCLEAR MEDICINE METHODS FOR GASTRO OESOPHAGEAL STUDIES

> "But is the art of medicine, or any other art, faulty or deficient in any quality in the same way that the eye may be deficient in sight or the ear fail of hearing, and therefore requires another art to provide for the interests...." Plato; Republic, Book 1.

The use of a radiotracer (10 to 20 mℓ of water or tea containing 0,5 to 1,0 mCi of pertechnetate) to examine adult oesophageal transit was first described by Kazem in 1972 (Kazem 1972). It was proposed as a means of providing "better understanding of oesophageal function", giving "a useful clinical test for the evaluation of dysphagia", and "the early detection of fistulas". The method was relevant to paediatric investigation and since 1972 much further information has been obtained. The first reported use to observe GOR was in 1976 (Fisher et al 1976) and in children in 1979 (Heyman et al 1979, Rudd et al 1979).

Radionuclide methods of assessing gastro oesophageal function have been used to investigate a variety of problems with considerable success. The first report was concerned with oesophageal carcinoma (Kazem 1972), but since 1972 many other conditions have been evaluated. These include achalasia (Gross et al 1979), in adults and children (Rozen et al 1982). All used a semi solid meal of cornflakes, the latter labelled with pertechnetate, the others with Tc-99m DTPA. Scleroderma (Leisner et al 1981), asthma (Kjellen et al 1981), oesophagitis (Leisner et al 1982), post partial gastrectomy oesophagitis (using Tc-HIDA) (Bortolotti et al 1985), pyrosis and GOR (Malmud et al 1982), abnormal thyroid function (Liu et al 1986), Sjögren's syndrome (Whan et al 1986), diabetes mellitus (Tornoczky et al 1985, Keshavarzian 1987), dysphagia (using Tc-DTPA) (Blue 1981), gastritis (Da Rocha et al 1986), ischaemic heart disease and myocardial infarction (Ramage et al 1985) and other conditions (Shih et al 1985) have been studied in this manner.

But more important from our point of view is the relation of GOR to apnoeic spells, SIDS, repeated respiratory problems, oesophageal stricture and GIT blood loss (Sty et al 1982). These and other relevant paediatric problems will be discussed more fully below. Evaluation of studies on paediatric patients have usually concluded that scintigraphy is a valuable investigation for function (and sometimes even for anatomical abnormality (Sty et al 1985)) and there has been a steady evolution in its technical details.

The characteristics of Tc-99m are well known (half life 6,02 hours, followed by a half life of $2{,}13 \times 10^5$y for Tc-99, moderately favourable chemical properties, ready availability in practical generators and convenient radiation characteristics with only a gamma emission of 140 keV). They are suited in many ways to current nuclear medicine apparatus and studies.

Tc-99m is the most suitable radionuclide for our purposes when used as Tc-99m sulphur colloid. However results using solutions of Tc-99m MDP (Kohno et al 1983), Tc-99m Phytate (Pinedo 1983) and Tc-99m DTPA (Leisner et al 1982, Simon et al 1985) have also been reported. Tc-99m is readily available virtually everywhere where nuclear medicine facilities are found. It is inexpensive, has appropriate physical and chemical properties in Tc-99m sulphur colloid and is easily prepared. Thus most work has used a Tc-99m radiopharmaceutical, usually a sulphur colloid, because it is stable and remains within the lumen of the gastrointestinal tract. Within the foregut it is neither secreted by parietal cells nor absorbable, for blood levels are negligible up to 60 min after swallowing (Fisher et al 1976). When mixed with the stomach and digestive secretions and when it stands after preparation, the amounts of free pertechnetate that form are small. This is important, for unattached TcO_4^- is readily absorbed into the circulation and captured by gastric mucosa cells, the thyroid and other tissues and would cause scintigraphic errors from a circulating background of pertechnetate or

fixation in gastric tissue. The amount of free pertechnetate in a water solution is 1,2% immediately after labelling of the sulphur colloid. Similar measurements made after marked colloid was added in turn to milk, to a very dilute solution of HCl and to acidified milk resulted in percentages of free TcO_4^- being detected of 1,3%, 12% and below 1% respectively (Heyman et al 1979, Heyman 1984). The binding sites are thought to be on lacto albumin and lacto globulin. Thus increased background should be negligible and this has been observed. More significantly the thyroid region failed to take up radioactivity, so confirming that circulating amounts of free pertechnetate are minimal.

The swallowed radiotracer moves along with the ingested material with which it is mixed, except in the important lesions involving abnormal mucosa or diverticula. Holdup at such lesions gives an additional diagnostic capability, which will be discussed later. For some studies investigating gastric emptying of two different types of food ingested simultaneously, Tc-99m and a second isotope, usually In-113m, have been used to label the different components of a meal. These are typically a liquid and solid phase (for example after ingestion of scrambled egg labelled with Tc-99m sulphur colloid and tap water containing In-111 DTPA (Kris et al 1986)) although different solutes and small resin beads simulating food particles leaving the stomach have also been studied with two radionuclides (Jordaan et al 1984). Gastric emptying using a radionuclide was first performed over 20 years ago in a very imprecise manner with oral administration of Cr-81 and a non imaging detector (Griffith et al 1966).

There is a very different technique which is relevant to the present work. This involves the deglutition of a solution of Kr-81m. Before the utility of Kr-81m for pulmonary ventilation studies was recognised, attempts were made in 1974 to make a solution of Kr-81m by bubbling the gas through a

beaker containing 10 to 15 mℓ of water (Mayron et al 1974). This was then swallowed after an equilibrium situation had been attained. Application of this tracer has been recently revived by the Brussels group in studies of paediatric (Ham et al 1985) and adult (Ham et al 1984, Sand et al 1986) oesophageal transit. They use a 5% solution of glucose in water as the solvent for Kr-81m. Further preliminary work in the Western Cape has passed water or a 5% solution of glucose through a newly designed compact Rb-81/Kr-81m generator. In this way about 10 mCi of Kr-81m is obtained in 10 mℓ liquid and rapid transfer to the patient allows a swallow of a Kr-81m solution to be recorded.

The physical and chemical characteristics of Kr-81m determine its manner of use. It is a radioactive inert gas in group VIII of the periodic table with a half life of 13,3s, hence it can neither be viewed nor quantitated for longer than a very few times 13,3s. Even so Kr-81m can provide useful information and its advantages are the greatly reduced radiation load to the patient, by a factor of several hundredfold, and the possibility of many repeated studies of oesophageal transit within a minute or so of each other, using different positions, pharmacological interventions or any other desired variations. Kr-81m generators are not available in many centres, including virtually all centres in France and many in the U S A, so their ready availability in South Africa, because of production by the CSIR Cyclotron Laboratory in Pretoria over the last few years, is a great advantage. The use of a solution of Kr-81m is being evaluated and it has demonstrated considerable potential for repetitive studies of the phases of deglutition (Wynchank 1987).

Another technique which should be mentioned uses an external non imaging gamma detector to detect GOR in children (Le Moing et al 1981). A recent version called a "single isotopic probe" uses a 3/4" x 3/4" NaI(Tℓ) crystal

with lateral collimation (Maurel et al 1987). However it is unlikely to be adopted generally for the same reasons which have prevented adoption of the nuclear stethoscope (Wagner et al 1976). Briefly, the lack of an image makes the positioning both difficult and critical and maldirection of the collimator renders the results invalid. For this reason, despite its low cost, this approach is unlikely to succeed, especially for gastro oesophageal studies in children where patient movement is even more likely than during adult cardiac studies.

There are differences in the methods used to administer the radiotracer and the term "milk scan" is in common use as a result of its adoption by Heyman et al (Heyman et al 1979, Heyman 1982) in their pioneering work using analysis of this type. One group routinely instills labelled colloid directly into the stomach of the patient (Sty et al 1982).

Typically 20 mℓ or more of marked liquid (milk) is swallowed, but some use the greater part of a normal feed. After swallowing the labelled preparation, an unmarked liquid is usually administered to clear the oesophagus of any remanent radioactivity which may still be adherent to the mucosa. Apart from liquids many radiolabelled solids have been used. The most tightly bound is Tc-99m sulphur colloid located within the Kupffer cells of a chicken's liver. The bird is injected intravenously ante mortem (Meyer et al 1976), killed and the liver swallowed raw or subsequently cooked and made into patē (Christian et al 1984). Also raw liver has been injected then cooked (Mannell et al 1984). Bran (Sagar et al 1983), resin (Wirth et al 1983, Gratz et al 1985), paper (Heading et al 1981), egg white (Velasco et al 1982), whole egg (Knight et al 1982, Vezina et al 1986, Kris et al 1986), noodles (Weiner et al 1981), fibre (Carlson 1978) and bread (McCallum et al 1981) have all been used. In spite of some reported differences between emptying rates of different components of a meal (Weiner et al 1981), it does

seem likely that in normal individuals, passage of food to the duodenum can only take place after trituration in the antral region (McCallum et al 1981). Thus the use of liquid for studies in patients of all ages allows a particular aspect of gastric emptying to be examined, that which occurs after the food has been suitably ground and mixed. Another advantage for liquids is that an intercomparison at different ages is more meaningful, for infants cannot be fed solids. Yet some advocate use of radiolabelled solids in adults because this allegedly increases sensitivity in detection of abnormality in oesophageal transit and presence of GOR (Leisner et al 1984).

The usual form of the scintigraphic study is to record dynamic images during deglutition of radiolabelled material. Then similar images of the lower oesophageal region are recorded to detect GOR. This scanning continues after the swallow to detect GOR. The duration of searches for GOR in paediatric patients is very varied, some recording data for up to 2 hours after swallowing (Cosgriff et al 1985, Baulieu et al 1985). However to allow the examination to be used as a routine study 30 min was adopted in this work. Problems in keeping paediatric patients still for longer times can be considerable (Cosgriff et al 1985). Also the results described below from the shorter GOR search justify its adoption. A final image is obtained after a further hour to search for pulmonary aspiration, or at varying times up to 24 hours after swallowing (Heyman 1984, Velasco et al 1984).

The first parameter which can be obtained from these studies is an oesophageal transit time (OTT) (Blackwell et al 1982). This is best done using a computer recording of appropriately spaced images in a time sequence although it is possible with sequential images from a persistence oscilloscope recorded on film, usually polaroid. A direct measure of the time required for a bolus to pass from the cricoid cartilage to the stomach can be readily obtained from the recorded images, knowing their exposure time. Also

graphical representations can be made to illustrate passage of the bolus through different regions of the foregut but correct interpretation depends on some experience (Blackwell et al 1984). These methods will be described more fully in Chapter 7 when evolution of the imaging and analytical techniques used in this work are described.

The computer can do much more than simply fulfil the function of a combined shutter and film transport mechanism. One approach favoured by some groups in the USA considers a single region of interest (ROI) containing the whole oesophagus. The oesophageal transit is then defined in terms of a "percent oesophageal transit at time t" (P_t) (Malmud et al 1982). At various times t after the start of the swallow the total counts remaining in the ROI are calculated (E_t) and

$$P_t = ((E_m - E_t)/E_m) \times 100 \quad \text{.....(Eqn 4,1)}$$

where E_m is the maximal count in the ROI.

A recent modification of this approach includes an allowance for independent random motion of the radiotracer within the bolus, as it passes through the oesophagus. A Markoff stochastic process is used to describe such a variable movement superimposed upon the bulk motion of the bolus. This is an example of the application of a random walk (Hart et al 1987). Similar calculations can be performed on activity-time curves obtained from individual regions within the oesophagus, but this approach is unlikely to become widely adopted for several reasons. The required calculations are complex and require significant amounts of computer time. It becomes much more difficult to obtain satisfactory curve fits when the oesophageal flow is disorderly. This of course is the most important and interesting situation. Finally the corrections resulting from this type of analysis are small and, for example, modify the oesophageal transit time by amounts less than about 5% (Hart et al

1987). Reasons for not adopting an approach considering the percentage emptying of the whole oesophagus will be given later.

Most workers prefer to examine the passage of the swallowed bolus through a series of ROIs (Blackwell et al 1982, Heyman 1982). This is particularly suitable for infants and children. Heyman et al (Heyman et al 1979, Heyman 1982) use images containing 64x64 pixels, obtained each 0,5s. These are analysed using 2 or 3 ROIs.

However recently more complex methods for the analysis of oesophageal transit in adults have been described (Klein et al 1984, Klein et al 1986). These include analysis of the activity-time curve obtained for a single ROI enclosing the whole oesophagus in terms of a simultaneous rapid decay and constant activity, the condensed image technique of Svedberg, which can employ list mode (Svedberg 1982, Gibson et al 1985) and plot motion of the centroid of the swallowed activity, parallel to a sagittal plane. In this way retrograde motion can be quantified. Similarly in infants and children other parts of the examination can be studied with a quantitative approach (GOR, gastric emptying and pulmonary aspiration). A recent assessment of the different methods mentioned above of investigating oesophageal transit concluded that, "a quantitative technique should always be used together with a qualitative technique" (Ham et al 1984). We have independently come to the same conclusion.

Results obtained from the various radiotracer methods mentioned above are usually obtained in circumstances which closely resemble the physiological conditions of normal feeding. Some successful attempts have been made to improve the sensitivity of a search for GOR by use of an abdominal binder (Malmud et al 1981), although in infants it may cause apnoea (Malmud et al 1982). In one institution its use was discontinued after a nearly fatal

apnoeic episode (Heyman 1984). Other reports too have described the use of increased intraabdominal pressure by means of an abdominal binder (Martins et al 1984, Rudd et al 1979, Malmud et al 1981, Hoffmann et al 1979, Leisner et al 1982, Conway et al 1979, Arasu et al 1980). Patient rotation has also been used (Jona et al 1981).

It is generally agreed that observations after swallows of food or liquid give more information than dry swallows (Johnson et al 1974). After studies of children in four different positions, when searching for GOR by a radionuclide method (Piepsz et al 1982), the highest sensitivity was found when the patients were supine. However other workers have not been able to find any significant difference in position for infants being scanned in this way (Peyraud et al 1985). This confirms the choice of this position in the present work, although pH studies in prone infants are considered more specific and sensitive (Boix-Ochoa et al 1980) than in other orientations, as has been noted already.

Not all published opinions concerning radioisotopic methods in paediatric gastro oesophageal studies have been favourable. Hiatal hernias are not always detected (Vansant 1978). At least one author, a surgeon, has found inconsistent results in paediatric patients examined with a radiotracer study (Hoffman et al 1979). He also considered pH reflux to be insensitive and therefore he decided to rely solely on Xrays, endoscopy and biopsy (Vansant 1984). This opinion is unusual and most reviews (Weissbluth 1981, Heyman et al 1979, Sty et al 1983, Sty et al 1982) and comparative studies, which will be considered below, conclude that radionuclide gastro oesophageal investigations are valuable for the study of many problems.

CHAPTER 5: A COMPARISON OF GASTRO OESOPHAGEAL STUDIES WITH AND WITHOUT RADIOTRACERS

"Then medicine does not consider the interest of medicine, but the interest of the body?"
"True", he said. Plato; Republic, Book 1.

Now that some characteristics of the various methods for studying paediatric disorders of the gastro oesophageal region have been described, it is important that we consider the results of comparisons between nuclear medicine techniques and non radionuclide methods. If it is then seen that there are advantages in the use of scintigraphy, then the further development of a paediatric scintigraphic gastro oesophageal examination is justified.

5.1 Xrays

Upper gastro intestinal tract Xray studies have been in use for many years, especially for GOR, an entity first described in 1935 (Winkelstein 1935). In spite of the advent of other methods of examination, barium studies are frequently the initial method of choice for a variety of relevant paediatric problems, because of their ready availability. In a recent publication Arthur et al conclude that, "A barium meal examination is currently the examination of choice in infants presenting with vomiting where the clinical assessment is not conclusive" (Arthur et al 1984). Others agree with this opinion (Macfadyen et al 1983, Willich 1986) but a deeper study of the application of scintigraphy in this context may allow an alternative opinion.

Virtually all comparisons of barium studies with scintigraphy in infants and children, examining both oesophageal transit problems and searching for GOR, find barium is significantly less sensitive and specific. Similar

conclusions were drawn after comparisons are performed searching for GOR in adults (Dodds et al 1981, Malmud et al 1981) and in studies of oesophageal motility (Russell et al 1981). Table 5,1 shows results of sensitivities for symptomatic infants and children. The result from (Seibert et al 1983), deserves further comment. It was the only one with a greater sensitivity for barium studies compared with scintigraphy and this was accompanied by reduced specificity of 21% for the radiological study and a specificity of 93% for scintigraphy. Another study using only Ba and nuclear medicine in 26 symptomatic infants, in which sensitivities were not given, found incidences of GOR to be 15% and 46% from the two methods respectively (Macfadyen et al 1983). The results obtained after similar radiological and scintigraphic studies in 18 infants and children were incidences of GOR of 22% and 44% respectively (Berger et al 1985).

The reasons for the barium studies usually being much less sensitive than scintigraphy are clear. Success with both modalities depends upon experience. Because of the radiation burden, many fewer Xray images can be recorded than scintigraphies so, for a GOR search and repeated oesophageal transit studies, Xrays may miss less frequently occurring malfunction. Yet as is well-known their ability to allow recognition of morphological abnormalities is far better. This is especially useful for diagnosis of strictures in paediatric patients and carcinoma in adults. To improve limitations in barium studies (restrictions on numbers of images due to the radiation dose, the non physiological nature of the swallowed contrast medium and its lack of quantitation), grading systems have been proposed. Since 67% of all infants under the age of 6 months have radiographic GOR its significance must be assessed. Most paediatricians do not insist on further studies unless the observed GOR is severe (Johnson et al 1981b). Those experienced in use of nuclear medicine suggest it be used as a first study for investigation of GOR and in circumstances where radiological investigations have already been done,

scintigraphy should be the next study (Le Luyer et al 1983). But there are still many who may have restricted access to scintigraphy and so suggest that barium studies be the first investigation (Johnson et al 1981b).

There seems little doubt that scintigraphy, which has a higher intrinsic contrast (Heyman et al 1979), is superior to barium studies for detection of pulmonary aspiration in infants and children (Boonyaprapa et al 1980, Willich 1986) as well as recognising GOR. In a discussion of 83 infants and children, Xray studies were insufficient in 22 to decide whether surgical correction of GOR was necessary (Schatzlein et al 1979). A variety of other investigations including pH studies, scintigraphy, oesophagoscopy and manometry proved essential for their management. This may not necessarily be the case for other studies.

5.2 pH studies

Most workers consider that recordings from a pH probe are the most sensitive and specific method for detecting GOR. However in those few studies where pH results were obtained simultaneously with scintigraphy, definite superiority for the latter was found, both in children (Paton et al 1984) and adults (Martins et al 1984).

Others have drawn all types of conclusion after similar comparisons, not performed simultaneously.

(a) Scintigraphy was better in detecting GOR in 23 infants who experienced a near miss of the SIDS (Jeffery et al 1983) and in fact it proved better than eight different non radionuclide methods (Malmud et al 1981).

(b) Scintigraphy was comparable to pH studies in detecting GOR (Seibert et al 1983, Velasco et al 1984) (though neither was favoured in comparison with barium studies and oesophagoscopy) (Hoffman et al 1979). For children with chronic respiratory problems GOR detection was again similar but no

direct scintigraphic search for pulmonary aspiration was made (Bonafous et al 1984).

(c) Scintigraphy was inferior to pH studies (Dodds et al 1981, Corazziari et al 1980, Leisner et al 1982) for detecting GOR. Although they could be explained solely on the grounds that the scintigraphic and pH studies were not simultaneous, those comparisons unfavourable to scintigraphy merit closer attention. In spite of drawing this conclusion Dodds et al acknowledge scintigraphy is, "especially useful in children" (Dodds et al 1981) but consider it only semiquantitative since they suggest that gamma absorption and gastric emptying prevent precise quantitation of the refluxate (Dodds et al 1981). We believe that we shall be able to show these objections are invalid. One recent report comparing scintigraphy with the combined results of manometry and pH (Davies et al 1987) finds that the radionuclide study acquits itself very creditably with a sensitivity of 67%. The combination provides a sensitivity of 72% and is of course invasive and relatively complex. An Italian group examined 32 symptomatic adults and found GOR in 14 using a pH probe, but a positive result in only two using scintigraphy with 2 mCi of Tc-99m DTPA in 500 mℓ saline on another occasion (Corazziari et al 1980). There are apparently no other similar reports in the literature.

Other results assuming that positive pH studies were an absolute criterion for presence of GOR, found a sensitivity of 79% and specificity of 93% for scintigraphy in infants and children (Seibert et al 1983) and a sensitivity of 89% in adults (Leisner et al 1982). Others have confirmed such results (Bouvard et al 1985). It has been suggested that the relation between GOR and pulmonary aspiration would be clarified by simultaneously using two pH probes, one in the upper oesophagus, the other more caudally placed (Johnson et al 1981a). Reflux detected only by the inferior probe is assumed to be less likely to enter the lungs. In other attempts to improve the value of pH studies a scoring system is used, but in a comparison with scintigraphy even

the scoring system was not useful during the first two hours after eating. In this work (Johnson et al 1981a) radionuclides were used in some of the 114 infants and demonstrated pulmonary aspiration infrequently. It has also been stated that a 24 hour pH study is the best way to correlate respiratory symptoms in infants and children with reflux. Many refluxes were noted during pH studies in normals who had swallowed apple juice (pH=3 to 4), (Johnson et al 1981b). Hence the Tuttle test using apple juice is liable to give many false positives. The usual criterion for GOR is that pH should be 4 or lower for more than 3,5 min per hour. But this may mean that short refluxes, of duration 10 s or so, which are clearly detected in scintigraphic images, may escape detection by the pH probe. Similarly a bile reflux, even if massive, will be missed with a pH probe. As noted above, such refluxes have been observed (Sawaf et al 1987). The non physiological nature of one or two intraluminal pH probes does not need further discussion.

An indisputable conclusion from all these comparisons is that pH studies can never be used as a screening procedure. In experienced hands radiotracer examinations are very informative in comparison to 24 hour pH studies and possibly more so.

Three patterns of GOR have been observed. These were continuous, discontinuous and mixed reflux (Johnson et al 1981a and b) and can as readily be recognised with scintigraphy as with the pH probe. The acid clearance test suffers from all the disadvantages of an intraluminal pH electrode and the additional problem that in some normal persons acid instillation causes oesophageal dysmotility.

5.3 Manometry

Fewer comparisons between radioisotopic methods and oesophageal pressure measurements have been made. These are concerned rather with oesophageal

motility and LOSP. In at least one institution LOSP measurements are no longer made since they did not make any useful contribution to decisions about the need for surgery (Johnson et al 1981b). In other comparisons nuclear medicine was considered an aid to diagnosis and management in symptomatic children, where scintigraphy diagnosed GOR in 20 out of 25, but LOSP was abnormal in only 14 (and barium studies in 15) (Rudd et al 1979). Another group found very similar results in a group of 30 infants and children (Arasu et al 1980). Likewise direct comparisons in adults showed radionuclide methods were usually more successful than manometry both for diagnosis of oesophageal motor disorders (Malmud et al 1982, Russell et al 1981, Rozen et al 1982), for the investigation of dysphagia (Kjellen et al 1984, Pope et al 1972) and for GOR (Malmud et al 1981). In another recent comparison in 52 adults with dysphagia using manometry, videoradiology and scintigraphy, the latter was the most sensitive in detecting oesophageal dysmotility (except in achalasia where scintigraphy and radiology were equally sensitive) and scintigraphy obviated the need for manometry in many cases (Llamas-Elvira et al 1986). However a few reports on the use of radiotracers are critical of the method. For adults both manometry and scintigraphy are thought of little use in searching for hiatus hernia with GOR (Vansant 1978, Taillefer 1984). But for studies of GOR (Pasquier et al 1985) and oesophageal spasm (Leccia et al 1985) in adults, scintigraphy was considered better than manometry. Another worker, who drew the same conclusion (Channer 1986), suggested that the question of false positives must also be considered and in the case of adult women with normal cardiac function this is a somatisation of underlying non organic disease.

It is clear that scintigraphic and pressure studies do not provide the same information but they can be used to investigate the same problem, whether dysphagia (Llamas-Elvira et al 1986), oesophageal dysmotility (Blackwell et al

1983) or LOS incompetence. Scintigraphy aquits itself well in direct comparison.

5.4 Oesophagoscopy

In paediatric patients oesophagoscopy, even with biopsy which can increase detection of oesophagitis threefold (Shub et al 1985), has rarely been found of use in deciding which infants should undergo surgery (Johnson et al 1981a). The results vary greatly with the biopsy method and apart from requiring special equipment and experience, there is discomfort and a definite risk to the patient (Datz 1984). With adults, the combination of oesophageal transit and GOR scintigraphic studies has been found of diagnostic value for GOR with confirmation by biopsy. Sensitivity and specificity were 70 and 87% (Blumhagen et al 1979). Transit abnormalities also were associated with GOR. One recent study in 78 adults comparing oesophageal transit, studied with swallowed radionuclides and oesophagoscopy concluded the former, "may demonstrate symptomatic oesophageal disorders missed by oesophagoscopy" (De Gara et al 1987).

5.5 Discussion

For oesophageal motor function studies the non radionuclide methods have important limitations; none is quantitative and although the Xray studies alone are non invasive, they can cause a considerable radiation dose to the patient. Acid clearance is an invasive procedure and at best is semi quantitative. Although intraluminal pressure measurements provide data depending on peristaltic action, their relation to passage of a swallowed bolus is not fully understood, for reasons that already have been noted. In contrast oesophageal scintigraphy of swallowed liquid is physiological, non invasive, quantitative, sensitive and well suited to investigate many problems of this organ.

A recent attempt to record variation of epigastric impedance to electromagnetic radiation at 0,1 MHz using 4mA, to follow gastric emptying of liquids in adults has been successfully confirmed by simultaneously monitoring the passage of Tc-DTPA (Sutton et al 1985). However subsequent distal spread of the liquid prevents the method from being applied elsewhere in the gut.

The quantitation and detection of GOR can only be performed with radioisotopic imaging. It is one of the few direct methods of visualising regurgitation. Others, apart from acid reflux studies and fluoroscopy, measure a quantity which at best correlates with GOR. Scintigraphy is non invasive, physiological, with a small radiation burden and has a high degree of sensitivity. Other methods do not have these advantages and are usually found to be less sensitive. In one broad series of comparisons in 30 symptomatic adults, GOR scintigraphy was significantly more successful, than other non isotopic tests: (with scintigraphy having 90% positives, radiographic hiatus hernia 60%, fluoroscopy reflux 50%, LOS pressure: 10 mm Hg or less 57%, 15 mm Hg or less 77%, phenol red reflux test 47%, acid perfusion test of Bernstein 63%, oesophagoscopy for oesophagitis 40% and histology for oesophagitis 47%). These percentages of positives were obtained by a comparison with the Tuttle test and a false positive rate of 2 in 20 normals was also found for the Tuttle test. These results (Malmud et al 1982), from pioneers in gastro intestinal scintigraphy, have been confirmed by others (Kaul et al 1986) and they sum up what we have indicated; apart from absence of the disadvantages enumerated, nuclear medicine in its own right has very much to offer as a diagnostic tool in some of the problems considered in this work.

Table 5,1 The sensitivity of scintigraphic and barium studies in searching for GOR in paediatric patients.

Number of patients	Sensitivity (%) Scintigraphy	Ba	Reference
39	88	38	Heyman et al 1979
36	90	33	Conway et al 1979
30	57	50	Arasu et al 1980
125	77	35	Jona et al 1981
34	65	38	Le Luyer et al 1983
132	78	24	Pinedo et al 1983
49	79	86	Seibert et al 1983
57	85	73	Baulieu et al 1984
54	69	37	Davies et al 1987

CHAPTER 6: PAEDIATRIC GASTRO OESOPHAGEAL PROBLEMS AND NUCLEAR MEDICINE

"Certainly the body has wants; for the body may be ill and require to be cured, and has therefore interests to which the art of medicine ministers; and this is the origin and intention of medicine, as you will acknowledge. Am I not right?"
"Quite right", he replied. Plato; Republic: Book 1.

"There is only one child in the world and the child's name is All Children". Carl Sandburg.

Most of the attention of nuclear medicine practitioners directed to paediatric gastro oesophageal problems has concentrated on GOR, because of the clear advantages of scintigraphy in its recognition and also because of the variety and importance of the many manifestations of GOR. However problems of oesophageal motility and gastric emptying can similarly be examined. Much less work has been done with the latter two conditions so in this chapter we devote less attention to them. However after our own work has been described their importance and relevance to scintigraphy will become clearer.

GOR can have a myriad of different manifestations (Le Luyer et al 1982, Macfadyen et al 1983, Walsh et al 1981, Bray et al 1977, Balistreri et al 1983). These include excess vomiting or regurgitation, haematemesis, repeated respiratory problems such as cough and wheeze and apnoeic attacks. Such accompaniments can be found at all paediatric ages. In addition neonates can refuse to feed, cry excessively, experience sudden episodes of pain, pallor or cyanosis with bradycardia. Infants may also have malaena, SIDS and failure to thrive. Both children and infants may manifest repeated bronchopneumonia, apparent CNS and behavioural disorders, iron deficiency anaemia and GIT blood losses. Certain syndromes, such as those of Sandifer (Sutcliff 1969) and Roviralta (Roviralta 1967), may also include GOR as one of their constant features. However GOR has different significance in neonates, infants and children, with varying emphases in the presenting problems.

In the neonate pathological GOR most commonly manifests itself as excessive vomiting after feeds. There can be a refusal to feed, with excess crying or sudden episodes of pallor, especially if there is an accompanying oesophagitis. Pain, usually post prandial or nocturnal, may also be the presentation. Haematemesis from oesophagitis and isolated cyanotic episodes with bradycardia are not common but are well recognised. More frequent are respiratory problems, notably nocturnal cough and wheezing (Le Luyer et al 1982, Kurz et al 1985).

Infants have a similar pattern to neonates but failure to thrive is an important concomitant problem. The four main clinical problems in infants are failure to thrive, respiratory disease, vomiting and gastro intestinal tract bleeding as a result of oesophagitis (Weissbluth 1981). Dysphagia may appear. Infants with GOR may present with symptoms and signs suggesting primary disease of the CNS such as dystonia, dysphagia, developmental retardation, irritability and seizures (Bray et al 1977). Treatment of the GOR was associated with prompt and dramatic improvement of the "neurological" abnormalities. The infant may also present with repeated respiratory problems which can typically be sited in the same region of the lungs. Oesophageal stricture is a serious complication following oesophagitis, which may again be accompanied by haematemesis.

It should be pointed out that GOR occurs to a minor extent as an incidental finding in about half of all barium meals performed in neonates and infants below the age of 6 months. It is more common in neonates than infants and is most common in preterm babies. This is usually ascribed to an incomplete development of the "pinch-cock" action of the LOS and frequently resolves by about the age of 9 months (Fisher 1987).

Unlike infants, children tend not to vomit though they may show other features similar to infants apart from SIDS. Also they may become anaemic due to occult blood loss from oesophageal erosions. Other congenital abnormalities have been found in 9% of refluxing infants and children with hiatal hernia in a local series (Rode et al 1982). Apart from seizures, the apparent CNS problems described above together with associated behaviour problems have also been observed in children with GOR (Bray et al 1977). As with adults, children often present with more than one symptom (Brindley et al 1979). All these varied and serious problems in neonates, infants and children deserve closer attention.

Vomitus may be food, clear liquid or bile stained. The latter can be associated with the phreno pyloric syndrome as described in work from the Children's Hospital (Rode et al 1982). This was accompanied by failure to thrive which is true of any form of excess vomiting. Antral dysmotility presents similarly (Byrne et al 1981). Two thirds of children with GOR have vomiting as their commonest presenting feature (Weissbluth 1981). It can begin at birth and so its significance can fail to be recognised because it can be confused with normal regurgitation or ignored in the presence of other severe problems.

The importance of the relation between GOR and recurrent respiratory problems is not always appreciated (Guillemeteau et al 1985). Duration of GOR episodes during sleep has been directly related to presence of respiratory symptoms in infants (Jolley et al 1981). The mechanism is pulmonary aspiration of a GOR, which was first detected with a radioisotope in 1977 (Reich et al 1977). In patients with a recorded near miss SIDS episode such aspiration is much more readily detected with scintigraphy than barium (Macfadyen et al 1983), although the latter detects massive quantities or very frequent aspirations (Leape et al 1977). Respiratory problems are found in

12% of those with GOR (Weissbluth 1981). The manifestations are varied and include dyspnoeic episodes, spasmodic nocturnal cough, repeated pneumonia etc. When GOR and episodes of apnoea or other respiratory distress are seen in the same study, it is clear that the GOR may or may not occur simultaneously with the respiratory problem (Weissbluth 1981) and in one study in infants, apnoea was equally likely to occur during times when there was no GOR (Walsh et al 1981). In fact detection of aspiration, even by scintigraphy, is not common. The figure of 2% has been quoted (Weissbluth 1981). But by using radionuclides, a cause of nocturnal asthma has been proved to be GOR in an adult (Greyson et al 1982). This association is also possible for paediatric patients (Kjellen 1985) as well as adults (Sontag et al 1987). Sometimes the straight chest Xray can arouse suspicion of GOR, if a distended distal oesophagus can be recognised.

Gastro intestinal tract (GIT) bleeding in an occult form occurs with 5-20% of GOR. It usually manifests as a chronic iron deficiency anaemia without frank bleeding (Mignon 1982). The mechanism is typically erosion of oesophageal mucosa after repeated GOR.

Failure to thrive can result from a myriad of causes. Its chief association with GOR is when there is excess vomiting. It is noteworthy that of those infants admitted to a hospital in Boston for failure to thrive in whom a specific diagnosis was made, 42% had GOR (Berwick et al 1982). Although failure to thrive is often poorly defined by many writers, it has been alleged to be present in 34% of children with GOR (Weissbluth 1981). Also the relation between cystic fibrosis and GOR has been clearly established and so scintigraphic studies of the type described here can be used to improve management of these patients (Scott et al 1985).

The worst association with GOR is the SIDS. This relation was first postulated in 1978 (Herbst et al 1978). Apart from those having had a near miss of SIDS or an affected sibling, it has proved very difficult indeed to recognise those who may be affected. A recent extensive British programme was described in which over 9 000 mostly apparently normal neonates had a variety of examinations including prospective 24 hour ECG and breathing movement recordings. Of those studied, 29 infants subsequently succumbed to SIDS and 10 to other sudden unexpected causes of death. From examination of the recordings no clear correlation could be found (Southall et al 1983).

The association between GOR and the SIDS was examined in 17 infants who suffered a near miss and GOR was found in 47% using radiotracers, but only in 12% with Ba (Macfadyen et al 1983). Others have confirmed there is a high incidence of GOR, detected by several methods including scintigraphy, in infants having suffered a near miss of SIDS (Jeffery 1983), although there is no increased risk of mortality in subsequent siblings of those who have died of SIDS (Peterson et al 1986).

It is important to investigate GOR because of the potentially serious sequelae. These are oesophagitis, oesophageal stricture, pulmonary complications, blood loss and possibly apnoeic spells. The significance of GOR differs for infants and older children. For the former it occurs often in a non pathological form, but when excessive a change in nutrition which is mainly liquid, other medical measures and natural maturation of the LOS usually result in a favourable response without recourse to surgery (Sty et al 1982). There is no substitute for a thorough history and clinical examination. A little recognised accompaniment to GOR is the presence of other anomalies. This was noted in 25 out of 55 patients with GOR. The abnormalities were almost all congenital (Johnson et al 1977).

There is also an association between severe mental retardation and GOR (Schärli 1985a).

A direct association between oesophagitis and GOR is probable (Stanciu et al 1974) although other mechanisms may be relevant in special circumstances (Holloway et al 1981). For example in pigs oesophago gastric ulceration may arise from an excess of the hypothetical hormone entero oxyntin (Watson et al 1983). In a recent study of 116 children with a variety of repeated lower respiratory tract symptoms who were examined with oesophagoscopy and mucosal biopsy, about half of them had oesophagitis and these had significantly more GOR, as determined by pH measurements, than those without oesophagitis (Baer et al 1986). Bile stained gastric contents were found in the oesophagus of about a quarter of those 66 in whom it was sought. Since this usually occurred in the presence of oesophagitis, it is likely that duodeno gastric reflux is associated with the pathogenesis of paediatric oesophagitis.

Twenty-five children and infants with pulmonary aspiration or severe GOR of liquids were found to have a correlation between these findings and a delayed gastric emptying, but there was no such correlation in the same patients with oesophagitis (Baulieu et al 1984). A suggested explanation for the coincidence of discontinuous GOR and slowed gastric emptying in infancy is a functional GIT dysmotility which can also manifest as the irritable bowel syndrome of childhood and/or incoordination problems in the pharynx and upper oesophagus (Jolley et al 1979). Both the absence of pain (Siegel et al 1963) and the presence of a normal gastric clearing rate for liquids (Csendes et al 1978) in adults with GOR oesophagitis were reported. In another publication the latter together with reduced antral region motility in the fasting state were noted (Behar et al 1978). Yet significant differences in gastric evacuation rates have been demonstrated for a mixed solid/liquid meal in patients with GOR, 60% of whom had proven oesophagitis (McCallum et al 1981).

Conventional wisdom in non surgical treatment of GOR has recently been challenged, since it is alleged that thickened formulae and clear liquids can result in hypocaloric intake and a head up position resulted in more GOR than the prone position (Orenstein et al 1983). This opinion differs with our experience and also that of the great majority of other writers. One interesting observation on the incidence of GOR is its relative rarity in black African infants in the Cape Province, who are raised in the traditional way. Why this should be so is not clear. Some possible explanations for this phenomenon can be suggested. These babies spend much time in the erect position and also may not be stressed by being on their mothers' backs. Finally they tend to be fed small meals more frequently on demand than infants raised in other cultural traditions (Fisher 1987). However this finding is not confirmed in observations of African babies from the Johannesburg/Soweto area (Mervis 1987).

Drugs reported to be of value in treating GOR, include domperidone (Grill et al 1985), metoclopramide (Leung et al 1984, Hyams et al 1986), bethanecol (Euler 1980, Sondheimer et al 1986), rantidine (Koelz et al 1986), antacids and cimetidine. In contrast some recent reports state that there is no advantage in using bethanecol (Orenstein et al 1987), metoclopramide and gaviscon (Forbes et al 1986) for treatment of paediatric GOR. In humans and dogs cisapride has been found to accelerate gastric emptying and colon transit (Dormehl et al 1985, Van Daele et al 1984). Our experience with its use will be described in Chapter 8. Nifedipine is also likely to be of use for some oesophageal problems (Richter et al 1985) but not for those of gastric emptying (Traube et al 1985). An analysis of the medical treatment of 600 paediatric patients who had GOR and whose gastric secretion rate was measured showed an association between lack of success of the management (posture, frequent small feeds and drugs) and high levels of acid output (Boix-Ochoa 1986).

Surgery is indicated in general if medical treatment is ineffective in the face of serious GOR, if there is a relapse after its cessation, if a complication ensues or if there is an underlying surgically correctable abnormality. A good surgical result does not depend on there being a post operative increase in LOS pressure (Johnson et al 1977). The most usual surgical technique for correction of GOR is the fundoplication of Nissen (Nissen 1961). However it has been suggested that this may be inappropriate for paediatric patients whose LOS is incompetent but otherwise healthy. Boix-Ochoa has proposed an alternative technique which restores the intra abdominal oesophagus, closes the diaphragmatic hiatus, decreases the angle of His and opens out the fundus (Boix-Ochoa 1986). In this way there is reinforcement of those anatomical relations upon which the necessary physiological factors are thought to depend to prevent GOR (Boix-Ochoa 1983). These have all been described above. In adults satisfactory surgical correction of GOR usually does not last longer than 5 to 6 years (Brand et al 1979). It is likely the same is true for paediatric patients.

A subgroup of patients receiving surgery for alleged GOR do not improve, in spite of technical success of the operation. Part of the present work suggests an explanation. Previously problems of oesophageal dysmotility were mistaken for GOR resulting from LOS incompetence. The scintigraphic study developed in this work allowed a clear distinction to be made with a resulting improvement in the success rate after surgery (Rode 1987). Oesophageal dysmotility is not rare, in the patients we have examined. But nuclear medicine methods do not always detect diffuse oesophageal spasm in adults (Styles et al 1984).

Much attention has been paid in the literature and clinical setting to GOR, but Foster discussed GOR with no mention of scintigraphy (Foster 1985). More strikingly a review entitled, "The role of radionuclide studies in

pediatric gastro intestinal disorders" (Sty et al 1982) did not mention oesophageal dysmotility nor gastric emptying. Its two authors together with a third published a book a year later in 1983 entitled "Pediatric Nuclear Medicine" (Sty et al 1983) and again their chapter on GIT nuclear medicine did not refer to these topics. The dearth of information on oesophageal motility studies does not indicate a lack of intrinsic importance but rather a lack of recognition of its relevance. Some children have both GOR and oesophageal dysmotility. In a reported series of 5 such children (Johnson et al 1977), surgical results were good. Studies of oesophageal transit in adults have shown there is equal sensitivity between radionuclide methods and pressure measurements (Blackwell et al 1983).

Another physiological property that is associated with all the problems considered so far is the rate of stomach emptying. This was first examined with a radiotracer, Cr-51, in 1966 (Griffith et al 1966). If there is an abnormally long retention of gastric contents, coexisting with an incompetent LOS or not, then according to the Yale Group the likelihood of GOR is increased. This has been investigated by them in 23 infants with and without GOR (Hillemeier et al 1981). Gastric contents were determined one hour after swallowing 100 mℓ of cow's milk and Tc-99m sulphur colloid. The percentages remaining then were 79% in infants with severe GOR and failure to thrive, 80% in those with GOR and recurrent pulmonary disease and 56% in infants with mild GOR, normal lungs and weight gain. An association between delayed gastric emptying and severe GOR with complications was implied. Another group goes further using this alleged association and states that a gastric half emptying time greater than 115 min is a positive result for an indirect gastro oesophageal reflux test (Le Luyer et al 1983). Such dogmatism is not confirmed in this work. The Yale workers have also published more extensive results in 126 adults, similarly measuring gastric contents after a balanced meal (McCallum et al 1981). After 90 min on average, patients with GOR

retained 65% and normals 52%, a significant difference but only 41% of adult GOR patients had abnormally high gastric contents after 90 min. Thus slow stomach emptying must not be accorded too much weight in adults when assessing GOR. This has recently been confirmed in a series reported by the Harvard group of 126 paediatric patients aged 0 to 16 years (y) who swallowed a 5% dextrose solution and the suggestion was therefore made that gastric emptying values may be related to age, rather than GOR (Rosen et al 1984).

Oesophagitis, often associated with GOR, may rarely be inherited (Matikainen 1986) and can have the serious complications of stricture and haemorrhage. These are not common in infants, although in a series of 114 infants and 67 children selected for anti reflux surgery, two aged 18 months were found to have advanced strictures due to GOR (Johnson et al 1981a). For this reason a reliable method for investigation of oesophagitis is necessary. The most direct means, oesophagoscopy with biopsy, is invasive and can be fallible (De Meester et al 1976). There are also other disadvantages already noted, which preclude its use as a first examination. More practical methods for an initial study are barium swallows, manometry and nuclear medicine. But according to Darling et al, "in children with peptic oesophagitis, the barium examination of the oesophagus appeared to be of diagnostic value only in the small number of patients with advanced disease" (Darling et al 1982). This has been confirmed in scintigraphic studies (Derksen 1985) even when the radiopharmaceutical is Tc-99m sulfacrate. This has a specific affinity for inflammatory erosions, but only the severest form of oesophagitis was imaged (Goff et al 1986). Use of both single and double contrast radiography has been advised, even though no statistical superiority of the latter was demonstrated after examination of 92 adults (Creteur et al 1983). In contrast, a Barrett's oesophagus in adults has been associated with a newly described reticular pattern after a double contrast barium study and characteristic manometric patterns (Bozymski et al 1982).

Nuclear medicine methods have been asserted to be the best for detection of oesophageal motor dysfunction arising from oesophagitis (Taillefer et al 1984). An increased oesophageal transit time without GOR in an appropriate clinical setting is considered by some (Leisner et al 1982) and the reduced amplitude of oesophageal peristaltic waves by others (Cucchiara et al 1986) to be suggestive of oesophagitis. Another sign of this condition seen with the use of swallowed sulphur colloid is its adherence to sites of inflammation of the oesophageal mucosa. Work with experimental oesophagitis in cats has shown this to be a most effective way of identifying such sites (Taillefer et al 1983) but results from the same workers are much less clear when the technique is applied to humans (Taillefer et al 1984, Singh et al 1985).

Much attention has been paid to GOR in paediatric patients and it is clear that it can be associated with serious and even fatal complications. Work by others has shown that scintigraphy has proved very useful in various isolated aspects of the problem hence there is a place for improving and bringing together the investigations mentioned into a single study with appropriate innovations. Since the different clinical presentations are very varied both in adults (Reidel et al 1985) as well as children, such a sensitive screening test could have a useful place in the armamentarium of the paediatrician who has access to nuclear medicine facilities. Thus because of available evidence it is suggested that scintigraphy should be the first study performed when special investigations are required in the circumstances described earlier, except when hiatal hernia, tracheal oesophageal fistula or associated anomalies and possibly pharyngeal incoordination are suspected. Then radiological examination is more appropriate. After scintigraphy, Xray studies, oesophagoscopy, pH measurements and manometry could be performed in this order if further investigations are necessary. However following (Willich 1986) this can be modified for, "the choice of procedures should depend upon the clinical symptoms and availability of equipment and

experienced physicians" (Shub et al 1985). For example in the absence of vomiting, radiological studies should have a lower priority since an anatomical obstruction is unlikely. Currently there does not seem a place for the more exotic investigations mentioned earlier.

CHAPTER 7: SCINTIGRAPHY: METHOD AND RESULTS

"Surely every medicine is an innovation, and he that will not apply new remedies must expect new evils". Francis Bacon; Essays.

7.1 Scintigraphic method

There is no universally accepted method for paediatric gastro oesophageal scintigraphic examinations and relevant scintigraphic investigations performed by others have been described. The majority of other workers studying function of the GIT with scintigraphy use Tc-99m sulphur colloid. Briefly, data on oesophageal transit is recorded using 0,5 to 1s per frame while the child swallows. Scanning to detect GOR continues at 20 to 60 s a frame for 1 to 2 hours. Two to 24 hours after ingestion of the labelled feed, images are recorded to detect aspiration. Most reports describe the study in the supine position, but some are done in the erect position. Gravity exerts an effect which in principle quickens passage of the liquid through the oesophagus when the patient is erect (Heyman 1984). The passage of water swallowed by adults is apparently unaffected by the patient's position according to some workers (Fisher et al 1982), although others disagree (Ham et al 1985).

The method described here is based upon results of 630 studies performed from 1981 to 1983 in the Hôpital Pellegrin, Bordeaux, France and over 270 studies subsequently done at the Red Cross War Memorial Children's Hospital, Rondebosch, South Africa (hereafter called the "Children's Hospital"). As a result of this experience the form of the examination derived is proposed as a standard method with wide application.

Shortly after this work was commenced in France some improvements

were introduced. The child swallowed in the normal position i.e. infants were held in the mother's or nurse's arms and older children sat while drinking. Frame rates for the oesophageal transit were increased from 1 to 2 Hz (0,5 s/frame) and images were recorded on a multi imager using Xray film rather than on polaroid photos. The volume of swallowed liquid was reduced from 50 to 5 mℓ. Abdominal pressure was not applied to the patient, positions other than the supine position were not used after completion of the swallow and all non physiological manoeuvres were eschewed.

In part the information available in 1981 influenced choices made between the alternatives which led to the protocol followed in this study. None of the considerable amount of material subsequently published has given any reason to modify those features which contribute to the uniqueness of the present work.

The programme was set up with the following aims. A study was to be devised which was easily performed by any nuclear medicine department satisfying the following reasonable criteria. A typical gamma camera connected to a computer is required together with technologists of average experience and ability. Simple and inexpensive radiopharmaceuticals and a Tc-99m generator must also be available. Finally patient co-operation in the examination should be minimal and the resulting information maximal in terms of relevant paediatric problems, yet all this must be obtained non invasively, in a reasonable time, under physiological conditions. Gastro oesophageal scintigraphy as described by others never satisfies all these criteria. Some perform studies that are invasive, non physiological, or too long or complicated, to be useful as a frequently performed examination in a paediatric nuclear medicine department with a typical workload to staff ratio.

It is an indication possibly that these aims were achieved, for within two years over 600 such studies were performed on both in patients and out patients. The parents were always invited to be present, if this was practicable for them, and to assist with the administration of the radiolabelled and unmarked liquids. Their presence and participation were especially useful for the studies of oesophageal transit in the youngest patients and also to reassure them, if this was required, while they lay quietly supine during the search for GOR. Even without the presence of the patient's mother, neither lack of cooperation nor fear of the examination were ever problems.

The full initial paediatric examination must permit a search for abnormalities of oesophageal transit, GOR over a period of many minutes and also pulmonary aspiration. Hence a radionuclide with a short half life such as Kr-81m is unsuitable for the full study. But it could prove invaluable for additional studies if the first part of a study with Tc-99m sulphur colloid uncovers abnormalities in the swallowing of a liquid.

The question of amounts of radioactivity administered to paediatric patients is of overwhelming importance and no nuclear medicine examination should ever be undertaken without consideration of this matter. Hence dosimetry will be more fully discussed in the next chapter. The final decision was to use 0,002 mCi (74 kBq) of Tc-99m per mℓ of the normal feed volume up to a maximum of 0,3 mCi (11 MBq) for infants. For each subsequent year of age this total was increased by 0,02 mCi upto a maximum of 0,6 mCi (22 MBq). Those patients whose mass or height was below the 10th centile received a total activity of 0,44 mCi (16,3 MBq) per m^2 of body surface area.

The apparatus used in Bordeaux was a large field of view gamma camera (CGR Acticamera, model 3400), coupled to a computer (IMAC, model 7640). Storage facilities included a Winchester fixed disc (20 MB) and double density 8 inch floppy diskettes. Displays on two monochrome monitors, mounted in the console and on the camera gantry, and on a colour monitor were available. Images were produced with a multi imager using Xray films and a polaroid camera. A multi coloured ribbon plotter and line printer were also available but seldom used. A parallel hole collimator of medium sensitivity and resolution was used. The window width set on the unique Tc-99m gamma was 15% and the imaging matrix employed was 64x64 pixels.

Swallowed material was liquid in all studies, except for one patient who usually choked on liquid feeds and therefore received radiolabelled mashed potato (Fig 7,11). For bottle fed infants it was their usual formula but older patients drank flavoured water. Expressed breast milk was also used. Liquids were not cooled. This procedure has recently been justified by the finding that swallowed cold water can cause inferior oesophageal and LOS paralysis (Kaye et al 1987). The study examined deglutition and gastric emptying and sought GOR and pulmonary aspiration routinely. Deductions concerning small gut transit were sometimes possible.

The examinations practised at the Children's Hospital are identical to those described above, except for the apparatus which comprises either an Elscint Dycomette and Dymax gamma camera system with both diskettes and paper tape for storage and/or transfer elsewhere, or later an Elscint Apex 415 SPECT gamma camera. A sheet film multi format imager is also available with each system.

7.1.1. Oesophageal transit

The patient is examined in a fasting state at the time of a meal. The field of view is chosen to include the mouth and stomach, so usually the cup or bottle is also imaged. The framing rate of 500 ms for each image is continued for 60 s. A lead shield can be placed around the container of the liquid and the liquid is swallowed in the erect position with the left lateral view presented to the camera. Modern computer controlled gamma cameras have a short minimum frame exposure time. Hence the framing rate is limited only by the number of counts recorded, not by any intrinsic limits in the framing speed. If there is more rapid transit in the erect position, this can be accommodated by an increased framing rate. Thus the erect position, in which meals are taken, can be used for this part of the study. An infant is held in the arms of an attendant, or preferably his mother, and so fed in his accustomed fashion and position.

The volume of marked liquid swallowed is 5 mℓ and this differs markedly from all other workers in the field. The larger this volume the more swallows are observed, but the transit of individual deglutitions can be very difficult or impossible to observe because the specific activity (concentration) of tracer, and hence the count rate, is low. The swallowing pattern of multiple transits typically indicates the same abnormality or normalcy in each. The youngest patients cannot swallow on command but their bolus is of small volume so, even with our reduced total amount of marked liquid, twenty-four or more individual deglutitions have been recorded in a single study (Figs 7,8 and 7,10). This is more than

sufficient. To maintain an identical study in all patients, liquid swallows only were used, except as noted above. Also dry swallows, impossible in the youngest patients, are less likely to stimulate abnormal oesophageal contractions than wet swallows (Janisch et al 1978). The data recording is started a second or two before the patient begins to swallow. After the marked feed has been consumed, the remainder without radio tracer is given to bottle or breast fed infants. Those who drink flavoured water are allowed to drink more unmarked liquid to satiety, but with a minimum of 100 mℓ. Its purpose is to wash the buccal cavity, pharynx and oesophagus to remove any adherent particles of sulphur colloid from the oesophageal or other mucosa. It is rare for any substantial amount of activity to remain in the oesophagus before the rinsing. Occasionally the unmarked liquid fails to dislodge the colloid particles from the mucosa. This is interpreted as mucosal abnormality in the regions of adherence, most probably inflammatory change. After finishing the unmarked liquid infants are made to eructate and all subjects are then placed supine beneath the camera for the next part of the study.

7.1.2 Search for GOR

The supine position, apart from being the most convenient and comfortable for a scintigraphic study of duration some tens of minutes, is also the posture in which infants are often placed after feeding and further it has been shown by one group to be that which has the highest sensitivity for scintigraphic detection of GOR in children (Piepsz et al 1982), although others dispute this (Peyraud et al 1985), asserting that position makes no difference.

The field of view for the GOR search includes stomach and cervical oesophagus. Usually small gut and mouth are also observed, especially in the youngest patients. Unlike some other workers (Conway 1972, Sty et al 1982) we do not find any necessity to use sedation routinely in any group of patients, nor any of a long list of devices (Conway 1972) intended to prevent patients from moving during this portion of the examination. Most frequently young patients would sleep, being replete. On the very rare occasions when there was excessive movement a polyurethane bag under vacuum filled with polystyrene beads manufactured by Nuclear Associates was used. It is firmly moulded to the enclosed patient's shape without exertion of any pressure and is radiolucent.

The duration of the search for GOR is at least 30 min. Images were recorded every 5 s by the computer and every 10 s on film in Bordeaux, each 20 s with the Dycomette and each 10 s with the Apex 415 at the Children's Hospital. A monitor oscilloscope was observed during this time. The sensitivity of detectable GOR is about 0,25 mℓ of refluxate (Paton et al 1985). If a GOR of duration 10 min was observed, the remaining part of the search was performed with the patient in the erect position. The time of occurrence of any relevant events, for example coughs, vomits, sudden pallor, dyspnoeic or cyanotic episodes and belches was recorded. This could be related to happenings observed on the monitor such as a GOR or appearance of radioactivity in the lung fields and the scintillating belch differentiated from a GOR. Gas rising from the stomach can carry a small amount of Tc-99m colloid with it which may result in a contamination of the oesophagus. This happening is rare

and usually is not repeated during a study. However it may arise from aerophagia (Willich 1986).

The liquid containing radioactivity was drunk in order to examine deglutition as has been already explained. Apart from this need some workers prefer to instil all the liquid directly into the stomach by means of a nasogastric tube (Sty et al 1982, Blumhagen et al 1979). The reason for this preference is to avoid aspiration during deglutition and so differentiate between activity in the lungs secondary to "neuromuscular inco-ordination of the swallowing mechanism or tracheoesophageal fistula abnormalities (Sty et al 1982)" and GOR. If there is not a known pharyngeal inco-ordination or tracheo oesophageal fistula (TOF) we prefer not to pass a nasogastric tube but to observe a swallow scintigraphically. No serious problem has ever occurred with our patients as a result of aspiration during swallowing. Use of the monitoring oscilloscope allowed early recognition of this possibility. Any patient receiving this scintigraphic investigation must already have swallowed many times so the chances of morbidity from the investigation per se must be very little.

Another difference between the quest for GOR described in this work and that of many other workers is their use of non physiological conditions to improve the chances of detecting GOR. The firm belief that merit of the examination reposes in its repetition of the physiological conditions of ingestion of a liquid meal prevented adoption of these measures. Similarly other manoeuvres, already described, were eschewed. A comparison of detection accuracy for GOR in infants and

children with and without abdominal compression, found the latter was preferable (Swanson et al 1981). Yet this relevant finding seems to have been ignored, possibly because the first scintigraphic studies of GOR were performed with an abdominal binder (Fisher et al 1976). Others followed this example. However its use allows the GOR search to be completed more quickly (Malmud et al 1980).

After the 30 min devoted to a search for GOR, a marker is used to identify the cricoid cartilage, mouth, shoulders and other anatomical landmarks. The mouth can also be imaged again for a recorded time if it contained any remanent radioactivity at the start of the search. In adults this proved useful when radiotracer was seen to appear suddenly at a localised region in the oesophagus.The images confirmed that the activity had moved proximally (Wynchank 1985). They could also be obtained for large children if the entire region of gastric and GIT radioactivity was unable to be imaged during the search for GOR.

7.1.3 Gastric emptying

Two static anterior views, including all activity in the stomach and distal gut, were obtained 30 and 120 min after the last liquid is swallowed. The main purpose of this data is to allow calculation of the amount of liquid remaining in the stomach and that which has passed through the pylorus. Since the relative anatomical positions of stomach and jejunum may vary, superposition of radionuclide in the two regions may be possible in an anterior view. Images are therefore recorded using other views, if necessary, to separate gastric activity

from that which is more distal. Often the image recorded after 120 min, shows passage of the liquid into the ascending colon.

7.1.4 Pulmonary aspiration

Between the recording of both images used to calculate the stomach emptying rate the patient may indulge in any activity in any position, is fed if necessary, but is encouraged to lay down. When the second of these images is obtained, an appropriate image, or images is recorded to permit any activity in the lung fields to be recognised. A suitable exposure time is used. The location and volume of the aspired liquid can also be determined. It is crucial that no error be made in its identification if any candidate activity in the lung field is seen. Recognition of uptake of free Tc-99m by the thyroid and of spilled Tc-99m on skin or clothes is possible if the static images are recorded using different viewing directions. Clothing is removed and the skin cleansed to remove superficial activity. Markers in the axillae, on the sternal notch, xiphoid process or elsewhere can assist localisation of any pulmonary activity. Radiotracer in the left lung base is the most difficult to to recognise, due to possible adjacent activity in the fundus. If it is necessary to identify the gastric region unequivocally in this case, further radiopharmaceutical can be swallowed and observed in the stomach.

Should aspirated liquid be observed in the image recorded for the first determination of gastric contents, any change in the liquid's relative position in the image recorded after two hours, allows an estimate of mucociliary function in the

proximal airways to be made. Clearance of Tc-99m sulphur colloid from the airways has been studied in Rhesus monkeys. In the distal passages only a decay equivalent to the physical half life of about 6 hours was seen. Labelled colloid more proximally placed resulted in a biexponential decay described by half lives 1,7 and 6 hours. The first component demonstrates rapid mechanical removal associated with ciliary action and the second, physical decay. Similar results with a much shorter half life have been obtained in humans (Iturralde 1984).

7.1.5 Data reduction

The immediate data analysis is included in a series of routine protocols derived for the purpose. For the dynamic series of images, especially passage through the oesophagus, the sequence of ciné images should be viewed in the form of a movie or series of stills as a qualitative investigation, in addition to the graphical and quantitative analyses. This together with the individual images viewed juxtaposed (Fig 7,12) allows overall movement to be evaluated independently. Regions of interest for analysis of the swallow always use 4 ROIs extending from the cervical to the distal oesophagus. Each provides an activity-time curve. As each bolus traverses the ROI a prominent peak in the curve results. The time interval between the first and last peaks allows determination of the OTT, which confirms the deduction from observation of the images. A modified form of Svedberg's condensed image treatment (Svedberg 1982) of the data acquired during oesophageal transit has also been used in this work.

The images obtained during the dynamic study of deglutition are compressed in the following way. Each image is used to obtain a single column of pixels. A given pixel of the column results from the normalised summation of all pixels in the image's corresponding row. Thus the nth dynamic image of the oesophageal transit study results in the nth column of the condensed image. These composite vertical lines are juxtaposed in sequence in a single image formed of (say) 64 columns. Column 1 is therefore the compression of image 1, column 2 of image 2 etc (Ham et al 1985d). Thus the progress of a swallowed bolus can be followed. When there are subtle differences in its movement in sequential swallows, these are clearly recognised in the condensed image as is discussed below. This form of analysis was first described by Klein (Klein et al 1984) and has been described as the method of choice (Ham et al 1985e). Its advantage over the compressed bolus-centroid method is that no information about the spatial distribution of the bolus is lost if for example, the bolus breaks into two or more parts. A potential pitfall is the danger of a failure to recognise the effect of a delayed component of oesophageal transit (Ham et al 1985e) due to, for example, a pouch.

An alternative method of analysis, outlined in Chapter 4, considers oesophageal emptying as proportions voided into the stomach at varying times (Tolin et al 1979, Gross et al 1979, Leisner et al 1982, Espinola et al 1982, Holloway et al 1982, Rozen et al 1982a, Datz 1984). This approach is undoubtedly useful for evaluation of achalasia (Singh et al 1985, Gross et al 1979, Rozen et al 1982b) but is quite unsuited for

paediatric needs. On the rare occasions achalasia was encountered in our patients, the abnormal swallows were adequately described in terms of OTT and the nature of the tracer movement, or lack of it. Most importantly oesophageal dysmotility, which can express itself as hold up at different oesophageal sites in successive swallows, would be unrecognised unless motion was simultaneously evaluated in terms of an integral describing passage through a very large number of regions of the oesophagus.

It is one of the important findings of this work that in paediatric patients oesophageal dysmotility plays an important and hitherto poorly acknowledged part in relevant paediatric problems. Thus the adopted choice of methods for analysis of data produced in the first part of the study seems justified in terms of both paediatric relevance and logic.

For the GOR search, a ROI is drawn in the distal oesophagus and the time activity curves and individual images scrutinised for reflux. Physiological GOR is common, especially in neonates (Godfrey et al 1979) and it is necessary to have a criterion to allow distinction between pathological and physiological GOR whenever a localised maximum in the curve is observed. The background in the ROI before a reflux is measured and the episode of GOR is considered pathological if the counts increase to more than three times the background. Any GOR that reaches the mid thoracic region is also deemed non physiological. It is further possible to classify GOR as severe or moderate. If refluxes persist for one minute or

more, or reach the cervical region, the GOR is considered severe).

The choice of ROI for gastric emptying measurements is usually straightforward although sometimes additional views are required as explained above to allow activity in the stomach and small gut to be measured. For this reason routine curves of activity for these ROIs against time was discontinued. The relative proportion of contents of stomach and small gut is an easy quantity to derive, compared with the absolute values such as mℓ or (mℓ per unit area of body surface) used by others (Cavell 1981). If absolute values are required then the necessary corrections are very complicated and not justified in the paediatric situation (Christian et al 1983), where allowance for absorption in superficial tissue is less important.

In all, a well defined method for reduction of the scintigraphic data has been evolved which allows the complete study to be performed as a routine.

7.2 Scintigraphic results

Unless stated otherwise all the results presented in this section were obtained at the Hôpital Pellegrin in Bordeaux.

7.2.1 Transit and GOR.

The indications for performing 630 scintigraphies are given in Table 7,1 for each age group. When there was more than one indication, the most important was chosen for inclusion in this table. Table 7,2 lists the numbers of

patients without GOR and with moderate or severe GOR, for each indication and age group. Mean oesophageal transit time (OTT) is listed in Table 7,3 in terms of age. Also the height of maximum observed GOR is included with associated values of OTT, together with their standard deviations (SD) where this is possible. Similar data for term and preterm neonates is given in Table 7,4. The relation between GOR with or without oesophagitis and variations in OTT is demonstrated in Table 7,5.

A comparison between the successes of nuclear medicine and Xrays in detecting GOR is possible by correlating the results of the two different examinations. The relevant data are presented in Table 7,6. When the two studies were performed in patients with oesophagitis diagnosed by endoscopy, another comparison is possible. Appropriate results are given in Table 7,7.

An analysis of observed GOR in terms of time after deglutition is possible from the grouping shown in Tables 7,8 to 7,11. The numbers of GOR observed in different time intervals after ingestion and the time of occurrence of the first and last GOR are listed for different age groups. Data included in the age range 0-1 y (Tables 7,8 and 7,10) are repeated as Tables 7,9 and 7,11 to allow the examination of results for neonates, both term and preterm. Lengths of GOR in terms of age and height of maximum observed GOR are used to provide Table 7,12. Similar results for neonates are listed in Table 7,13.

7.2.2 Gastric Emptying

The data obtained from measurements of gastric contents 30 and 120 minutes after ingestion are given in Table 7,14 as functions of two age ranges and level of the highest GOR. For neonates the corresponding results are given in Table 7,15. The two measurements of gastric emptying are also given in terms of the time of start of the last GOR and age range in Table 7,16 for patients of all ages and for neonates in Table 7,17. The mean gastric contents for 88 infants under 3 months in age are given (Table 7,18) in terms of the liquid swallowed (human milk or infant formula) age range, time after deglutition and whether term or preterm.

7.2.3 Pulmonary aspiration

Pulmonary contamination (Figs 7,25 to 7,28) was observed in 14 patients of whom 7 were aged under 1 year. In these 7 patients the indications for the study were a near miss of SIDS for 5, or a sibling who had died of SIDS in the remainder. One had a tracheo oesophageal fistula which was later confirmed by Xray studies. Two aspirated stomach contents immediately after a massive GOR which was observed during the 30 min following swallowing. One of these two experienced an episode of coughing at the moment of aspiration. The other 4 infants and the 7 more than 1 year old contaminated their lungs in the period between 30 and 120 min after ingestion of the radiotracer. A significant amount (above 0,5 mℓ) entered the pulmonary passages of eight. The three who aspirated lesser amounts contaminated their left basal zone and two had no observed GOR. Seven of the 11 had GOR observed earlier in the study and the other 4 had delayed gastric emptying.

7.2.4 Some results from the Red Cross War Memorial Children's Hospital

The results from the Children's Hospital are given in Table 7,19 et seq and comments are as for the corresponding tables already described. Pulmonary aspiration were more frequently observed, in keeping with the different nature of the patients. Twenty-five such episodes in 24 patients were noted, 17 referred for repeated respiratory problems (9 having had recurrent pneumonia), 6 for excess vomiting and one for near miss of SIDS. GOR was seen in all except two. All aspiration occurred between 30 and 120 min after swallowing the marked colloid. The right lung was contaminated in 13 studies and the left in 12 (Table 7,20). A delayed gastric emptying was seen in only 5 of these studies. One of them (94% after 30 min yet 21% after 120 min) showed no reflux in the first study. Yet in a second study this patient again demonstrated aspiration and many thoracic GOR were seen.

Since the South African patients were in general iller than their French counterparts, a higher incidence of abnormality is not unexpected. One striking difference, which is likely to be of importance, is the frequent demonstration of varying oesophageal spasm in young paediatric patients.

Of 150 complete studies performed without any drugs, and with liquid swallowed in the erect position, only 34 are normal, 4 demonstrated only an abnormal swallow, 59 only GOR and 43 showed both reflux and transit abnormalities. This low proportion of normal results clearly demonstrates the difference between the two patient populations. It is noted

that when oesophageal transit is prolonged due to failure of progression of peristalsis, it is not always associated with delayed gastric emptying. The gastric contents after 30 and 120 min may be average or greater or less than average (Table 7.21). This indicates that any foregut abnormality observed may or may not be restricted to a particular part of the GIT. Results for the Children's Hospital patients seen to have oesophageal spasm are given in Table 7,21.

In Tables 7,22 and 7,23 results from the Children's Hospital are given which describe the GOR observed. This corresponds to the contents of Tables 7,8 and 7,10 respectively. Similarly comparisons between results of scintigraphy and barium Xray studies to detect GOR are given in Table 7,24. These are comparable to those of Table 7,6 although numbers are smaller. Various illustrations of these results, both normal and abnormal from both hospitals, are presented as Figs 7,1 to 7,61. These demonstrate the power of the scintigraphic method within the range of observed pathological processes and are discussed further below.

FIGURES

(All condensed images represent a time scale from 0 to 60s after deglutition unless otherwise marked or indicated in the caption. The graphs are plots of counts÷10 obtained from a ROI against time in seconds).

Typical Swallows

Fig 7,1i

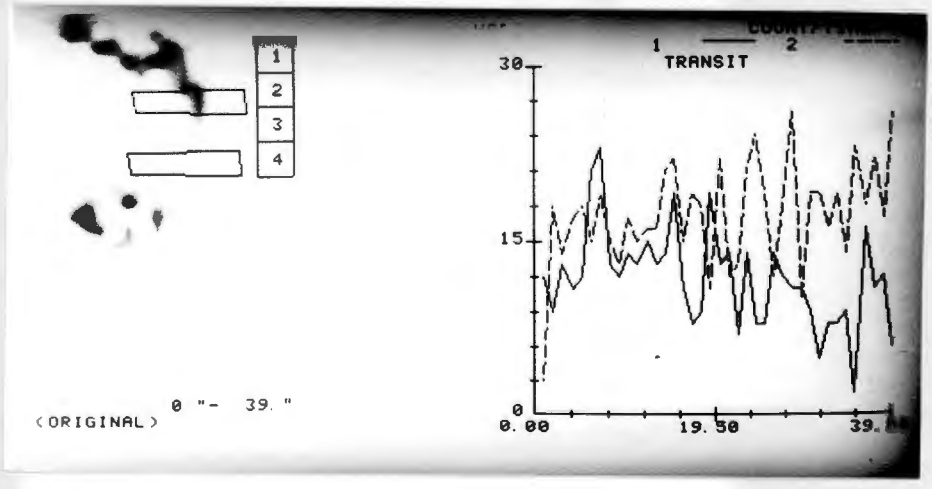


Fig 7,1ii, iii

Fig 7,1i to iii — This 27 day old male was born at term but excess vomiting and regurgitation were observed and peristed. Ba studies were normal apart from a J-shaped stomach. The swallow illustrated by ciné images, ROIs and graphs clearly shows the passage of each deglutition. Fig 7,1i demonstrates individual frames of the ciné record. When ROIs as shown in Fig 7,1ii are drawn the resulting curves clearly distinguishes between individual deglutitions (Fig 7,1iii).

Fig 7,2i

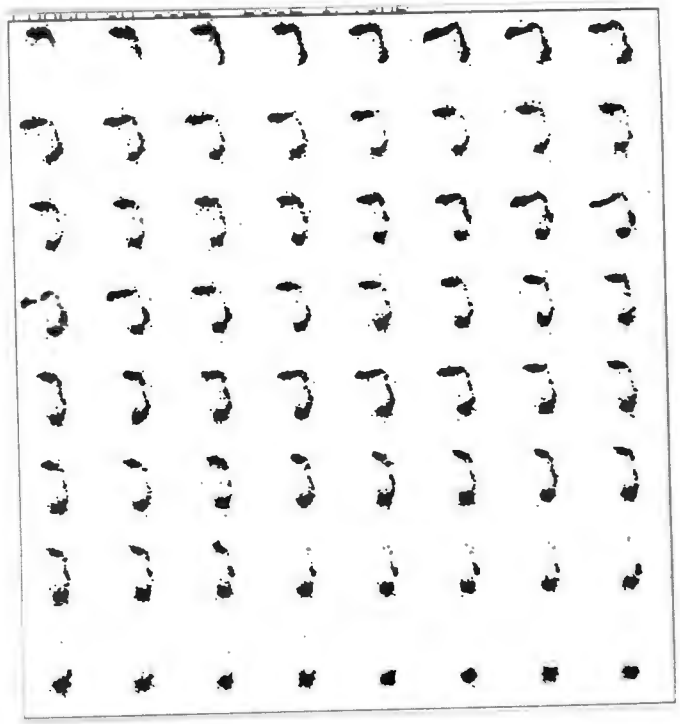


Fig 7,2ii

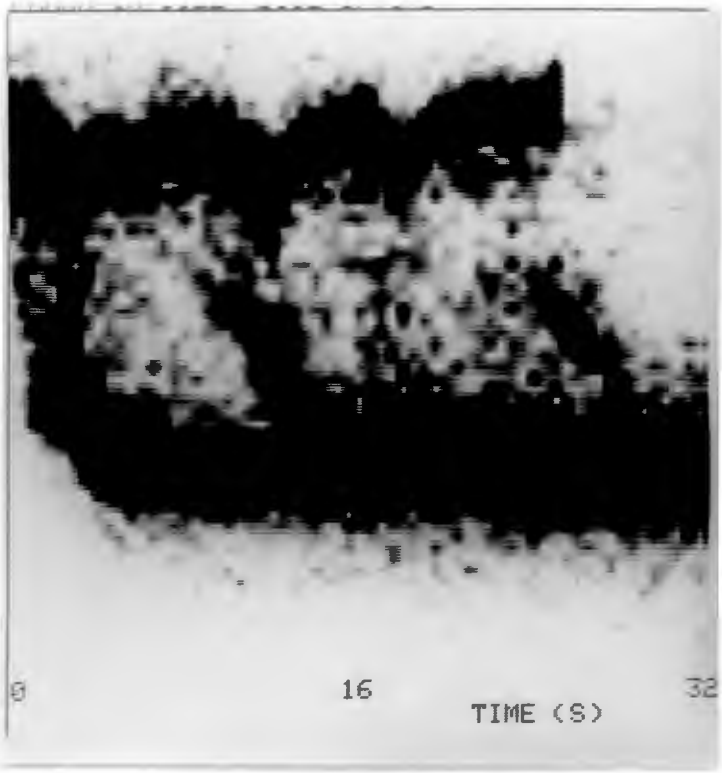


Fig 7,2i, ii This 6 month female demonstrates four swallows with clear inferior oesophageal slowing, both in cinē (Fig 7,2i) and condensed images. (Fig 7,2ii). She had recurrent pneumonia but no abnormality was detected apart from an OTT of 5,2 $\pm$ 1,7s.

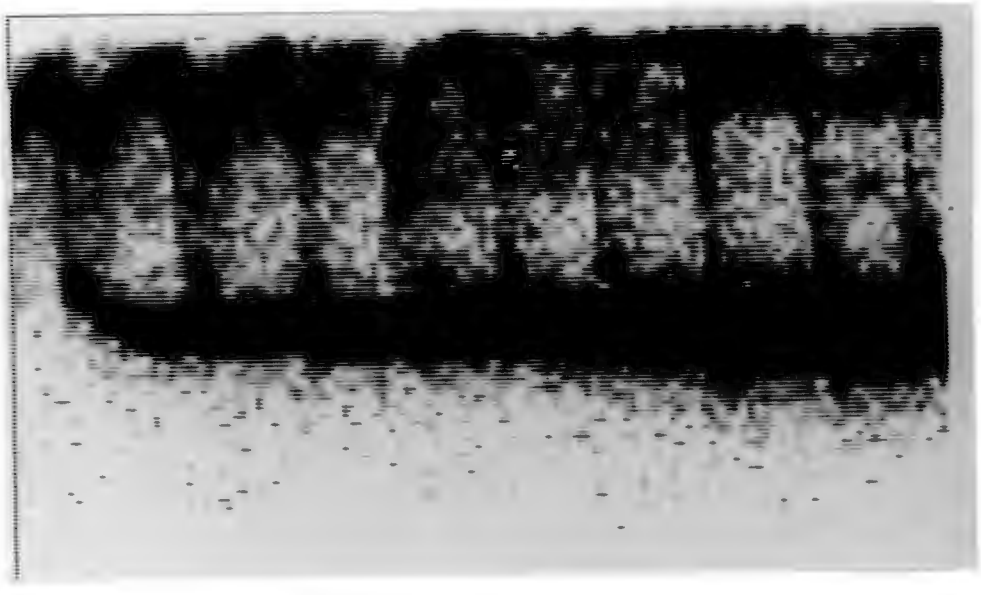


Fig 7,3i

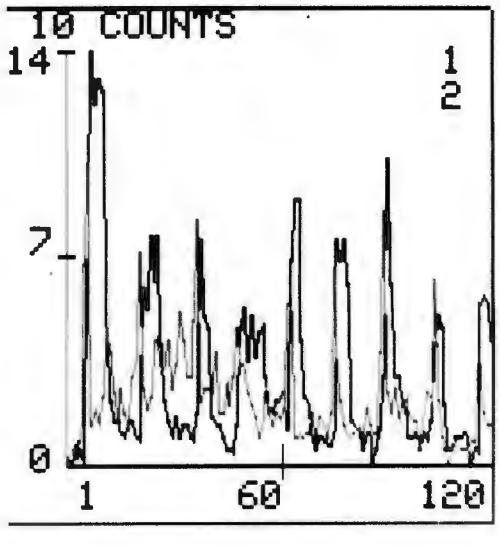


Fig 7,3ii

Fig 7,3i, ii Nine clear swallows are presented on this condensed image of a 41 month old female who presented with recurrent pneumonia. She also had a diagnosis of asthma and the Wolfe-Parkinson-White syndrome (Fig 7,3i), graphs resulting from ROIs demonstrate the passage equally clearly (Fig 7,3ii).

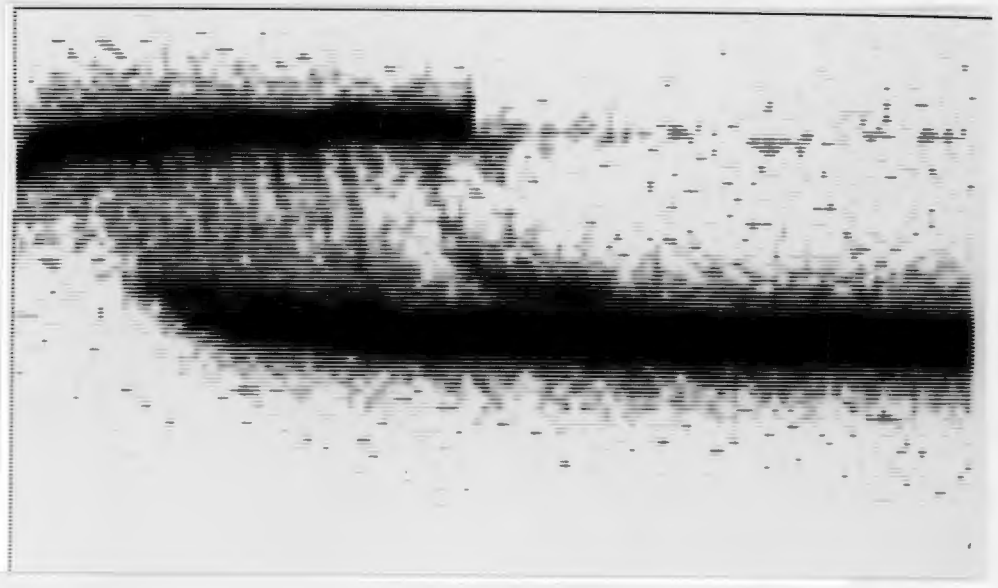


Fig 7,4

Fig 7,4 This 11 month old male had persistent pneumonia with thrush and TB. About fourteen normal swallows are seen, the penultimate having some pre LOS hold up in this condensed image with mean OTT 3,2 ± 1,6s.

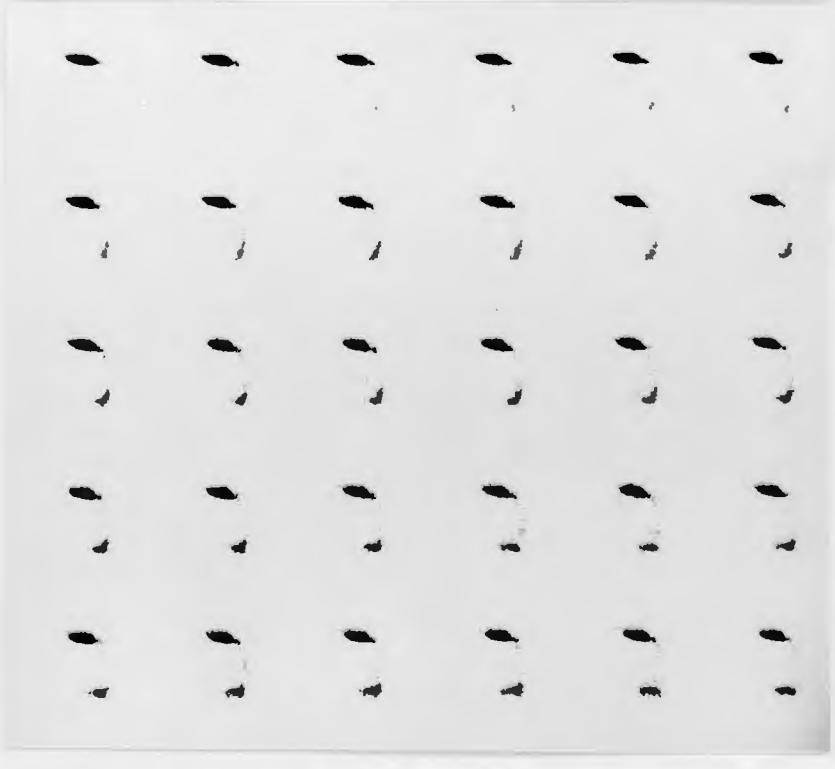


Fig 7,5i

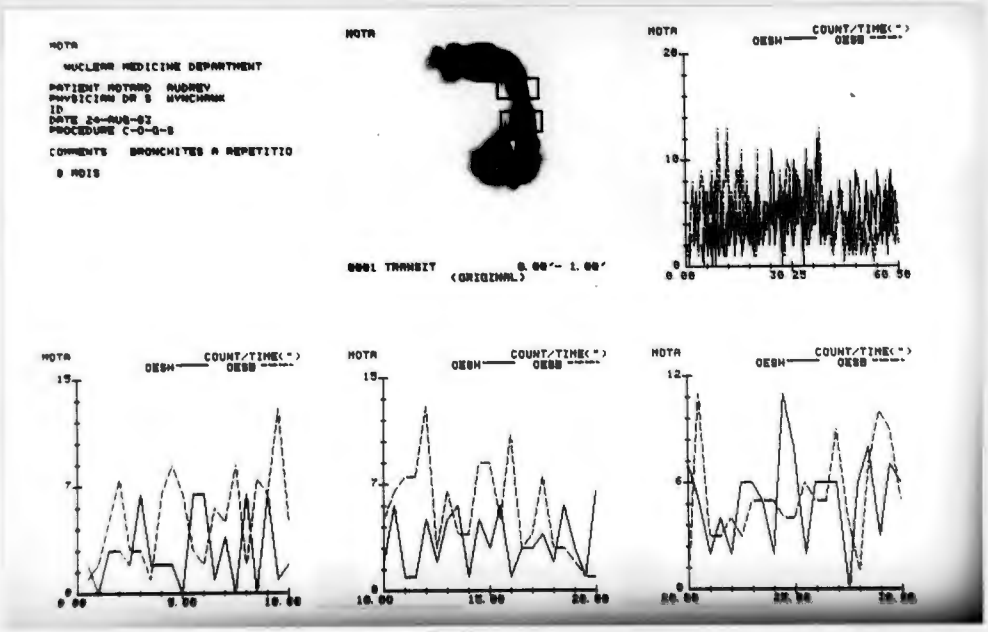


Fig 7,5ii-vii

Fig 7,5i to vii

This female aged 9 months 19 days had experienced repetitive bronchitis since the age of about 3½ months and was examined with a nuclear medicine study. Twelve days earlier a subsegmental right upper lobe atelectasis and diffuse bronchial wall thickening were observed on chest Xray. This remained essentially unchanged 9 days later. The swallow (Fig 7,5i) provides a graph clearly showing pairs of peaks more readily distinguished than individual swallows on the ciné images. (Fig 7,5v to vii). Regions of interest are drawn in Fig 7,5iii and the resulting graph (Fig 7,5iv) is seen to be uninterpretable unless the time scale is suitably expanded.

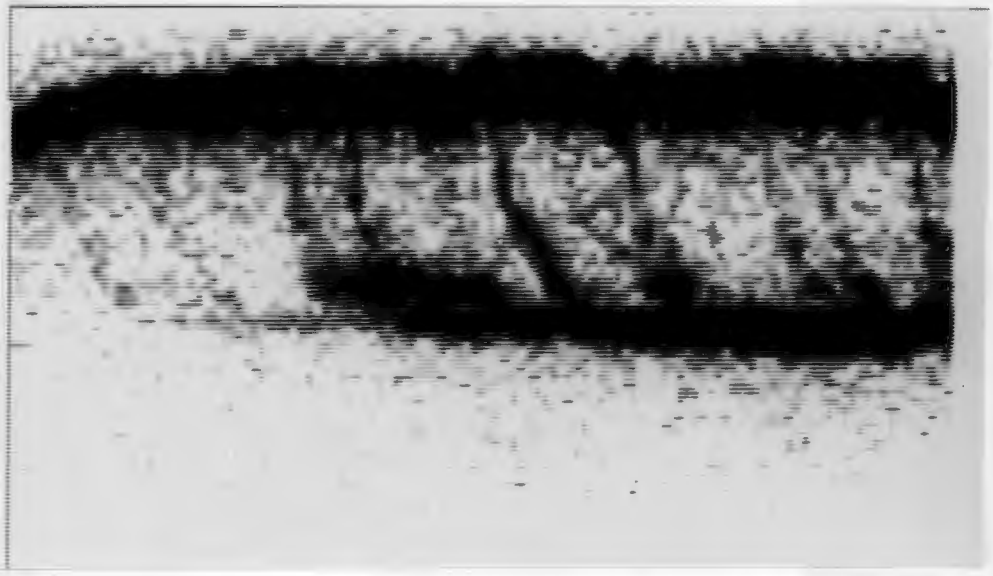


Fig 7,6

Fig 7,6

This 14 month old male with repeated respiratory problems (bronchiolitis and pneumonia) shows about 12 deglutitions in a condensed image, with varying amounts of hold up at the LOS. The mean transit time is 5,3 $\pm$ 1,7s which is longer than usual for a child of this age.

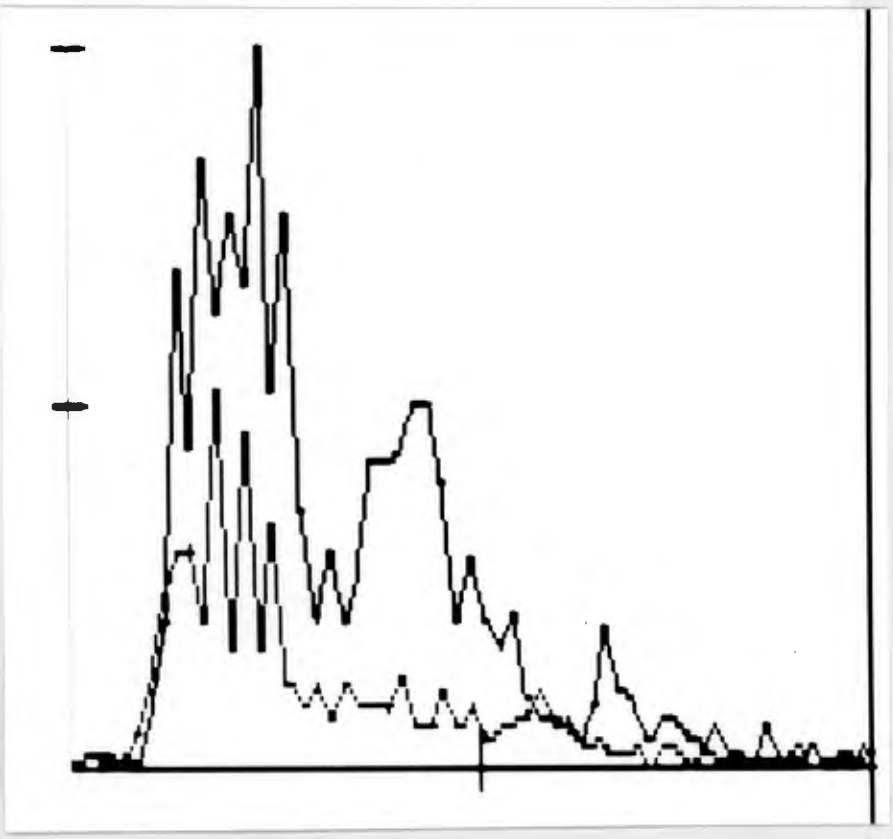


Fig 7,7i

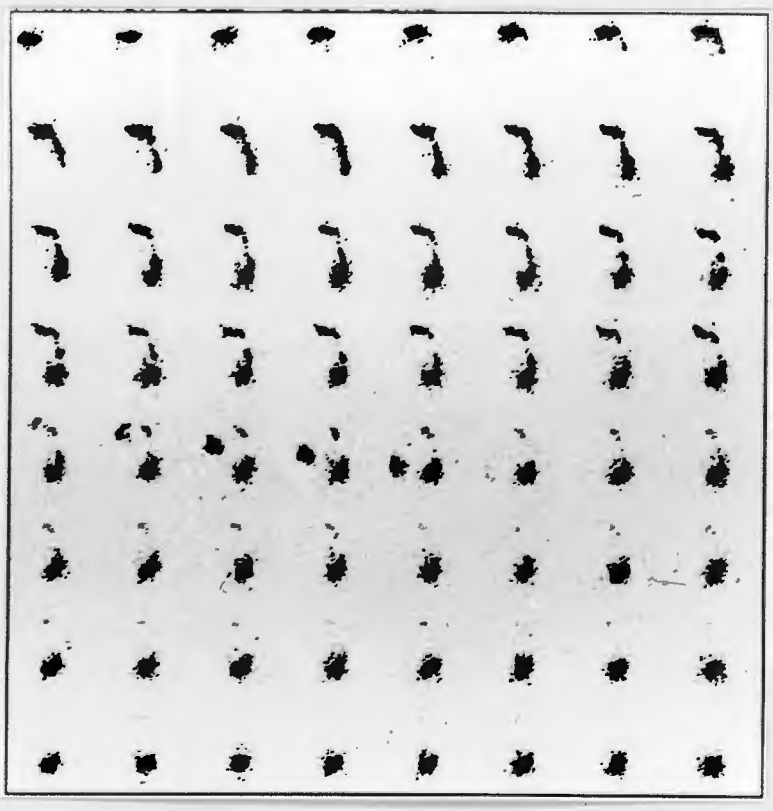


Fig 7,7ii

Fig 7,7iii

Fig 7,7i to iii — This 14 month old male had previously suffered an unexplained cyanotic spell. His swallow when analysed graphically clearly shows associated pairs of peaks from the passage of a bolus through upper and lower ROI (Fig 7,7i). They are somewhat less distinct in ciné (Fig 7,7ii) and condensed images (Fig 7,7iii). An image of the bottle appearing in the 5th row of the ciné images has been removed from the condensed image, by summing only columns 18 to 23. (The time represented is from 0 to 32s after deglutition).

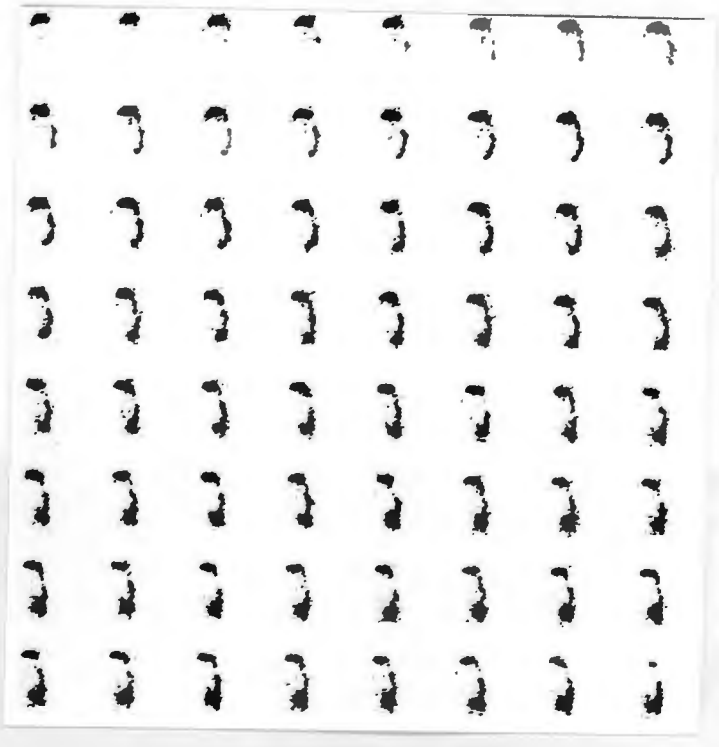


Fig 7,8i

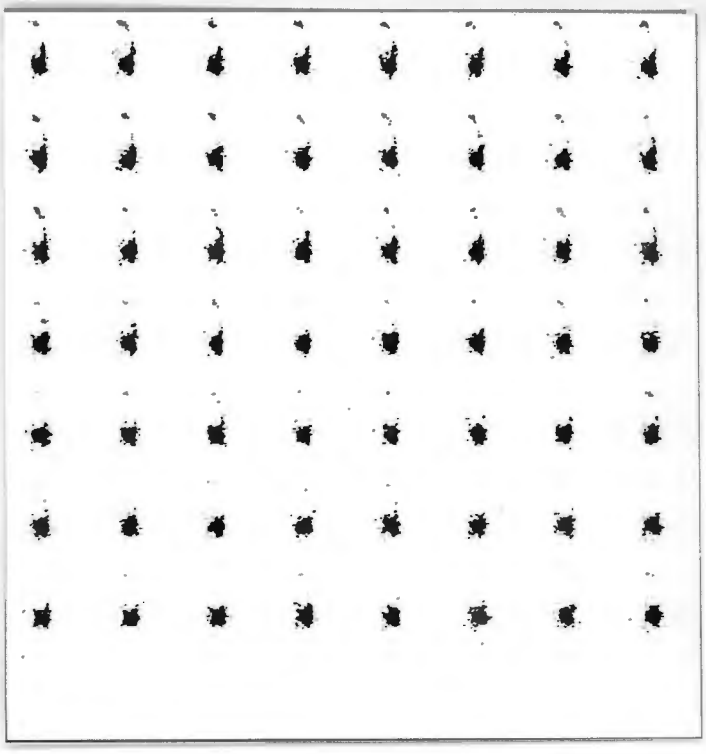


Fig 7,8ii

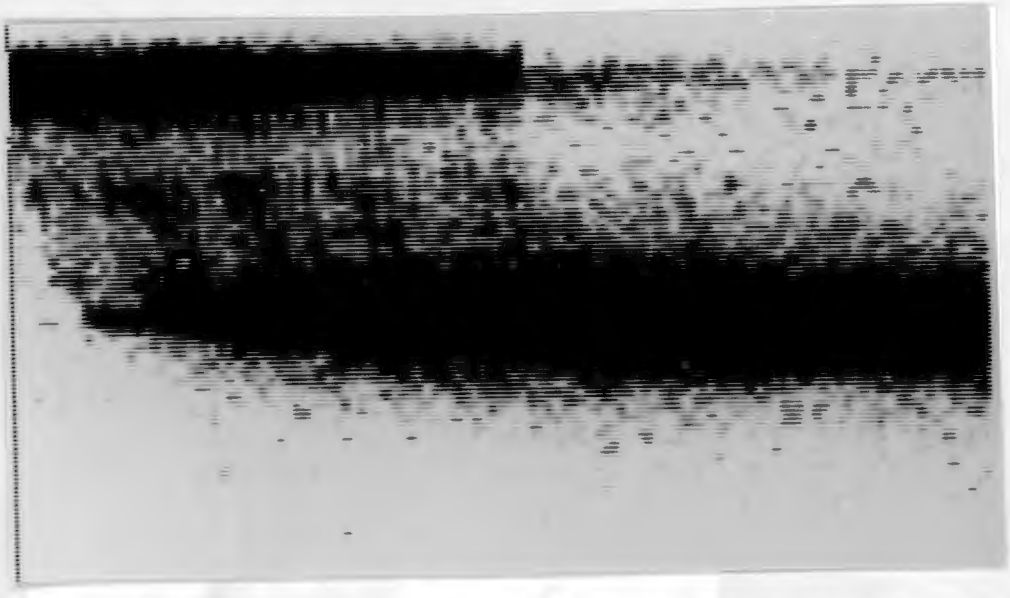


Fig 7,8iii

Fig 7,8i to iii This 14 month male had repeated hospital admissions for upper and lower respiratory tract disease. Subglottic stenosis was present and tracheostomy was necessary during an episode of pneumonia at age 13 months. 24 deglutitions are recorded and the swallowing is normal, whether viewed as cinē (Fig 7,8i, ii) or condensed images Fig 7,8iii.

Fig 7,9i

Fig 7,9i, ii Repeated broncho and lobar pneumonia had been diagnosed several times for this 23 month girl. Ciné images of the swallow were normal but activity from the feeding bottle was superimposed on the images (Fig 7,9i). However when the condensed image was formed, only columns 25-64 were used, thus eliminating the bottle (Fig 7,9ii). Both these images represent the first 32s of the swallowing study.

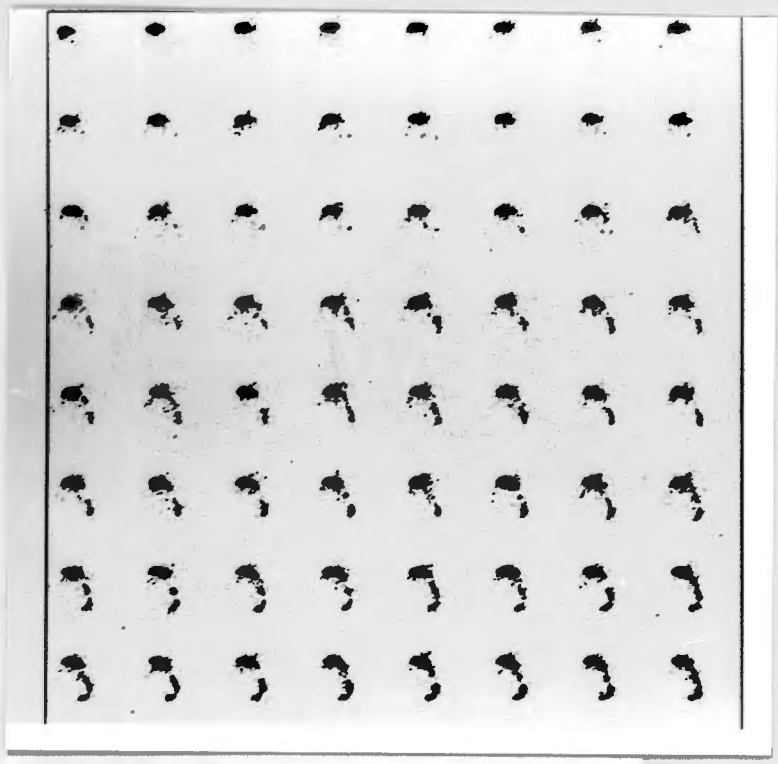


Fig 7,10i

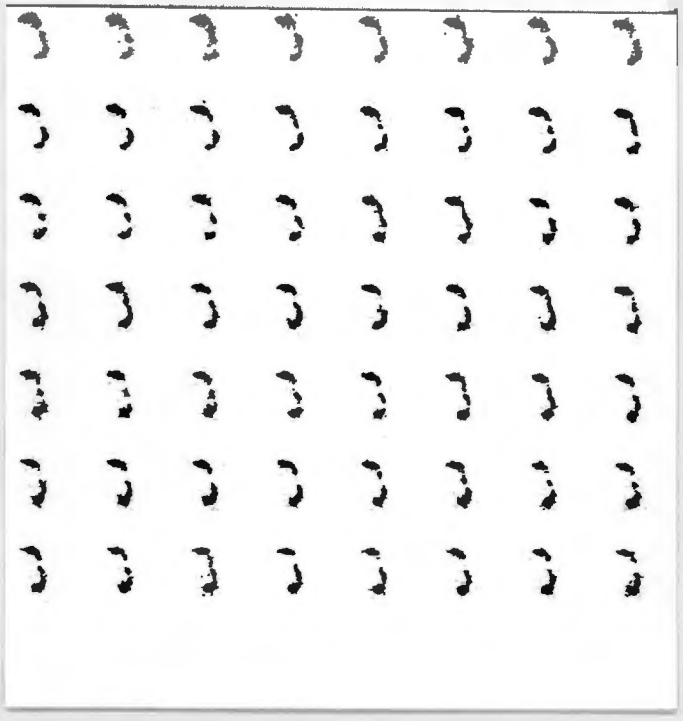


Fig 7,10ii

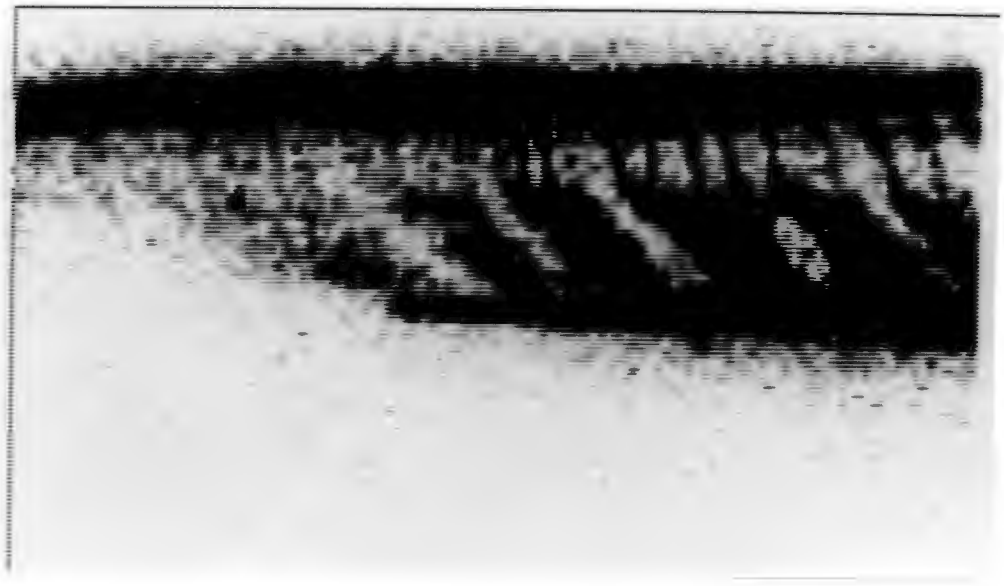


Fig 7,10iii

Fig 7,10i to iii The history of this 5 month male included repeated right upper lobe pneumonia and one cyanotic attack. 26 deglutitions are represented with fast descent in the superior oesophagus. Every 3 or 4 swallows catch up with slow descent in the inferior oesophagus (Fig 7,10iii). Repeated buccal and cervical GOR were detected.

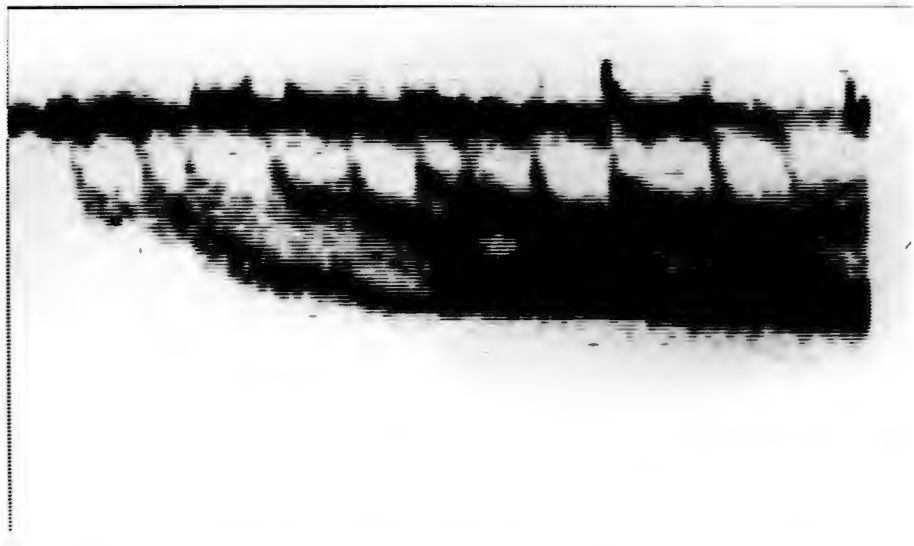


Fig 7,11

Fig 7,11 Several cyanotic spells and a variety of repeated respiratory problems were recorded for this 17 month male. His swallow shows an exaggerated normal response with slowed descent below the mid oesophagus. Because he choked on milk feeds this image was obtained with mashed potato.

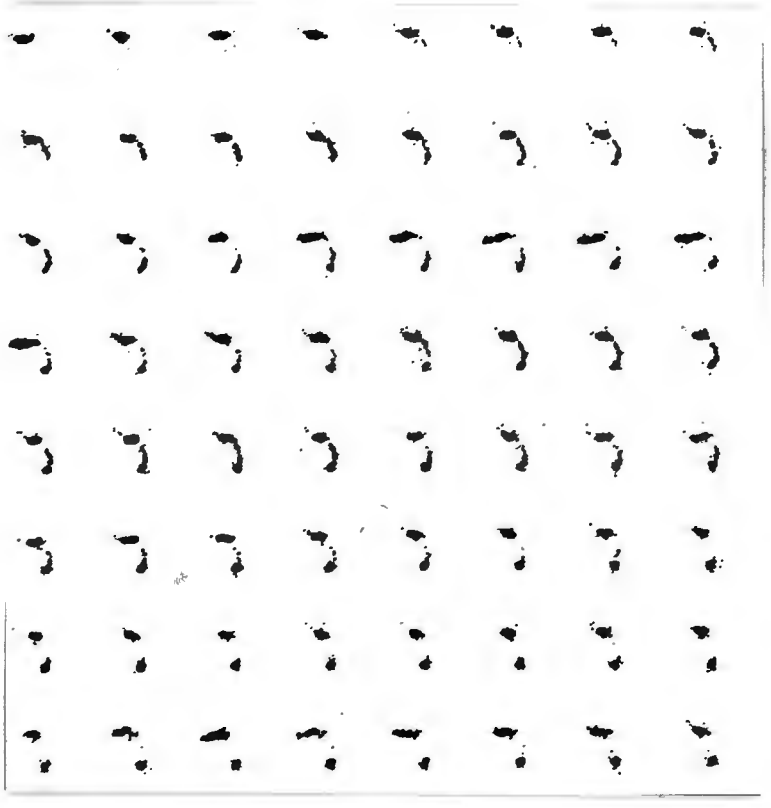


Fig 7,12i

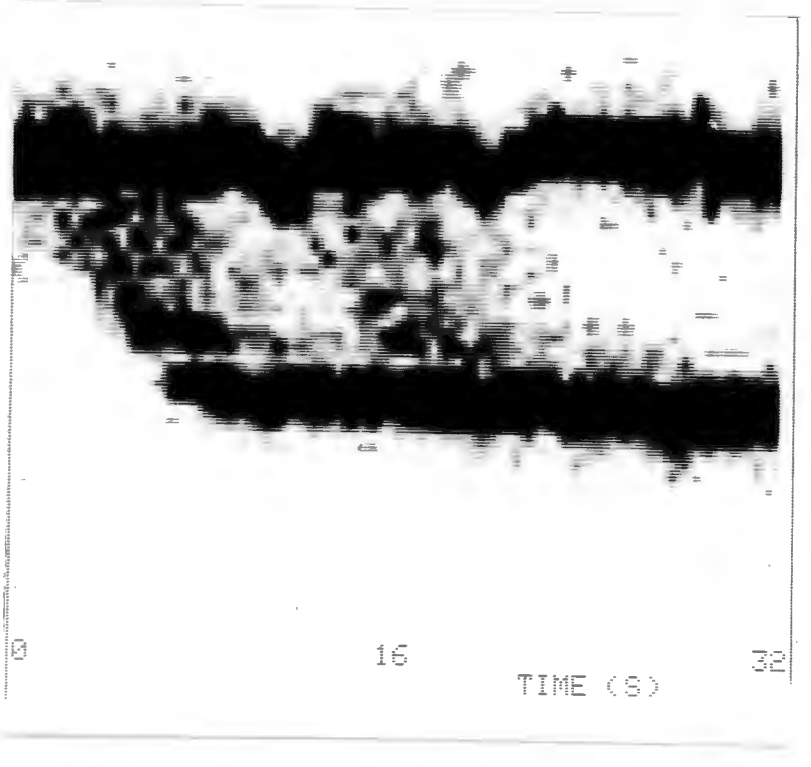


Fig 7,12ii

Fig 7,12i,ii This 3 month old male having had a correction of high congenital anorectal malformation suffered repeated respiratory problems. Oesophageal transit was normal and the last of a series of rapid deglutitions is clearly seen to cause the LOS to open and allow passage of swallowed liquid from inferior oesophagus into the fundus in both cinē (Fig 7,12i) and condensed images (Fig 7,12ii).

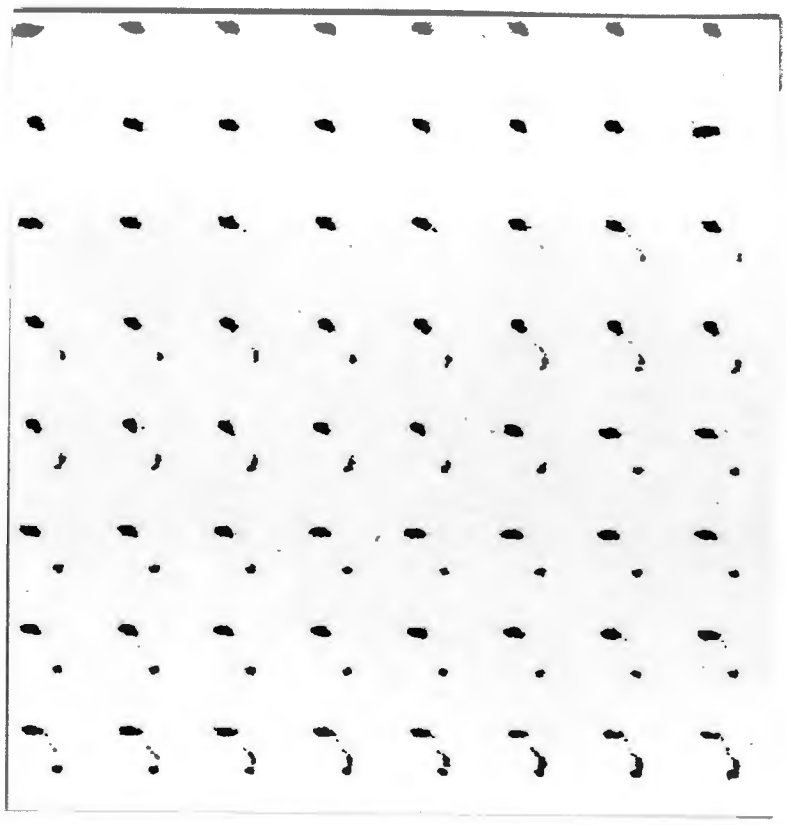


Fig 7,13i

Fig 7,13ii

Fig 7,13i,ii This 4 month old female suffered worsening of excessive vomiting since birth. Her swallow was normal and again the last of a rapid series of deglutitions is seen to cause the LOS to open both in ciné (Fig 7.13i) and condensed (Fig 7,13ii) images.

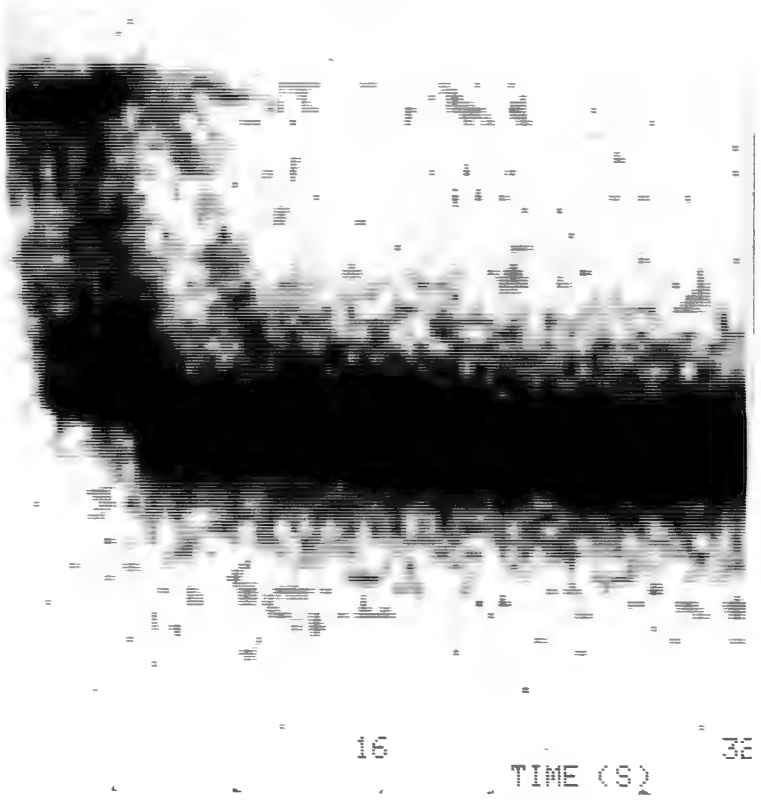


Fig 7,14

Fig 7,14 This 10 month old male infant is described in the caption of Fig 7,39. His swallow is normal and a last deglutition is seen to be slower than its predecessors.

Fig 7,15

Fig 7,15 This 17 month female had four repetitions of respiratory infection and her nuclear medicine study was normal. A slow last deglutition is demonstrated. This image represents the first 32s after the start of swallowing.

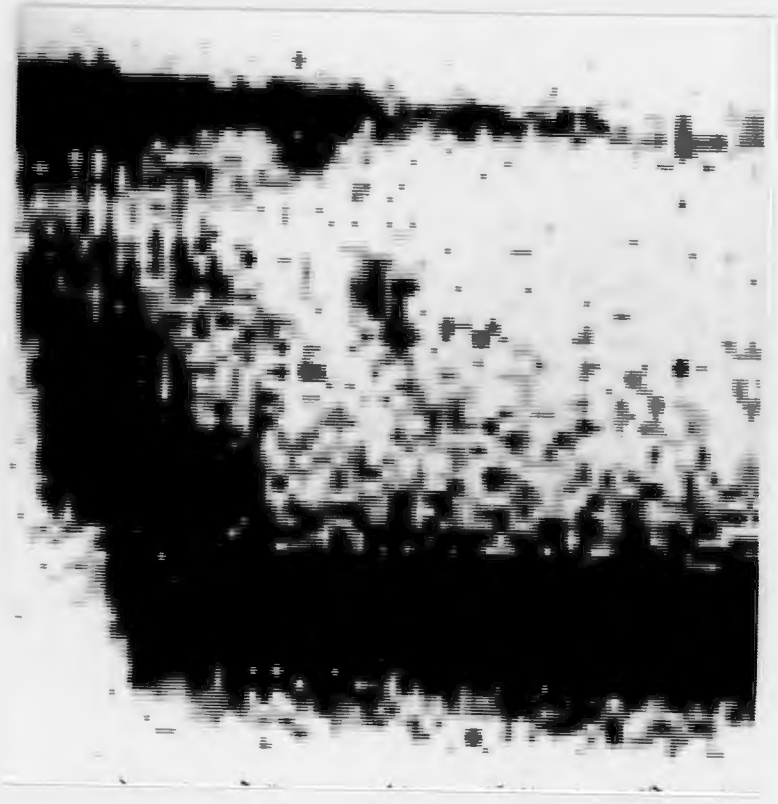


Fig 7,16

Fig 7,16 This 8 year old female had mild mental retardation of unknown aetiology and recurrent chest infections. Her studies were all normal but the last deglutition is seen to be slower than its predecessors although it contains little activity. The first 32s after the start of the swallowing study is represented here.

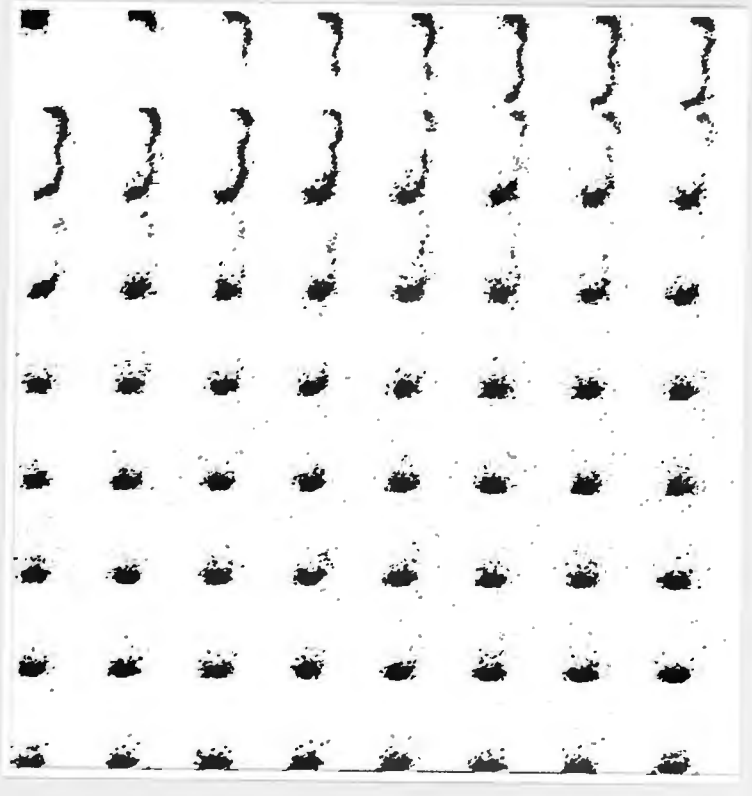


Fig 7,17i

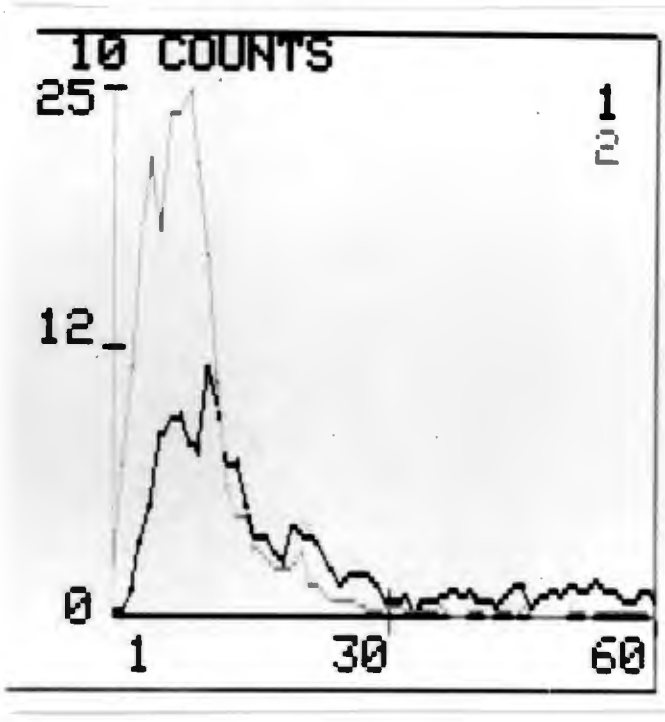


Fig 7,17ii

Fig 7,17i,ii This 16 month old male experienced recurrent chest infections since the age of 6 months requiring 6 hospital admissions. The swallow's ciné images demonstrated a kink in the oesophagus unsuspected after radiological and other investigations (Fig 7,17i). Otherwise the study was normal (Fig 7,17ii).

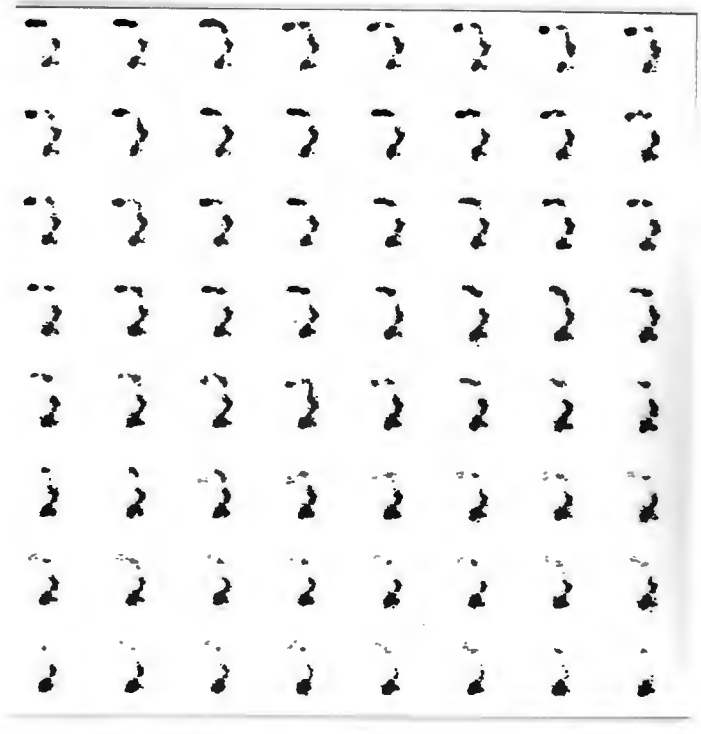


Fig 7,18i

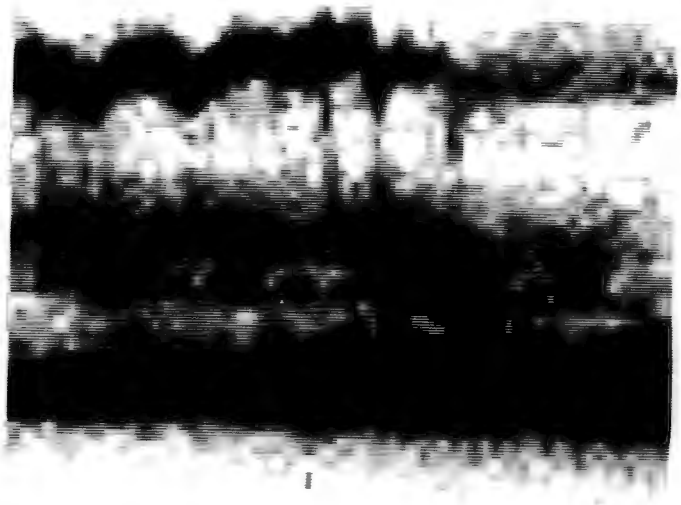


Fig 7,18ii

Fig 7,18iii

Abnormal Swallows

Fig 7,18 i to iii This 32 month old male suffers from the Vater syndrome and has experienced many oesophagoscopies and dilations and a Nissen fundoplication. A mid oesophageal hold up is clearly seen both in cinē (Fig 7,18i) and condensed (Fig 7,18ii) images (representing the first 32s of the study) proximal to the structure. The image recorded 2h after swallowing showed retained activity (Fig 7,18iii). On the left is an anterior view and on the right a right anterior oblique view. The deduction of oesophagitis in this region was confirmed by an oesophagoscopy shortly afterwards.

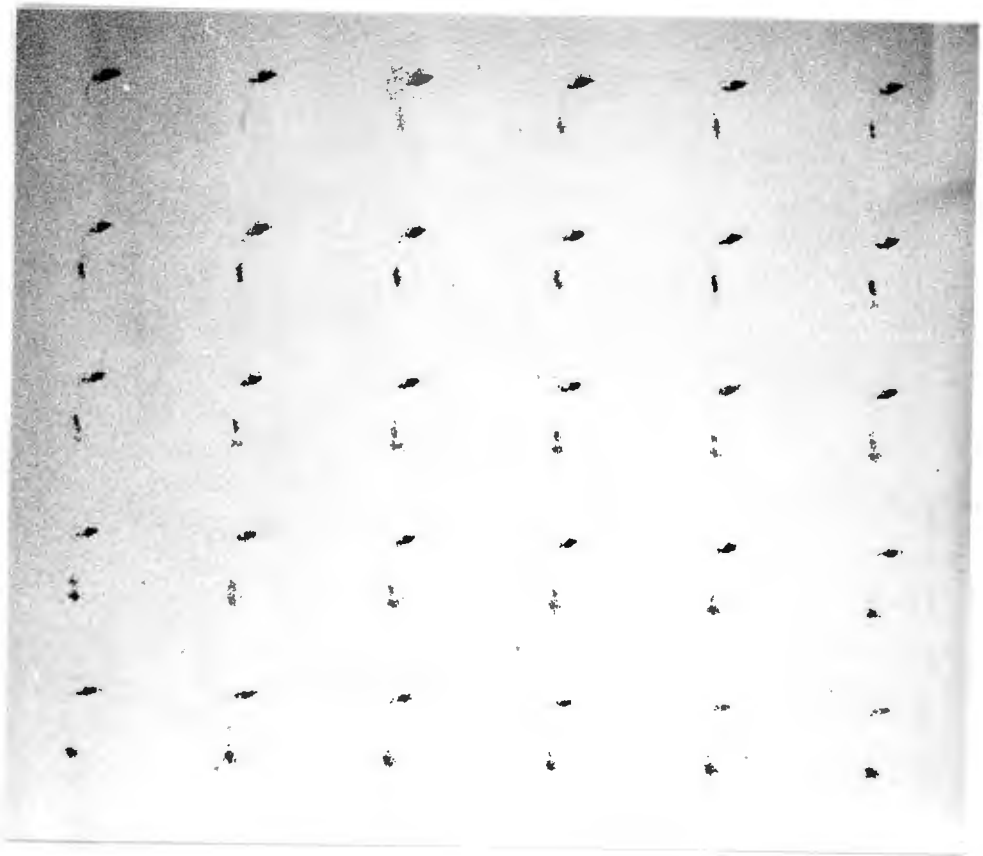


Fig 7,19

Fig 7,19 Images from the swallow of a 34 day old female born at term after a normal pregnancy. The nuclear medicine study followed several apnoeic spells with hypotonia and a normal Ba swallow. Oesophageal spasm of duration over 5s is seen in the cinē images. In contrast the GOR search showed only one reflux of 10s duration reaching the high thoracic region.

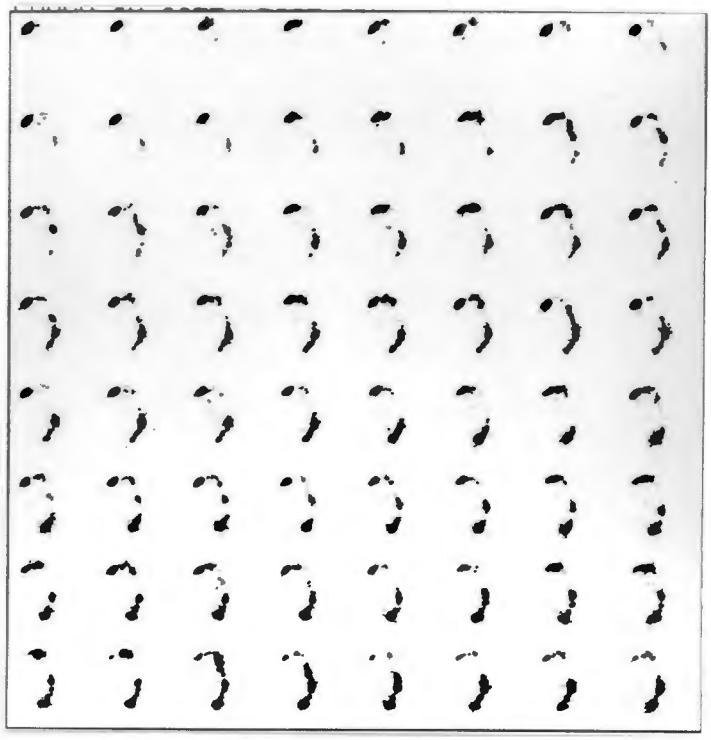


Fig 7,20i

Fig 7,20ii

Fig 7,20i,ii This 4 year old male had suffered repeated respiratory problems and excess vomiting. The ciné images (Fig 7,20i) of the 32s after the start of swallowing clearly show mid and lower oesophageal sites of arrested transit. The condensed (Fig 7.20ii) image representing 60 seconds also shows the same features but a reflux between 23 and 30s can also be recognised. Very many refluxes up to the cervical level and a right apical pulmonary aspiration were also noted during the next 30 min.

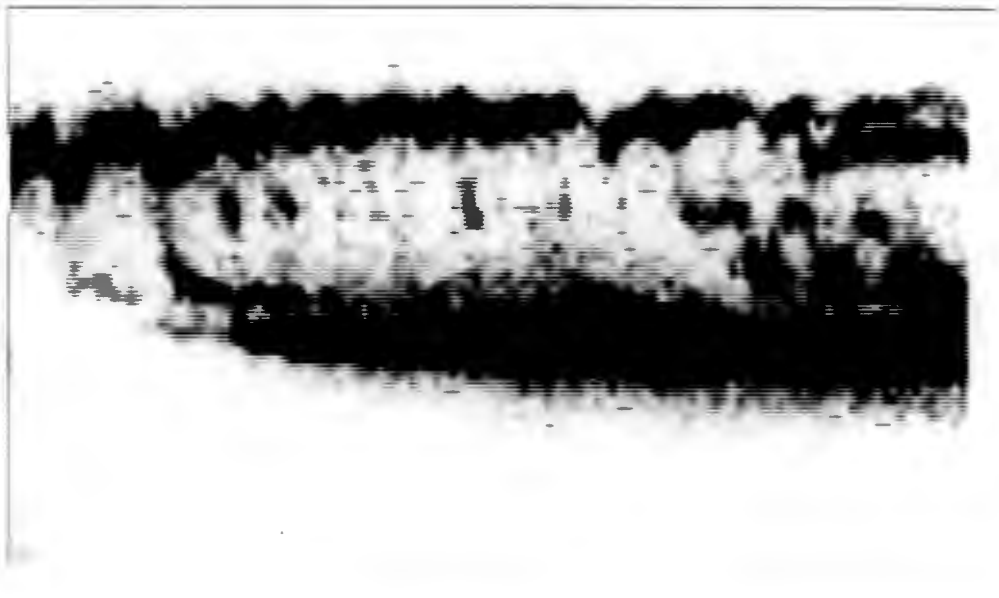


Fig 7,21

Fig 7,21 This 27 month old showed repeated mid oesophageal hold up and retrograde oesophageal motion in the condensed image. She had experienced repeated respiratory problems, including two episodes of pneumonia.

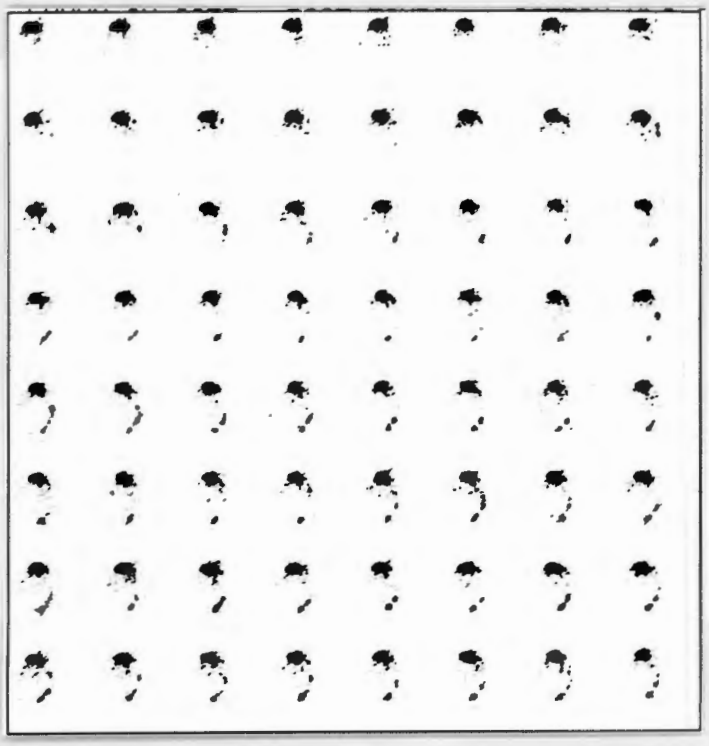


Fig 7,22i

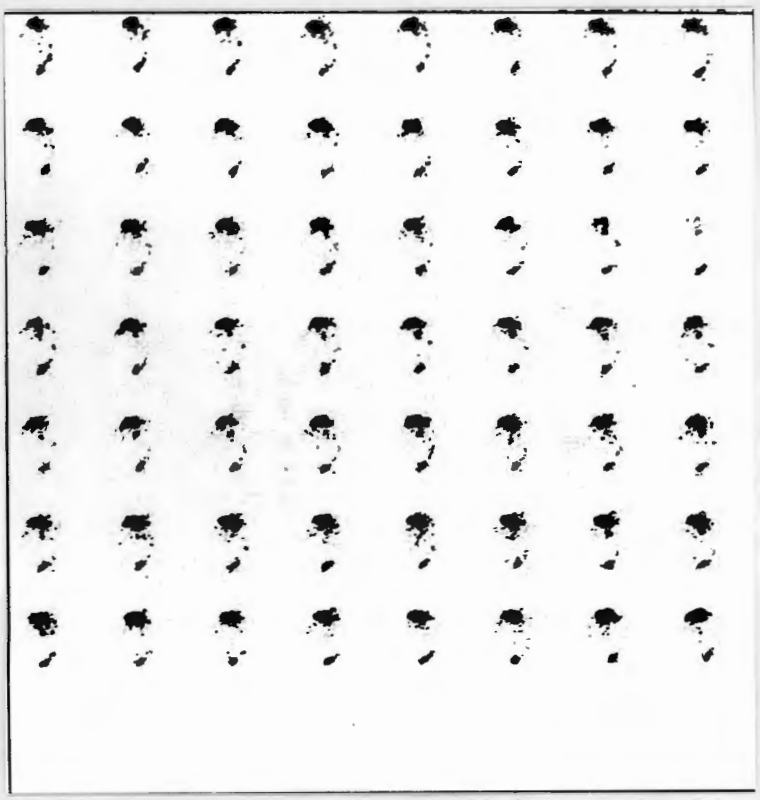


Fig 7,22ii

Fig 7,22iii

Fig 7,22iv

Fig 7,22i to iv This 30 month boy had a history of repeated hospitalisation for pneumonia and had coughed frequently since birth. Two months before this scintigraphy he required intensive care with nasal prong oxygen. A presumptive diagnosis of pulmonary aspiration after GOR was made and then an alternative diagnosis of laryngo tracheal incoordination. These diagnoses remained uncertain after Ba swallows, pH studies and oesophagoscopy and tracheoscopy. This scintigraphic study demonstrates tracheal aspiration and its expulsion during the swallow (Figs 7,22i, ii) especially during the last 28s (Fig 7,22ii). The condensed image of all columns of the cinē images (Fig 7,22iii) clearly shows some hold up at the LOS. When columns 1-30 only comprise the condensed image of the last 28s of the swallowing study (Fig 7,22iv) oesophageal activity is eliminated and unequivocal demonstration of the swallowed liquid in the tracheal region (marked T) is seen. The only other activity recorded in this image is in the buccal cavity (B) and stomach (S).

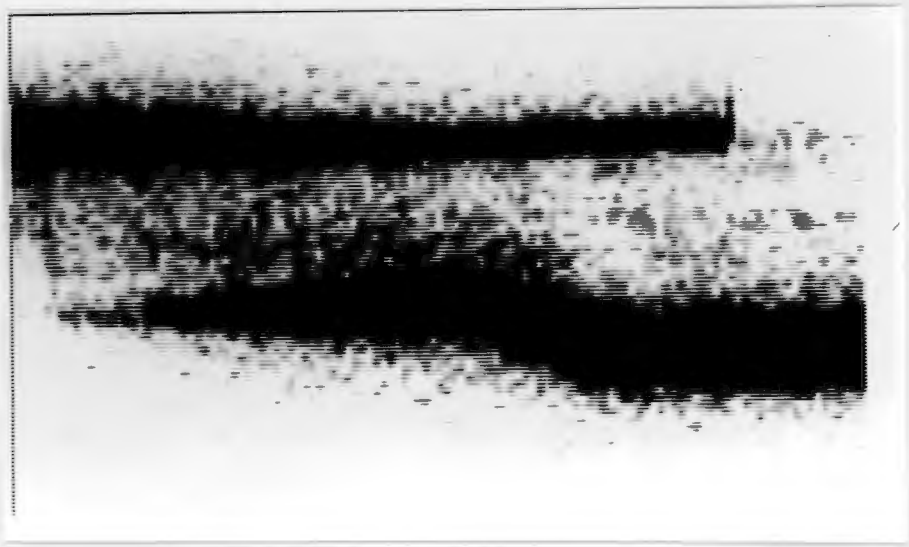


Fig 7,23

Fig 7,23 Oesophageal atresia in this 20 month girl was corrected at birth with colonic interposition. The interposition was revised after one day and a cervical fistula repaired 13 months later. Persistent coughing suggested the presence of GOR and aspiration. This could not be detected with barium studies. The scintigraphic swallow is abnormal with hold up at the LOS for the first 39s. The many individual deglutitions (about 28) are rapid but indistinct. Gross persistent GOR to the buccal level was also detected by scintigraphy. Thus correction of GOR by a fundoplication was deduced to be inadvisable.

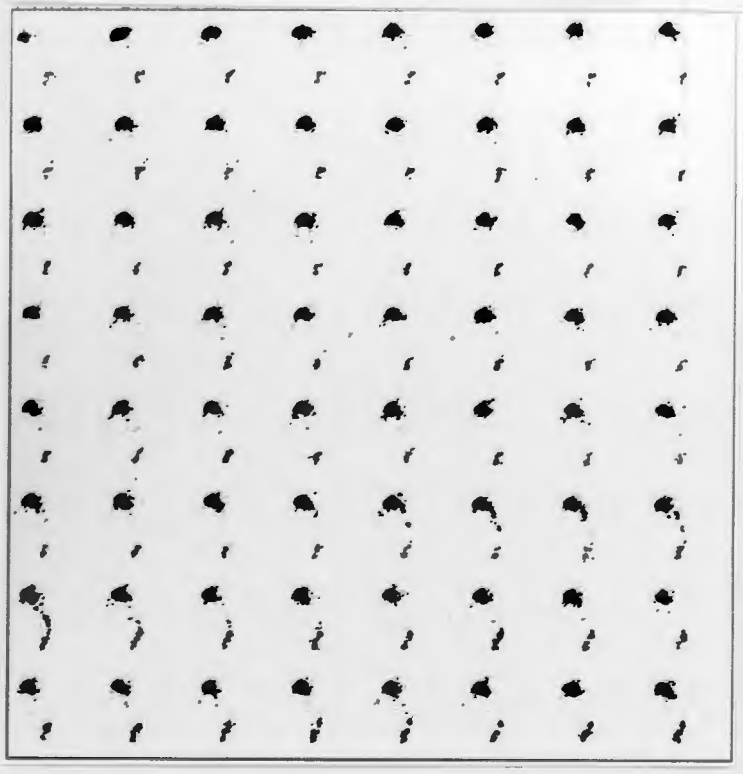


Fig 7,24i

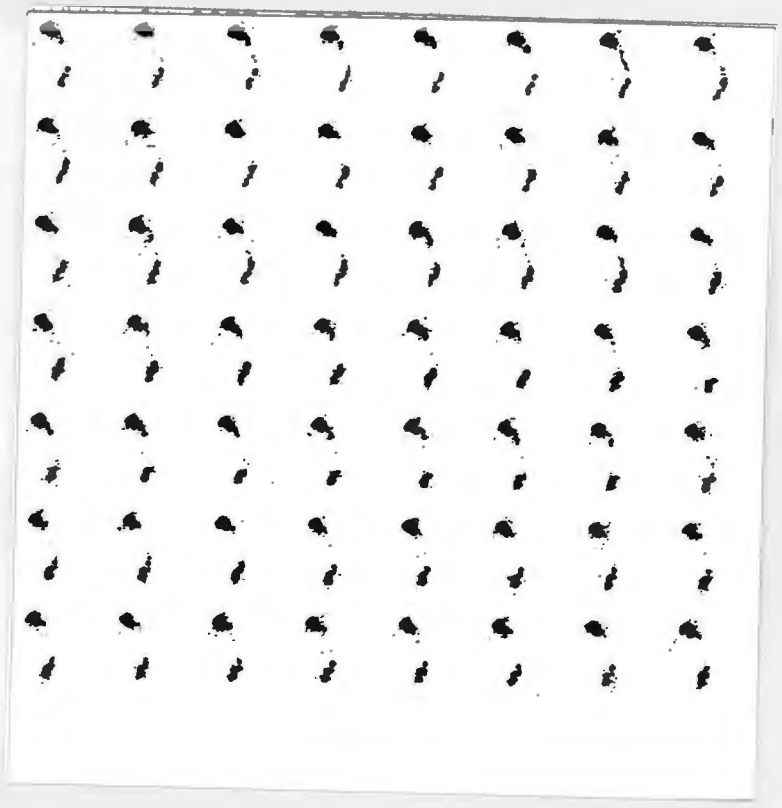


Fig 7,24ii

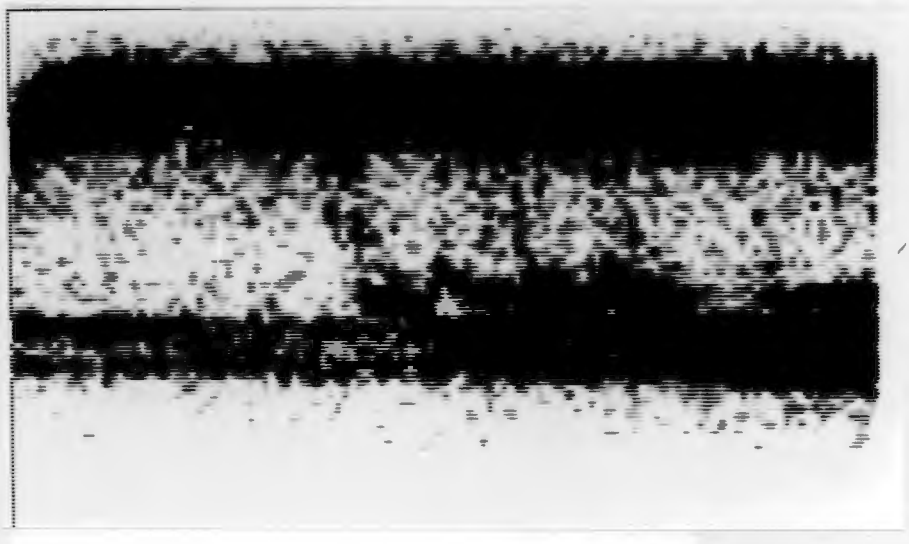


Fig 7,24iii

Fig 7,24i to iii Recurrent respiratory problems since the age of 2 months had necessitated several admissions to a district general hospital for this boy aged 20 months. The usual manifestations were wheezy cough, dyspnoea and pyrexia. Right upper lobe fibrosis and collapse were detected. The swallow demonstrates hold up in the region of the LOS and above in the cinē (Figs 7,24i, ii) and condensed images (Fig 7,24iii). He also had gross GOR and rapid gastric emptying. Surgical correction of the GOR was not attempted at this stage because of the oesophageal problem.

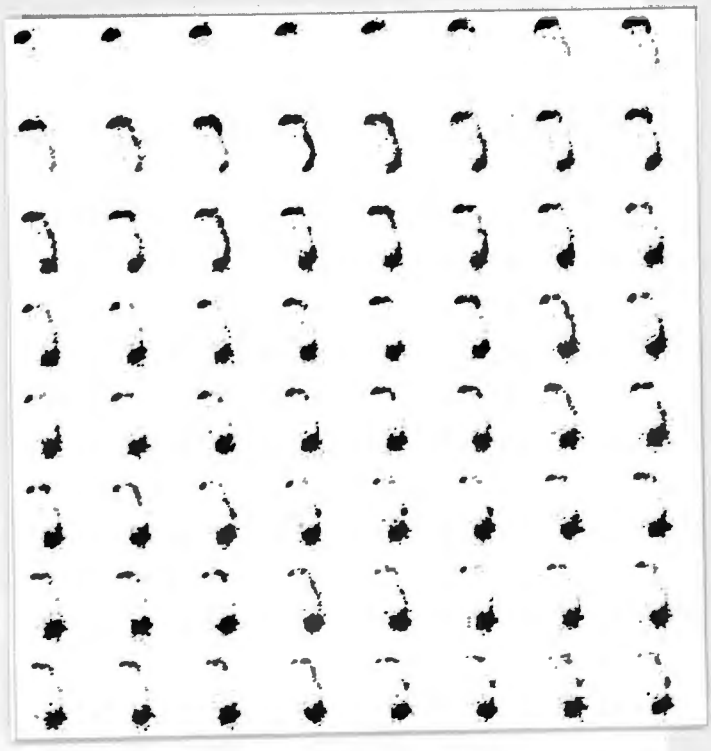


Fig 7,25i

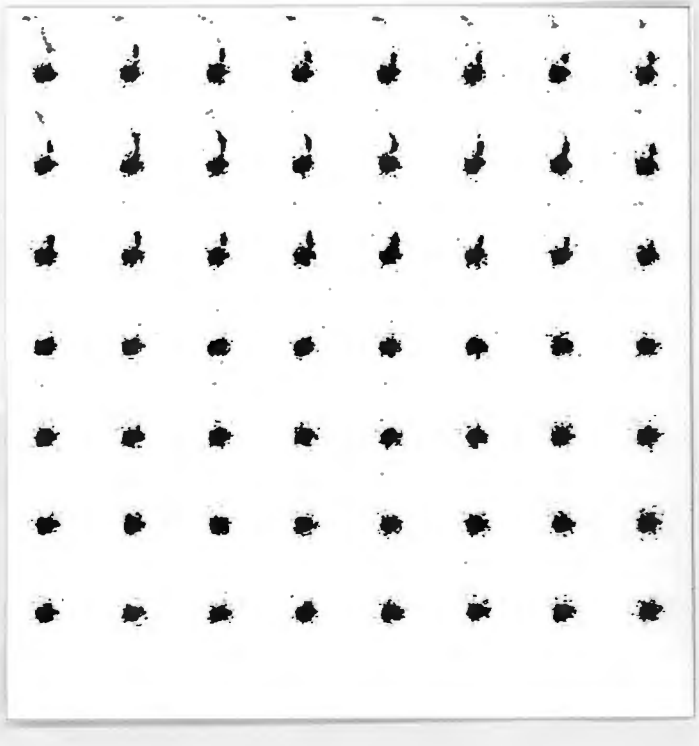


Fig 7,25ii

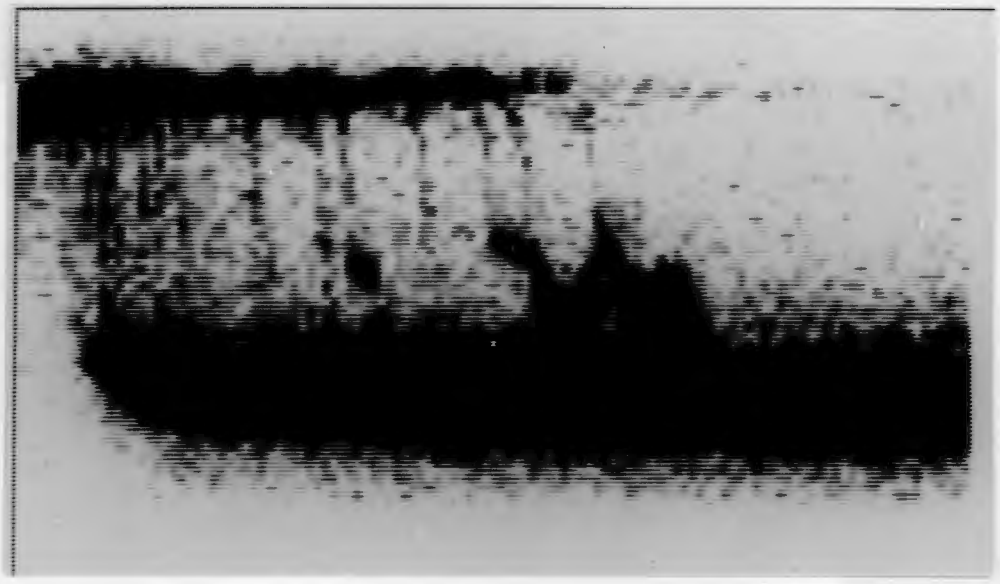


Fig 7,25iii

Fig 7,25i to iii This 4 year old girl was asthmatic, requiring 11 admissions, had the Wolfe-Parkinson-White syndrome and several previous episodes of left sided pneumonia. Hold up and clear retrograde motion in the lower oesophagus are recognisable in cinē images (Figs 7,25i, ii) but very clearly demonstrated in the condensed image (Fig 7,25iii). No GOR was detected. Her previous scintigraphy (Fig 7,3) was normal.

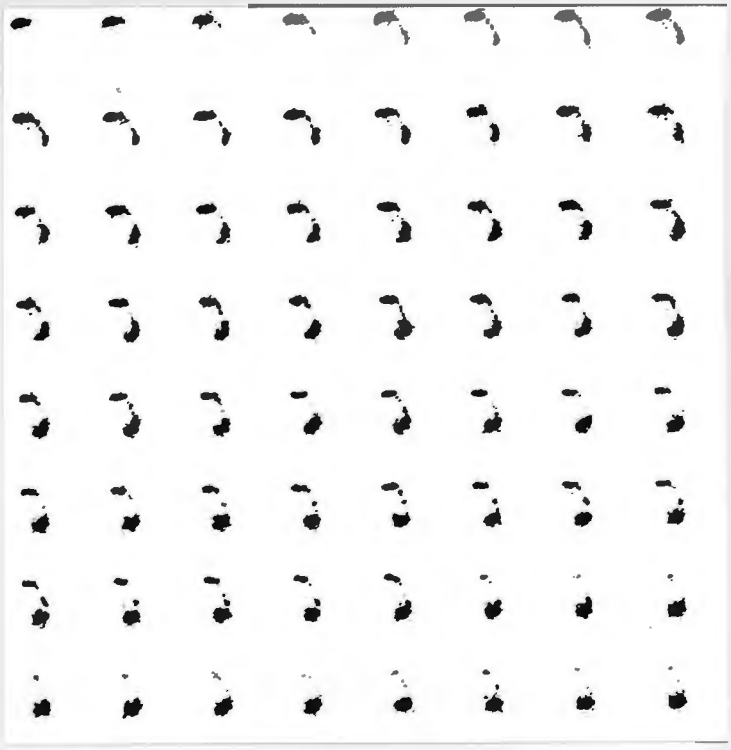


Fig 7,26i

Fig 7,26ii

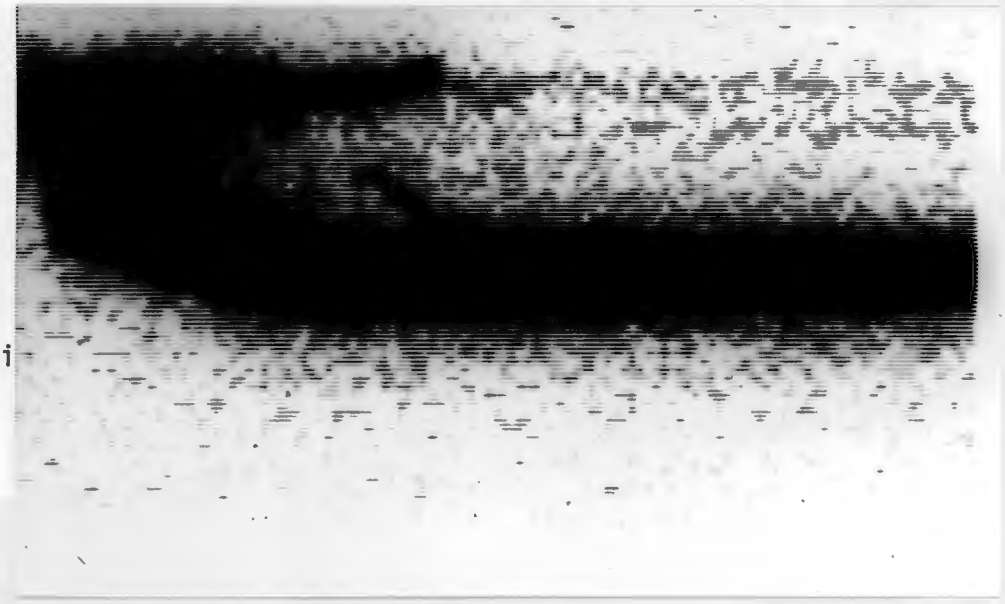
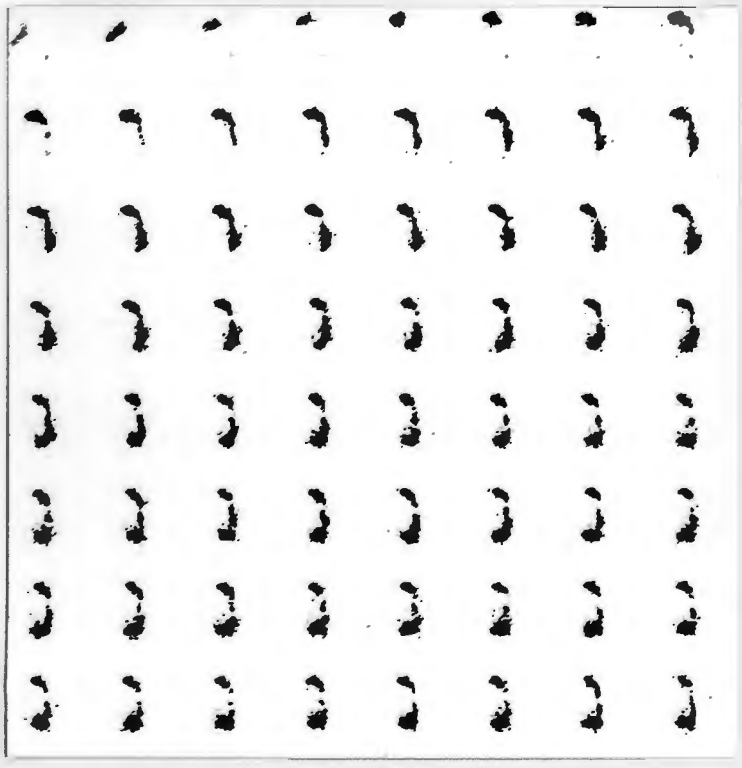


Fig 7,26i, ii Frequent apnoeic attacks and vomits since birth had worsened in the previous 3 weeks for this 2 month old girl. Neurological and other clinical examinations and barium studies were described as normal. A previous scintigraphy during a course of cisapride had demonstrated tracheal aspiration during swallowing and later pulmonary aspiration. A new conservative treatment including maxalon and gaviscon was initiated. One possible apnoeic attack was reported, hence a further scintigraphy was requested to monitor progress. Hold up at the LOS for about 20s and a slow final swallow are seen in both ciné (Fig 7,26i) and condensed images (Fig 7,26ii). Since neither pathological GOR nor aspiration were observed the treatment was continued.

Fig 7,27i



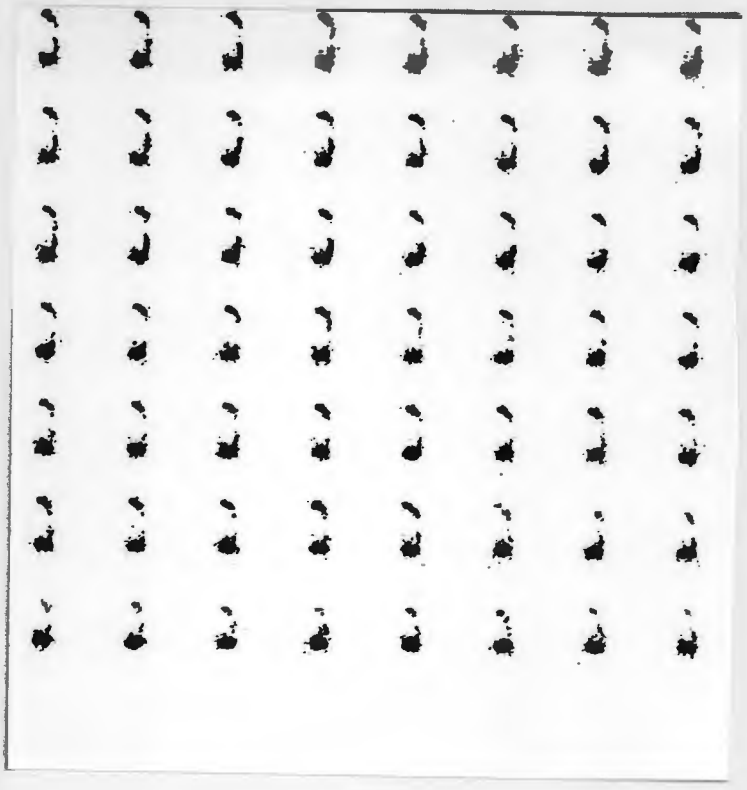


Fig 7,27ii

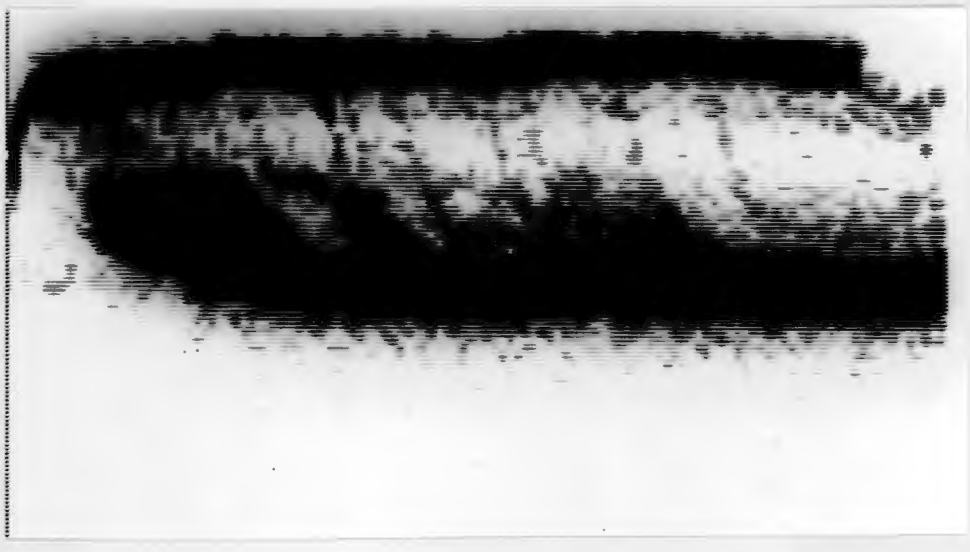


Fig 7,27iii

Fig 7,27i to iii Excess vomiting since birth, occasionally projectile, but without blood or bile, were reported for this 7 month boy. Increasing wheeziness and less vomiting were noted in the previous 2 months. Variable hold up in the inferior half of the oesophagus is seen in both ciné (Fig 7,27i, ii) and condensed images (Fig 7,27iii). No pathological GOR could be demonstrated.

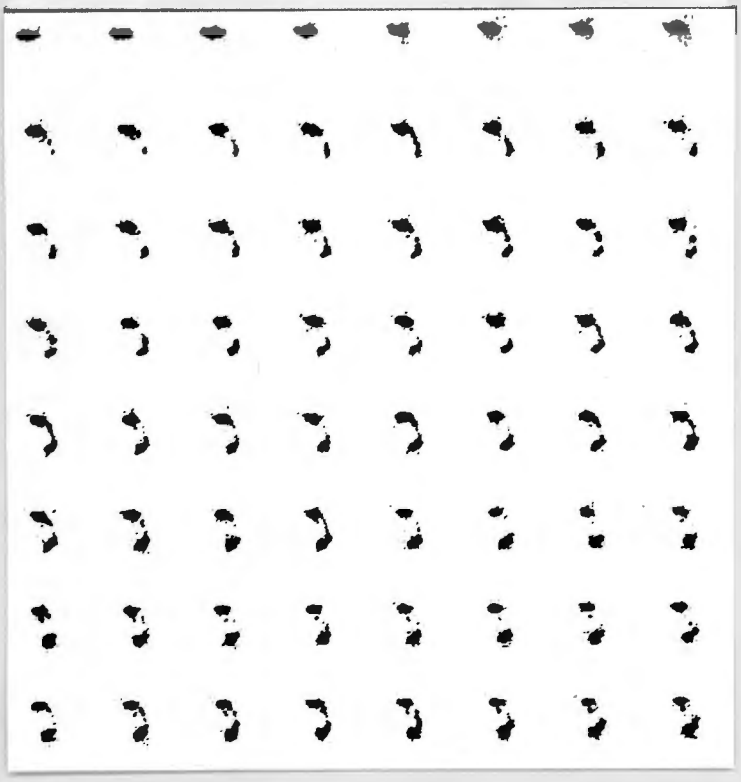


Fig 7,28i

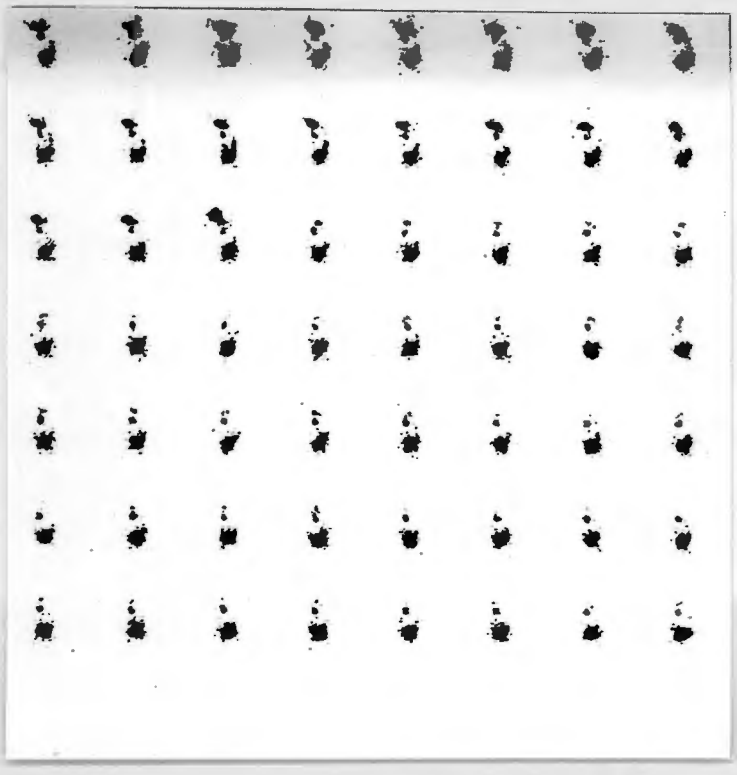


Fig 7,28ii

Fig 7,28iii

Fig 7,28i to iii This 5 week old boy vomited soon after birth (a normal vaginal delivery, at term, weight 3,1 kg, with Apgar scores 9 and 10). Frequent projectile vomiting continued. This was treated with positioning and drugs. Some improvement was apparent. However occasional spluttering with feeds continued. The swallow shows some hold up with persisting activity in the region of the larynx for the last 40s of the study (Figs 7,28i, ii, iii). In addition gross GOR to buccal level was demonstrated.

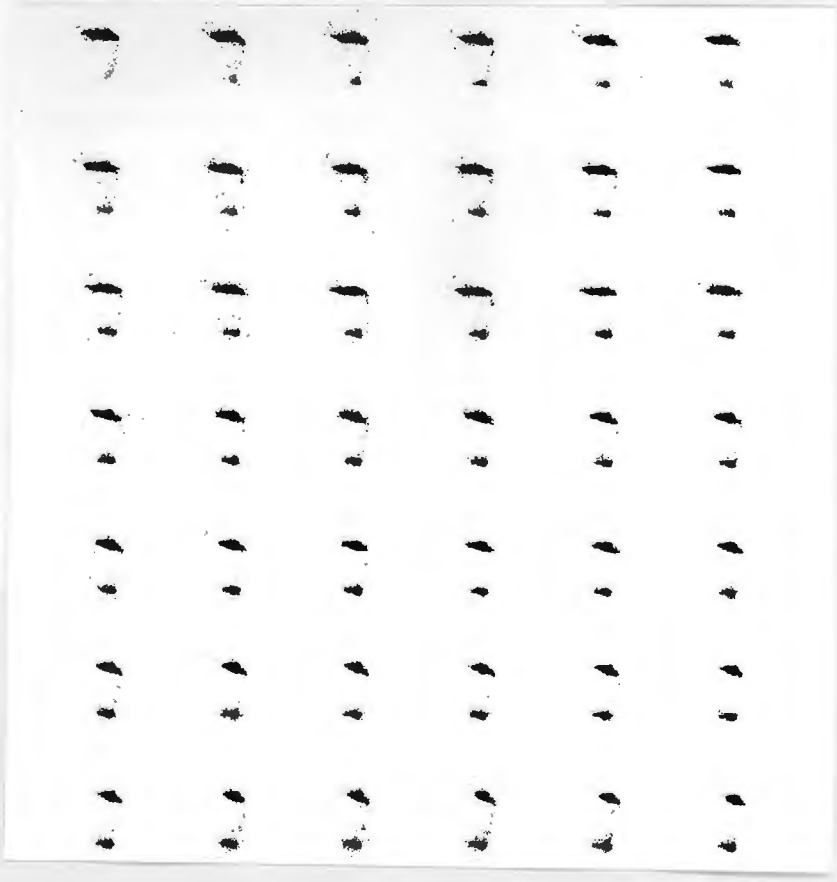


Fig 7,29i

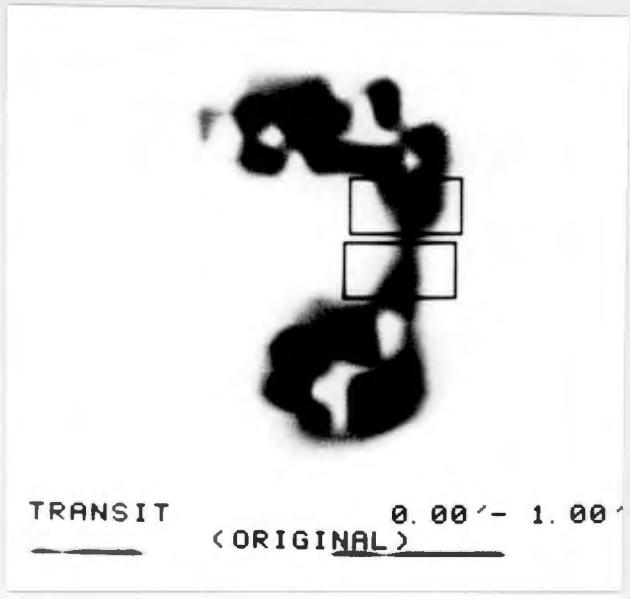


Fig 7,29ii

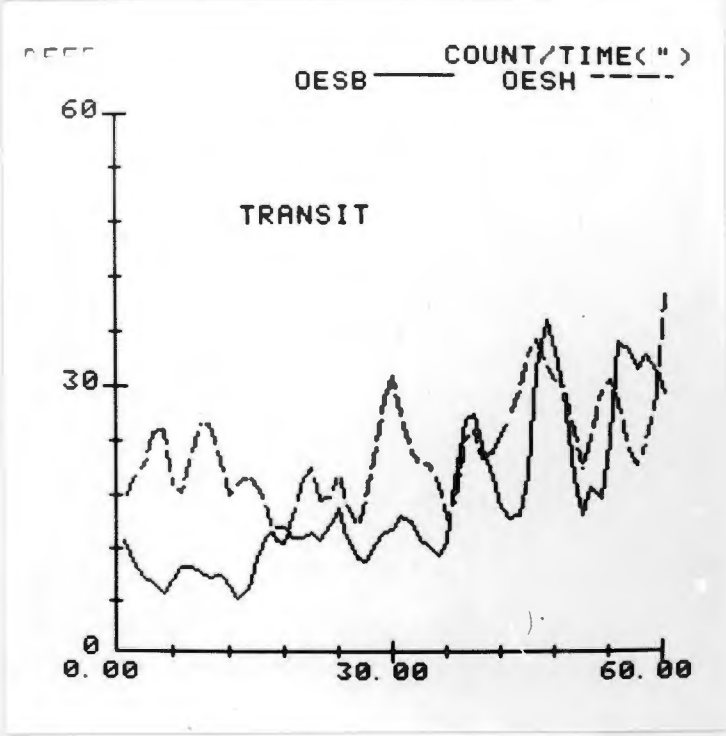


Fig 7,29iii

Fig 7,29i to iii This 15 day old male had a near miss of the SIDS. All subsequent examinations proved normal. In the ciné images of his swallow slight hold up at the LOS is noted, especially in the final row (Fig 7,29i). Each deglutition produced a pair of maxima (Fig 7,29iii) obtained from oesophageal ROIs (Fig 7,29ii).

Fig 7,30

Fig 7,30 This 9 day old female whose images of GOR are given in Fig 7,51 demonstrates slowing in the inferior oesophagus and LOS closure in the last row of images.

Fig 7,31

Fig 7,31 This 6 year old boy presented with symptoms of GOR and negative radiological results. His swallow shows mid oesophageal slowing and again the last swallow has longer transit in the distal part of the oesophagus.

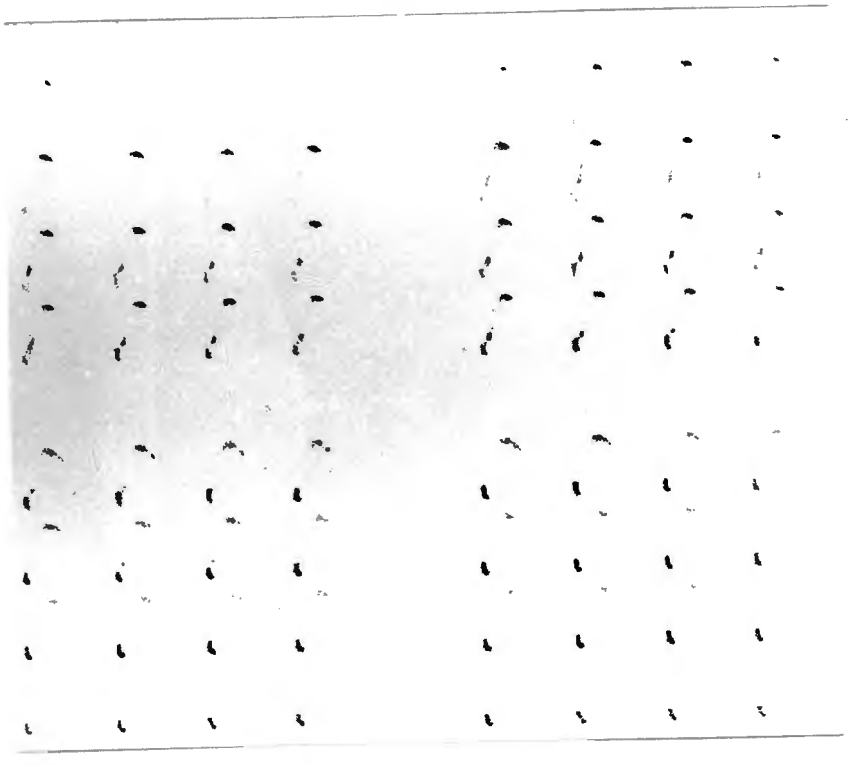


Fig 7,32

Fig 7,32 This 25 month old male had repeated hospital admissions for respiratory disease including wheezing bronchitis and pneumonia. Ciné images of oesophageal transit show hold up at different sites.

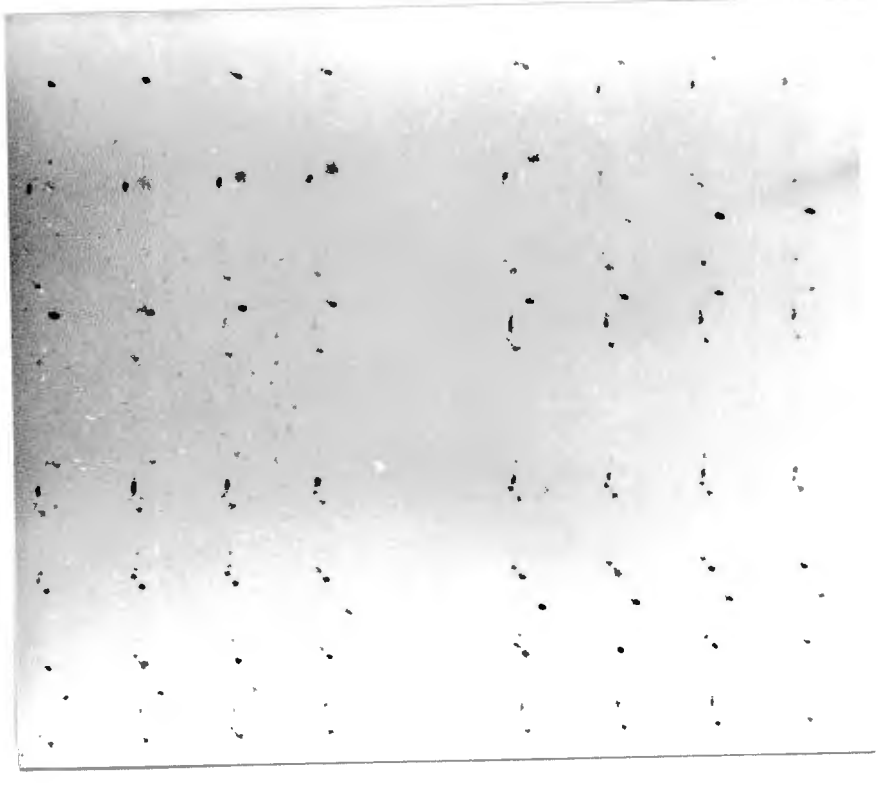


Fig 7,33i

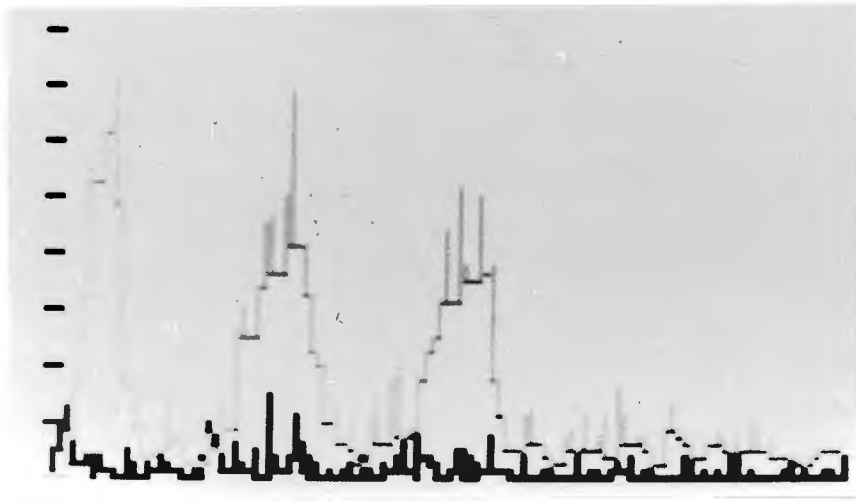


Fig 7,33ii

Fig 7,33i, ii This 16 month old female with a hypoplastic right lung had repetitive episodes of pneumonia. Little GOR could be found with this study and pH studies. Hold up at various sites in the oesophagus is seen in ciné images (Fig 7,33i), but graphs from ROIs give less information (Fig 7,33ii).

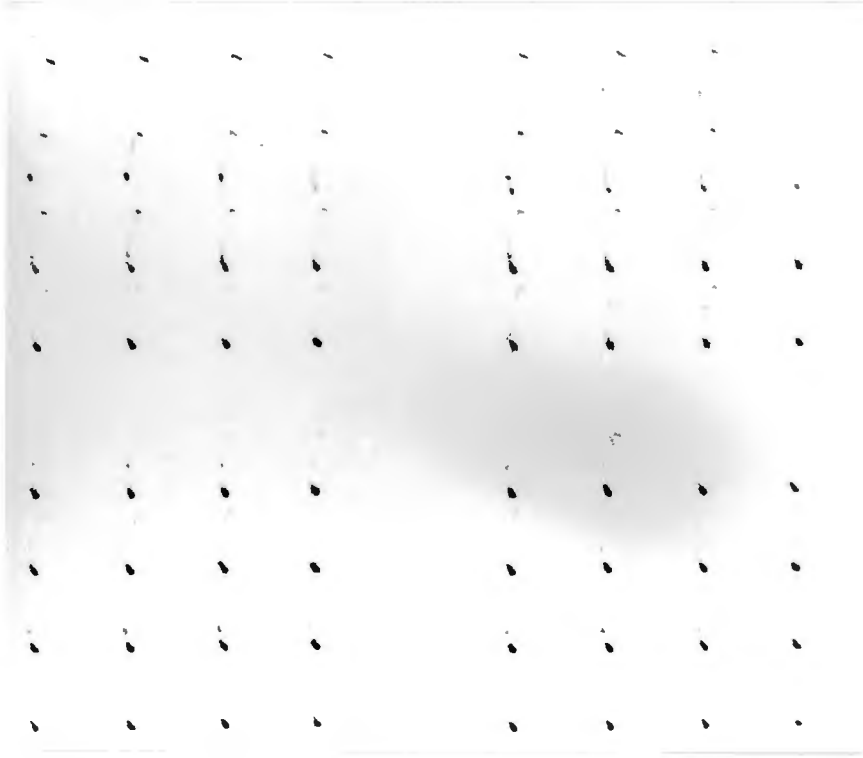


Fig 7,34i

Fig 7,34ii

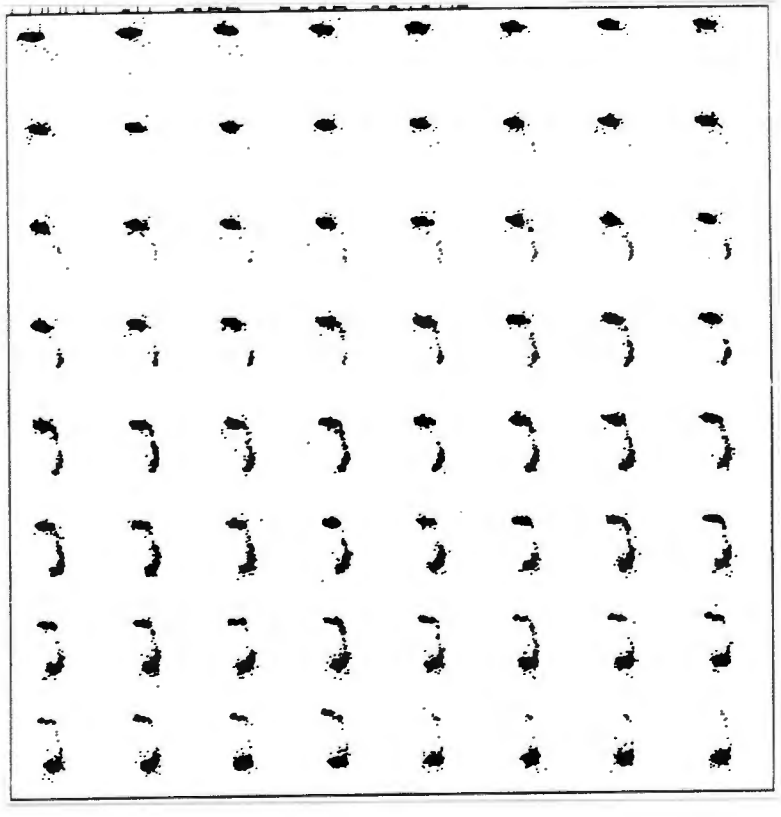


Fig 7,34iii

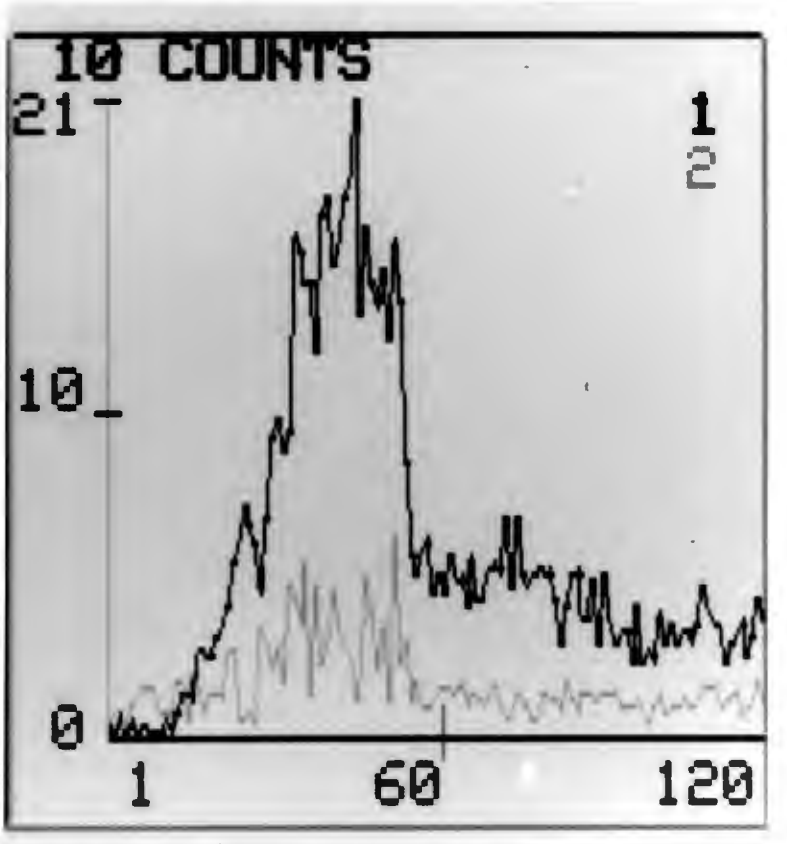


Fig 7,34iv

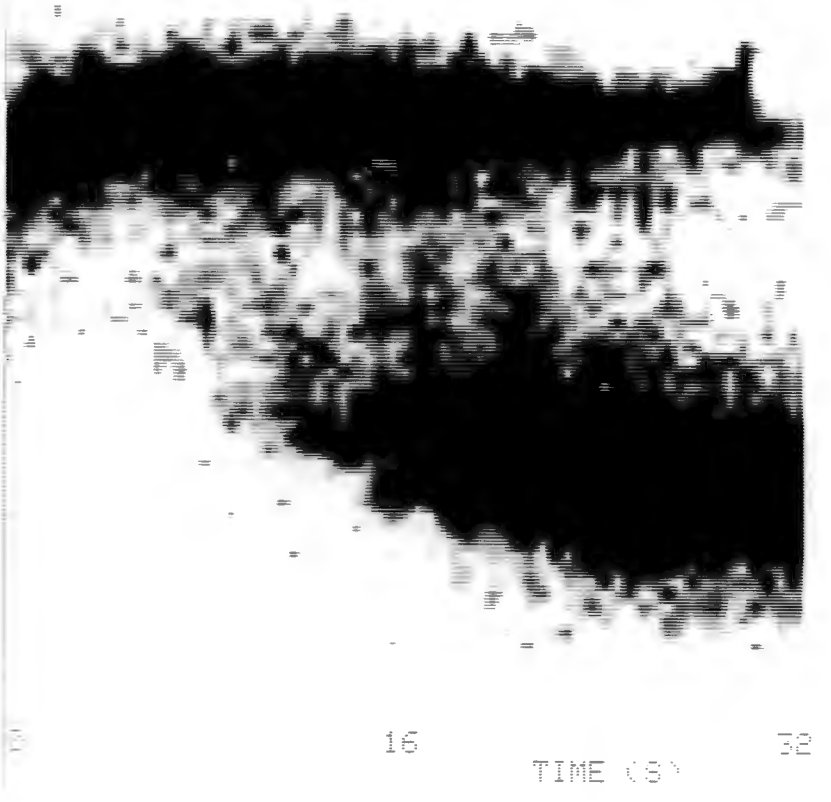


Fig 7,34v

Fig 7,34i to v This 14 month old female had recurrent chest infections. Three admissions to the intensive care unit were necessary. Oesophageal hold up at different sites is clearly seen on the ciné images (Fig 7,34i). Graphs from ROIs do not clearly show increased transit in the distal oesophagus (Fig 7,34ii). Six months later the same phenomenon was seen in ciné images (Fig 7,34iii) and also clearly in the resulting graph where the lower oesophagus suddenly empties as a spasm resolves (Fig 7,34iv). The condensed image does not show this so distinctly (Fig 7,34v).

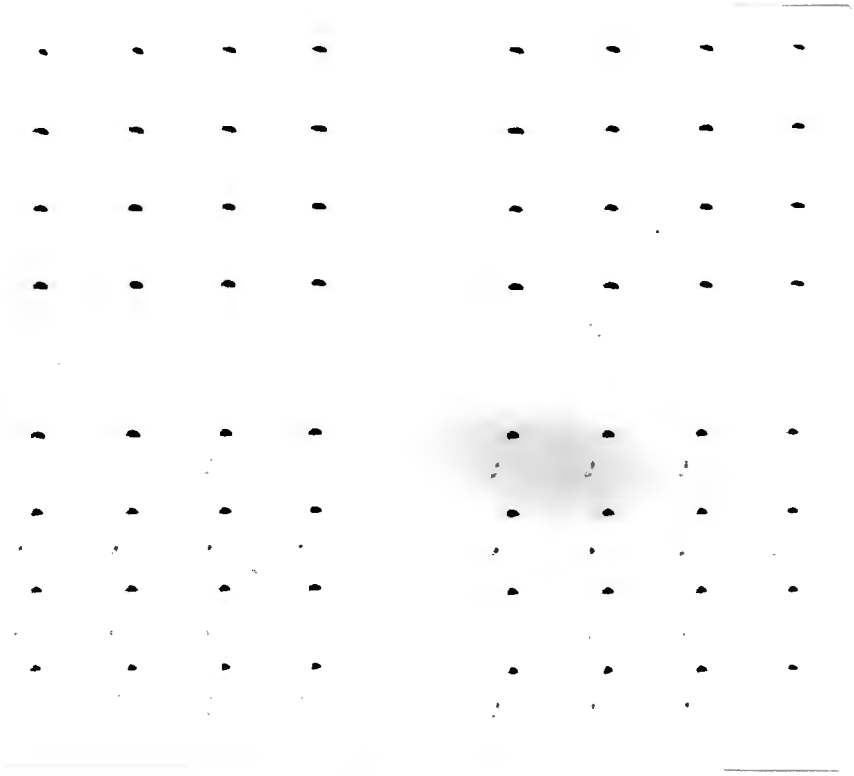


Fig 7,35

Fig 7,35 This 3 month old male vomited after each feed and had lower respiratory tract infection. Many refluxes were seen and treatment with cisapride was successful. Ciné images of the swallow show holdup at different sites in the inferior oesophagus

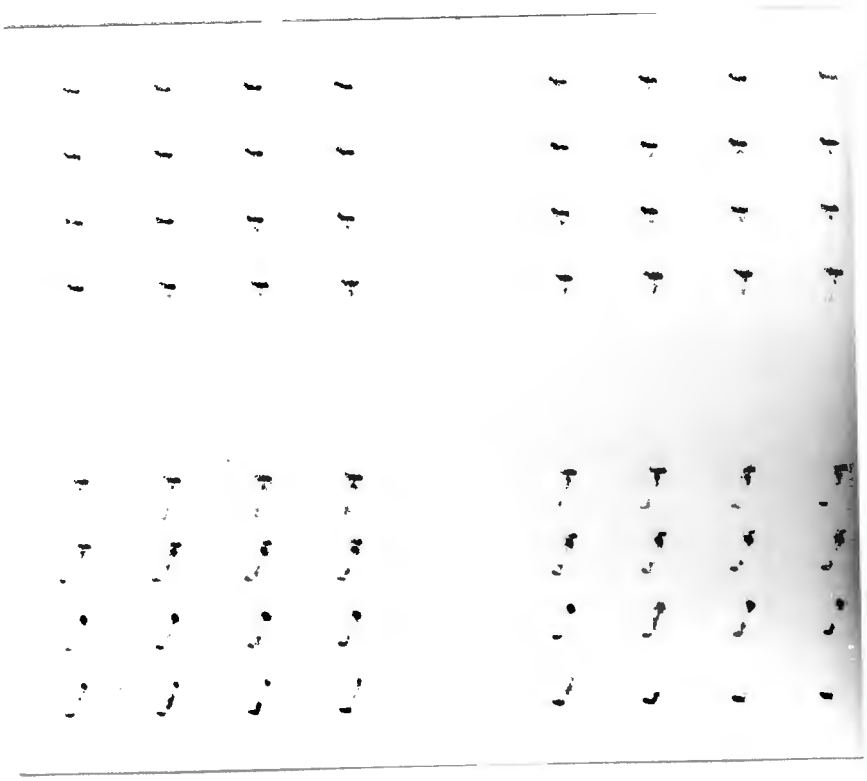


Fig 7,36i

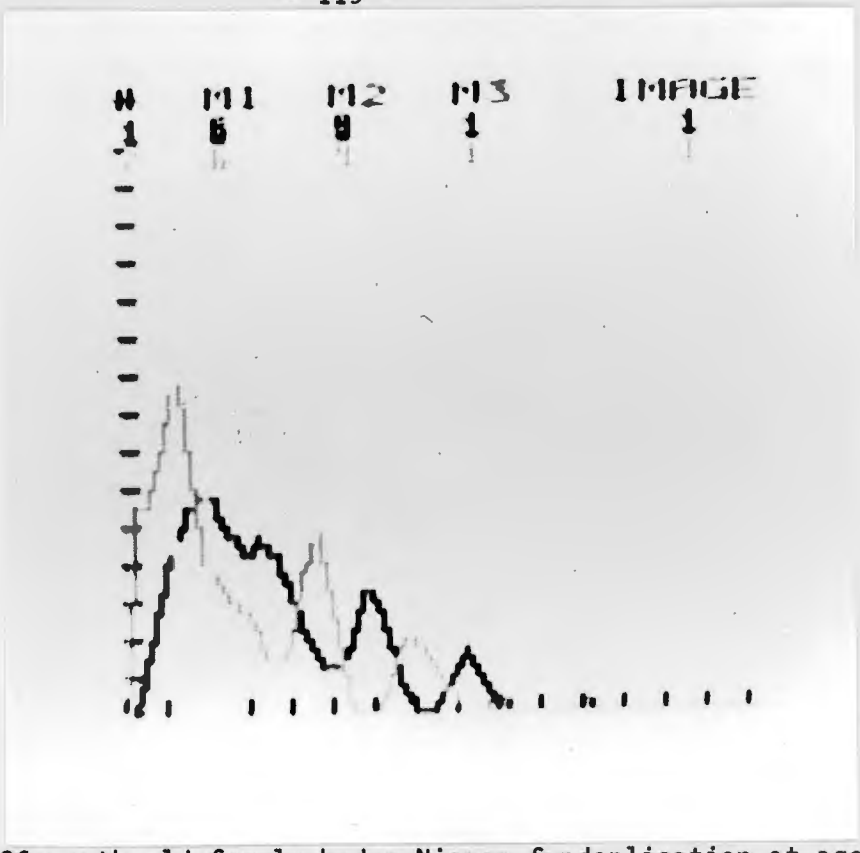


Fig 7,36ii

Fig 7,36i, ii This 26 month old female had a Nissen fundoplication at age 8 months for presumed GOR causing chronic lung problems and lung destruction. Although no subsequent GOR were demonstrated respiratory problems continued. Incoordination of oesophageal peristalsis is clearly seen in cine images (Fig 7,36i) with spasm detected in ROI graphs (Fig 7,36ii) where the first deglutition is broadened.

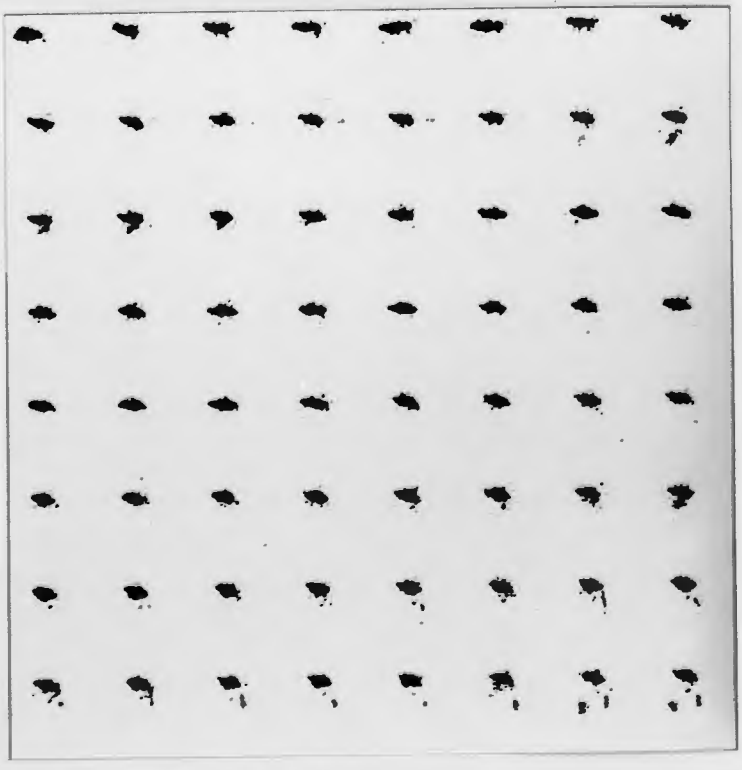


Fig 7,37i

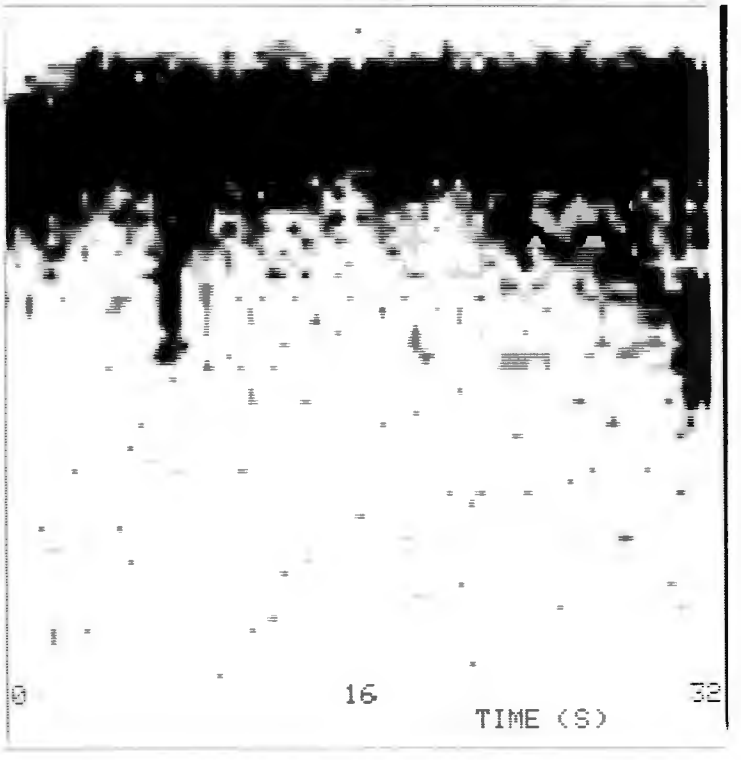


Fig 7,37ii

Early Inhalation

Fig 7,37i, ii This 2 month old female presented with failure to thrive and excess vomiting. In both ciné (Fig 7,37i), and more strikingly in condensed (Fig 7,37ii) images, a shortlived inhalation, 8s after the start of the study, is seen. Seven GOR up to buccal level were also seen during the study.

Fig 7,38

Fig 7,38 This 13 month old female suffered repeated lower respiratory tract infection with excessive vomiting. The condensed image shows before the first deglutition four unambiguous rapid inhalations of activity each followed by ejection. The swallows clearly show slowing in the inferior oesophagus. Six GOR were later observed. The barium studies were negative.

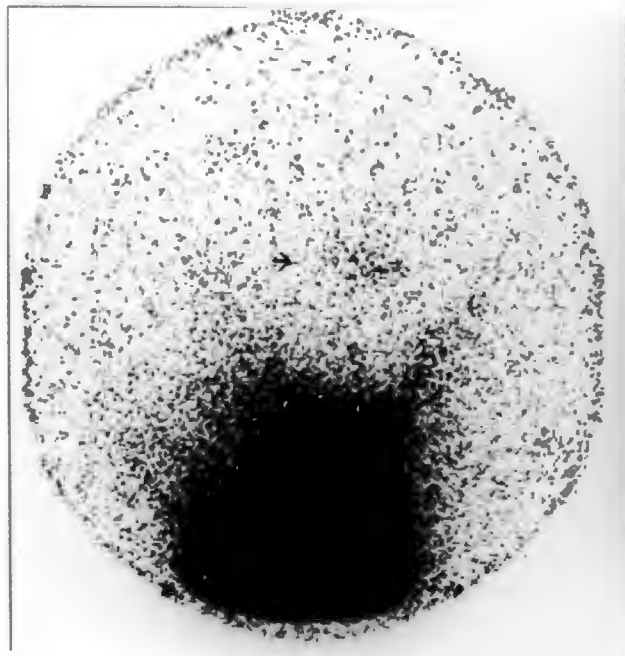


Fig 7,39

Pulmonary Aspiration (anterior views)

Fig 7,39 This 10 month old male was admitted with lower left lobe consolidation, after two episodes of bronchiolitis and two of right upper lobe pneumonia. Ciné images of a search for GOR showed five small thoracic GOR each lasting 10 or 20s. Only thoracic GOR were observed throughout the 30 min of the study, yet 120 min after the first swallow a left apical aspiration was detected and is indicated by an arrow.

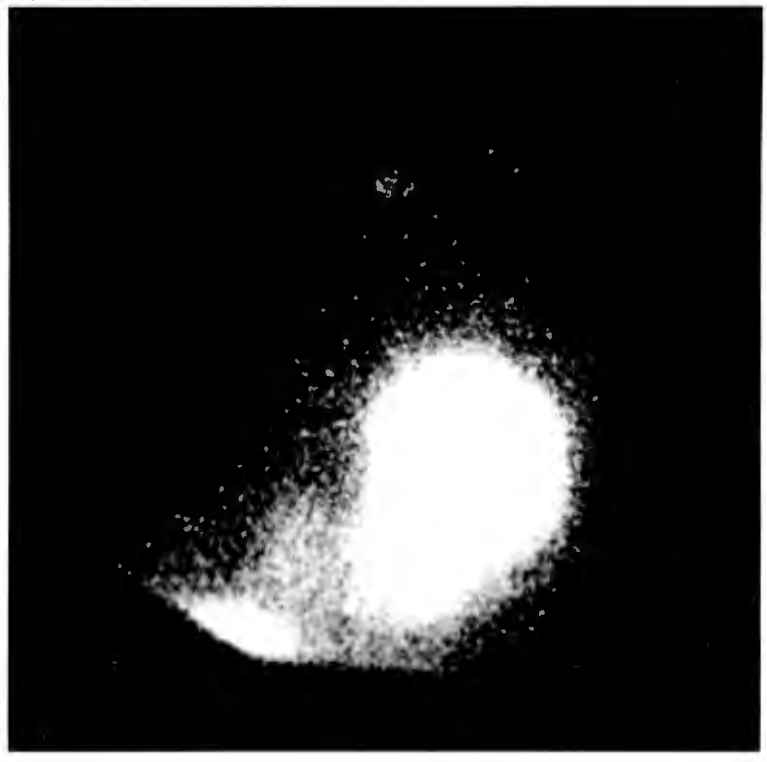


Fig 7,40

Fig 7,40 This 7 month male had a brother who died of SIDS. The patient had a normal birth at term with mass 3,38 kg. However since the age of about 4 months he experienced repetitive bronchitis, cough, usually nocturnal, and apnoeic spells. Pulmonary aspiration two hours after deglutition is seen in the region of the right mid zone.

Fig 7,41

Fig 7,41 This 5 month old male had vomited excessively for the previous 2 months, failed to thrive and had one cyanotic episode. Aspiration into the right mid lobe of 0,32 mℓ of liquid is clearly seen.

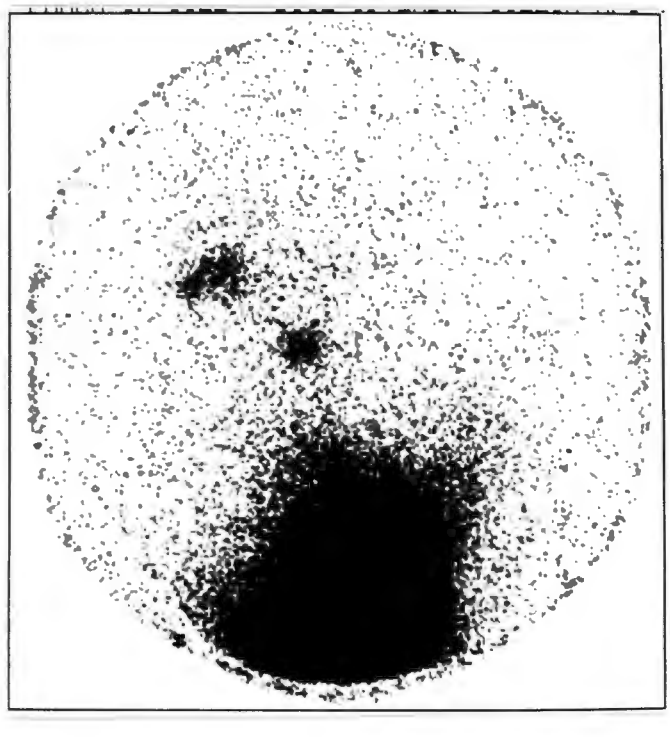


Fig 7,42

Fig 7,42 Petit mal was diagnosed in this 43 month boy at age 14 months. A calcified focus in the right temporal lobe was detected by CT and this was also the site of an abnormal spike and wave discharge on EEG. For the last year he had been vomiting excessively, mainly at night, but with normal weight gain. The results of the swallowing part of the scintigraphic study were normal, but many GOR were recorded up to buccal level. Pulmonary aspiration into the right mid zone and right apex is clearly seen in the figure, recorded 2h after swallowing. Treatment with cisapride, after this study, provided an improvment in symptoms, GOR and gastric contents at 120 min after swallowing.

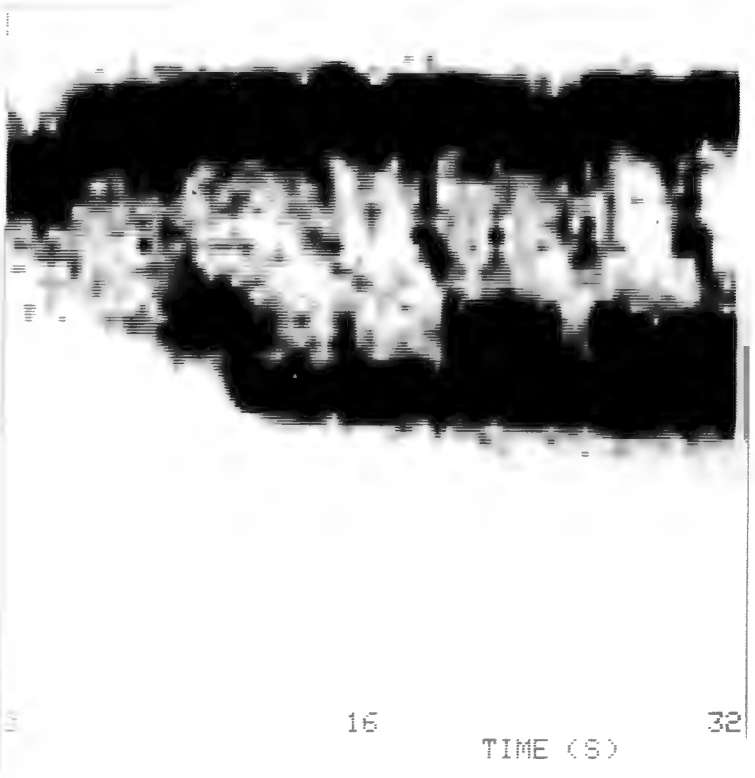


Fig 7,43i

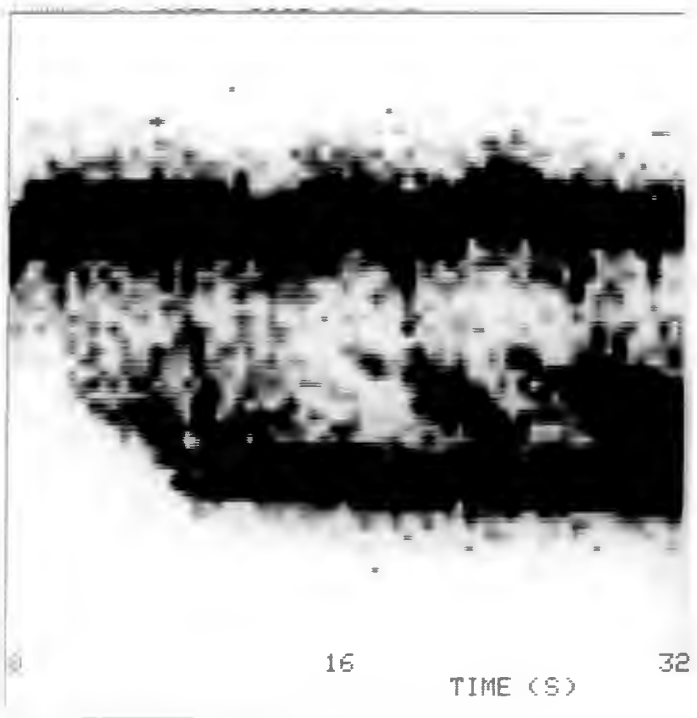


Fig 7,43ii

Cisapride Studies

Fig 7,43i,ii This 8 month old male had congenital abnormalities including a hemiatrophy. Also he experienced repeated respiratory problems. In this condensed image of a pre cisapride swallowing study (Fig 7,43i) inferior oesophageal and pre LOS hold up are seen. The post cisapride study (Fig 7,43ii) of oesophageal transit does not differ significantly from the pre cisapride study.

Fig 7,44i

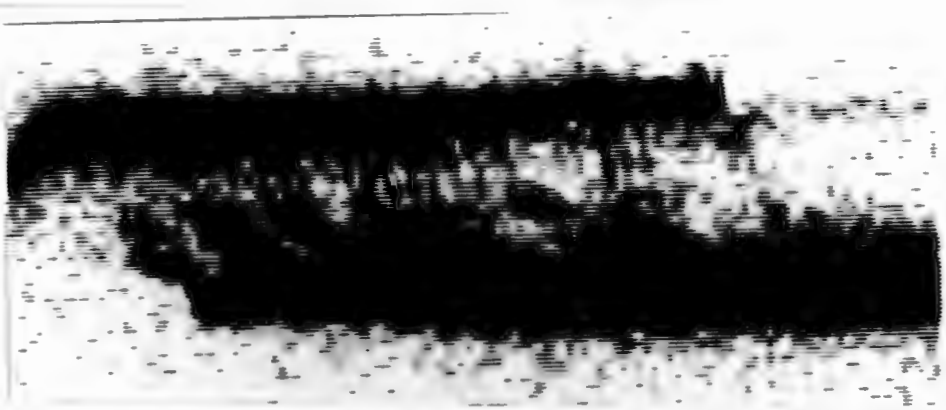


Fig 7,44ii

Fig 7,44i,ii This 8 month female showed extreme failure to thrive and had suffered three episodes of pneumonia. A pre cisapride study demonstrated slow inferior oesophageal transit and pre LOS hold up in the condensed image (Fig 7,44i). Also 16 episodes of GOR at all levels including three to the mouth were noted. After cisapride the swallows are unchanged as observed on the condensed image (Fig 7,44ii) but only 6 GOR were seen.

Fig 7,45i

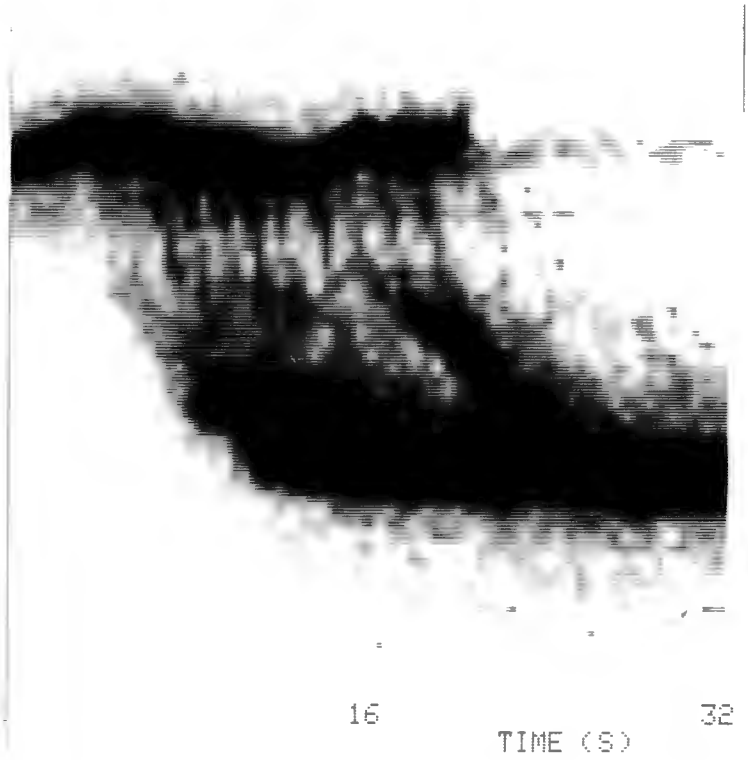


Fig 7,45ii

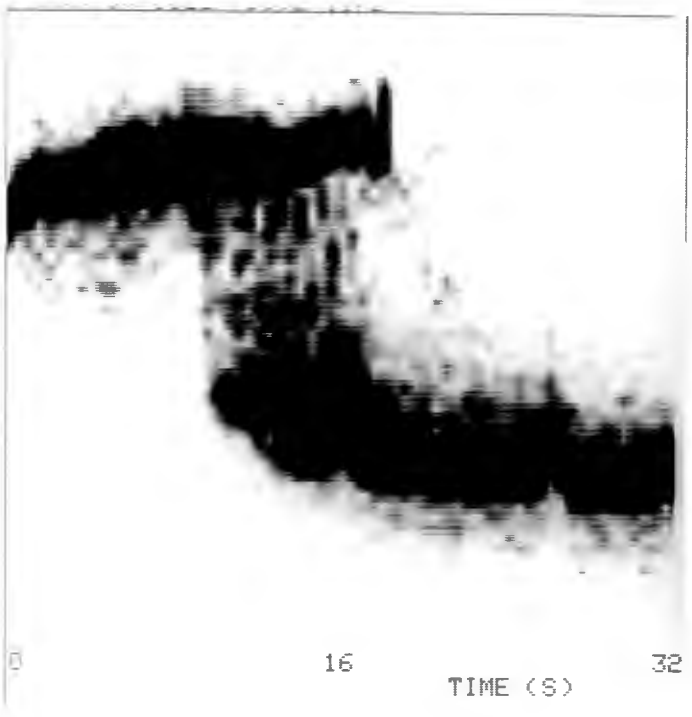


Fig 7,45i,ii This 7 month old male presented with excess vomiting. In this study performed before cisapride was used (Fig 7,45i) about 7 fast deglutitions with LOS hold up is seen. Then there is a slower oesophageal transit. This study of a swallow displayed as a condensed image recorded after the use of cisapide (Fig 7,45ii) is essentially unchanged from that before its use. The last deglutition, slowed inferiorly, is very faint because little liquid remained.

Fig 7,46i

Fig 7,46ii

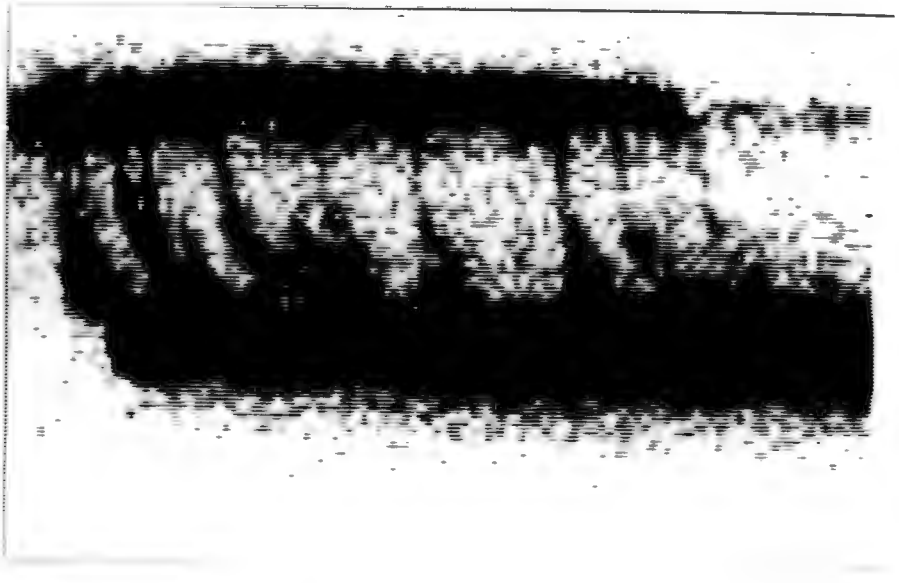


Fig 7,46i,ii This 20 month old girl had a long history of repeated chest infections with wheezing, requiring frequent hospitalisation, since the age 11d. The swallow shows slow transit through the lower oesophagus with hold up at the LOS (Fig 7,46i). The oesophageal transit was essentially unchanged after a week's course of cisapride (Fig 7,46ii) although gastric emptying and incidence of GOR were improved.

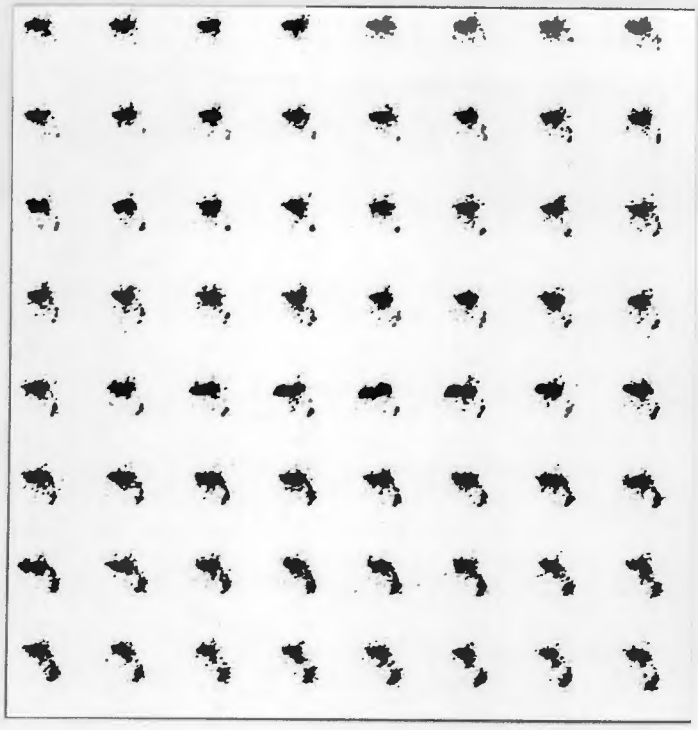


Fig 7,47i

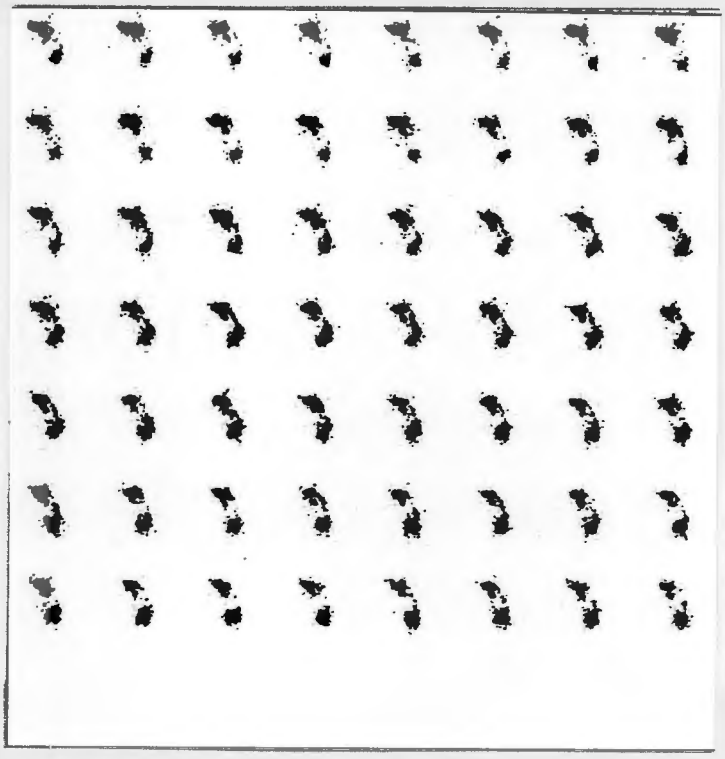


Fig 7,47ii

Fig 7,47iii

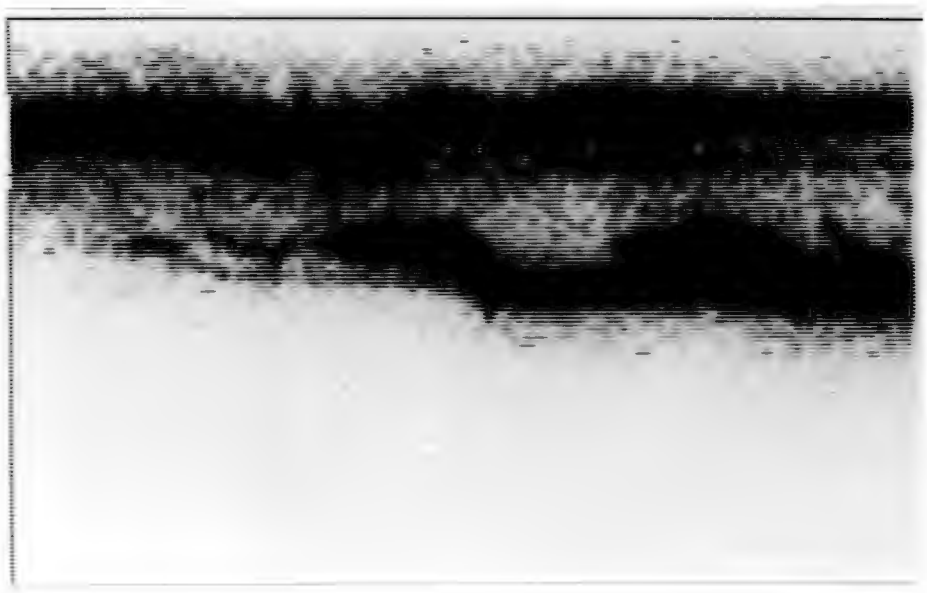
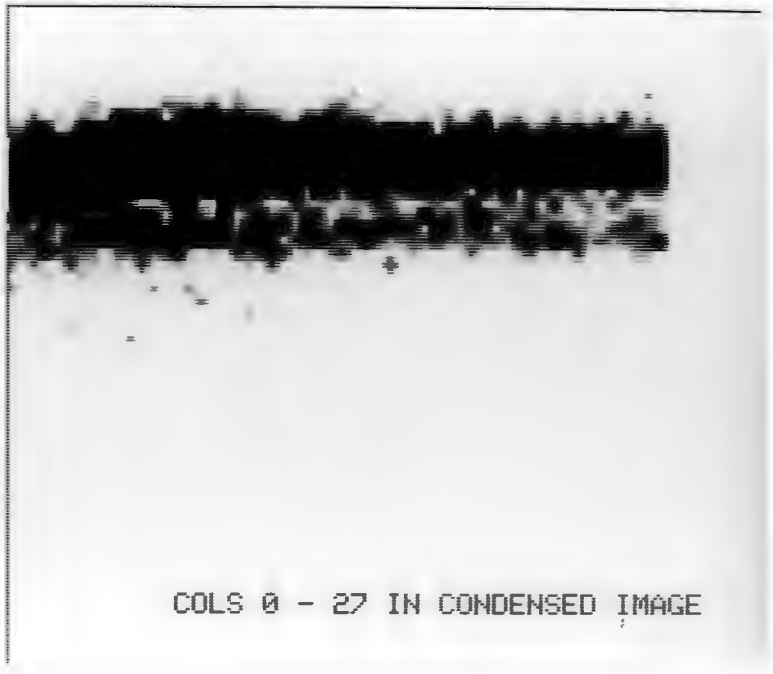


Fig 7,47iv



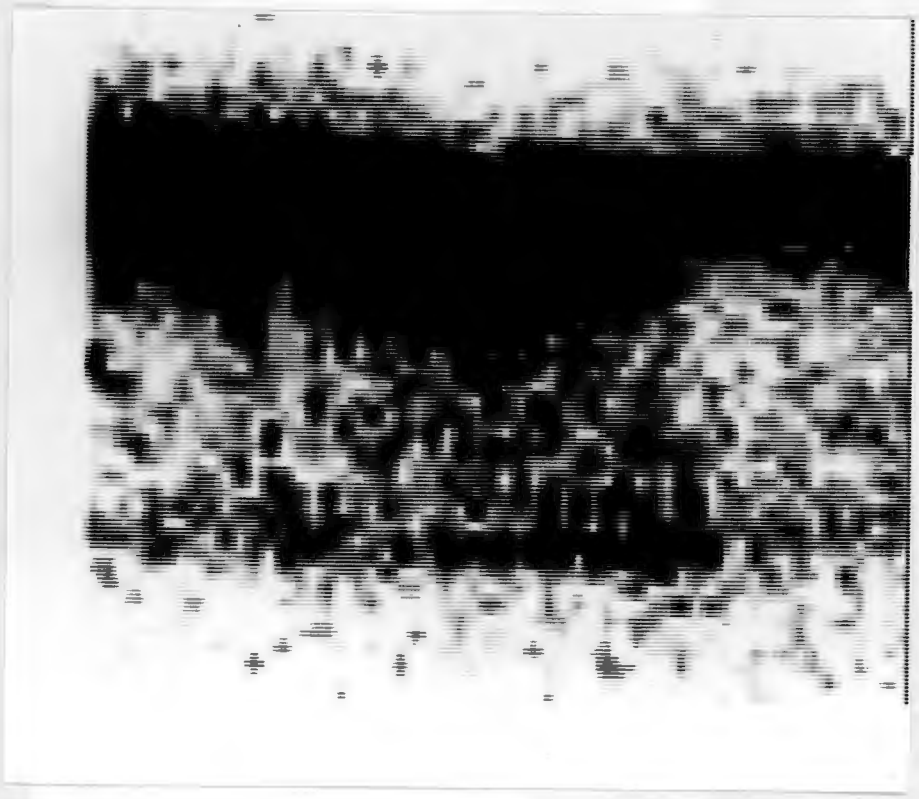


Fig 7,47v

Fig 7,47vi

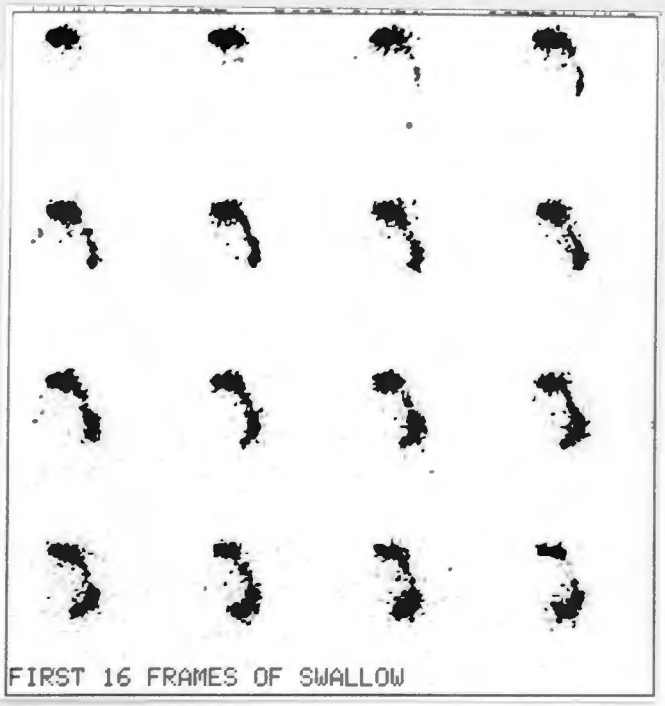


Fig 7,47vii

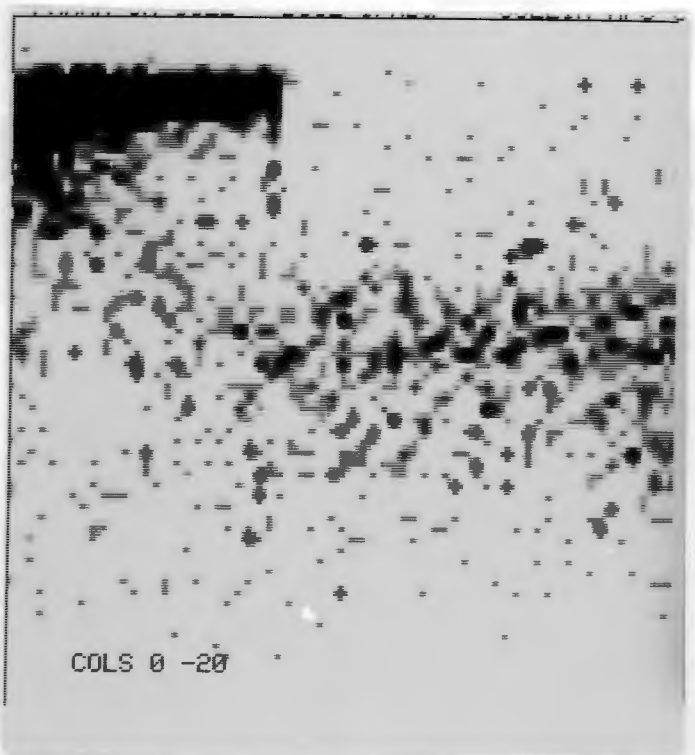


Fig 7,47viii

Fig 7,47i to viii This patient, described in the caption of Fig 7,26 was also investigated before any drug treatment. The resulting study showed clear entry into the trachea of swallowed material in the ciné images (Figs 7,47i, ii) but this was less distinct in the condensed image derived from all 64 columns (Fig 7,47iii). Hence further condensed images were constructed of the first 28 (Fig 7,47iv) and last 36 (Fig 7,47v) columns of the second page. Tracheal activity is clearly seen in the earlier columns (Fig 7,47iv) in the lower horizontal band (the upper band being buccal activity). The remaining columns show only descent in the oesophagus without tracheal activity (Fig 7,47v). Also there was remanent activity (Fig 7,47vi) recorded 2h after the swallow, in the trachea and right lower zone of the lung seen in an anterior view. After a course of cisapride entry into the trachea was still present, though reduced, during the swallowing study. Again this was more clearly demonstrated in a condensed image of the first 21 columns of the ciné images recorded in the first 32s after start of the study (Fig 7,47viii), than in the individual ciné images (Fig 7,47vii).

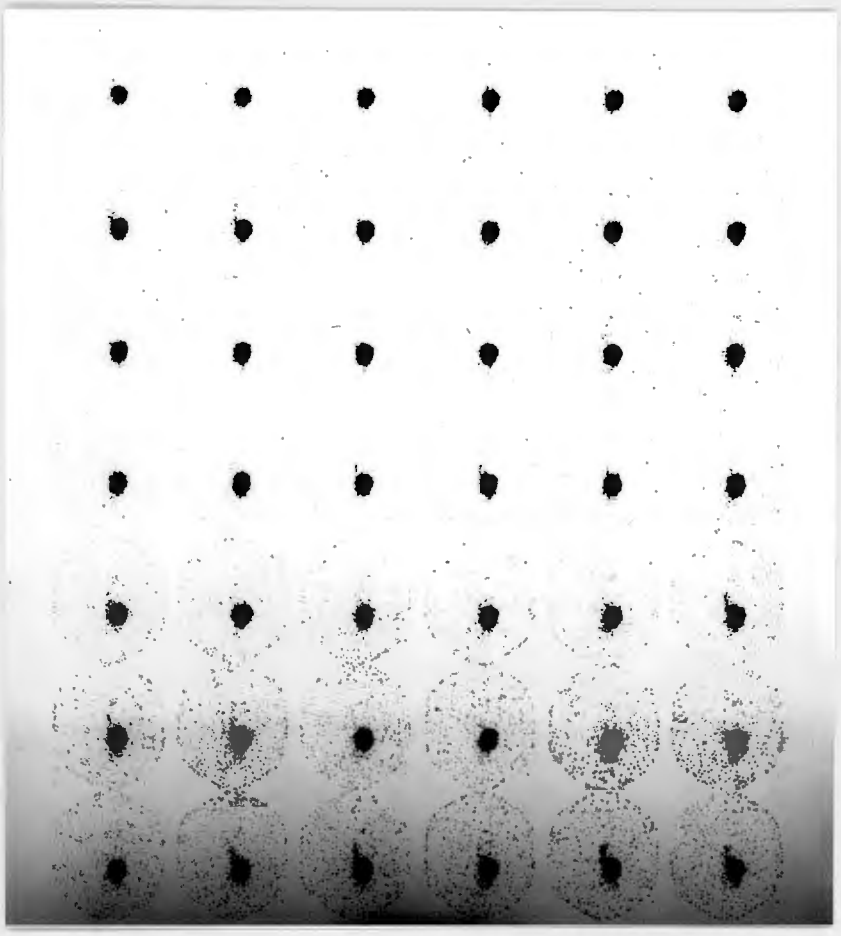


Fig 7,48i

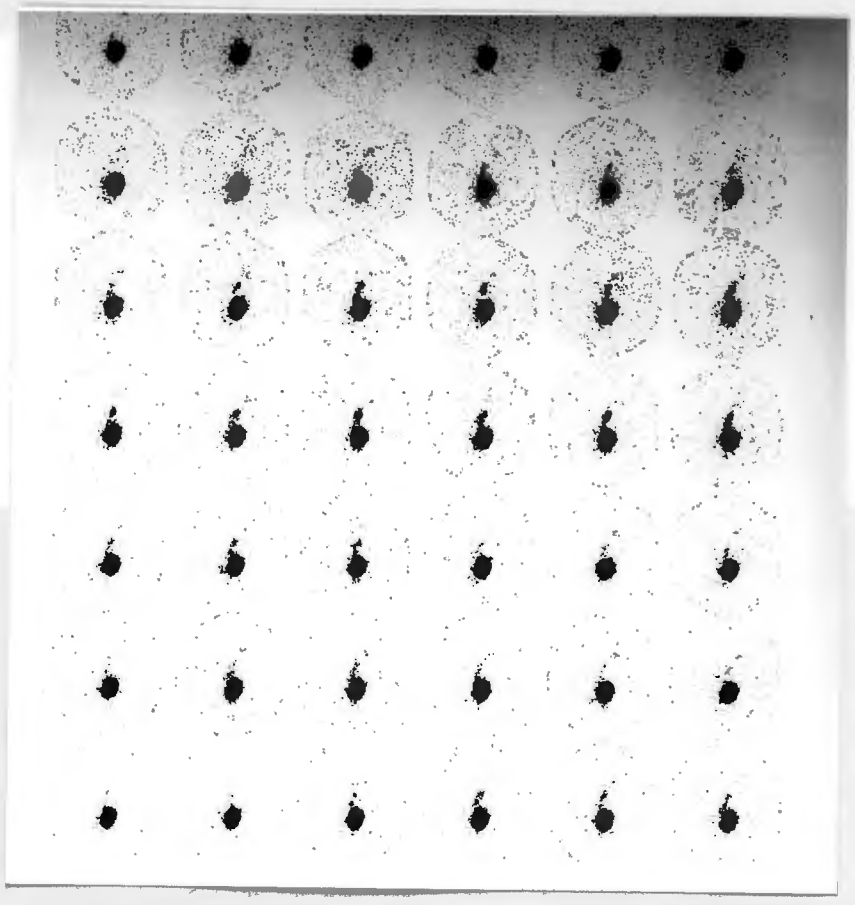


Fig 7,48ii

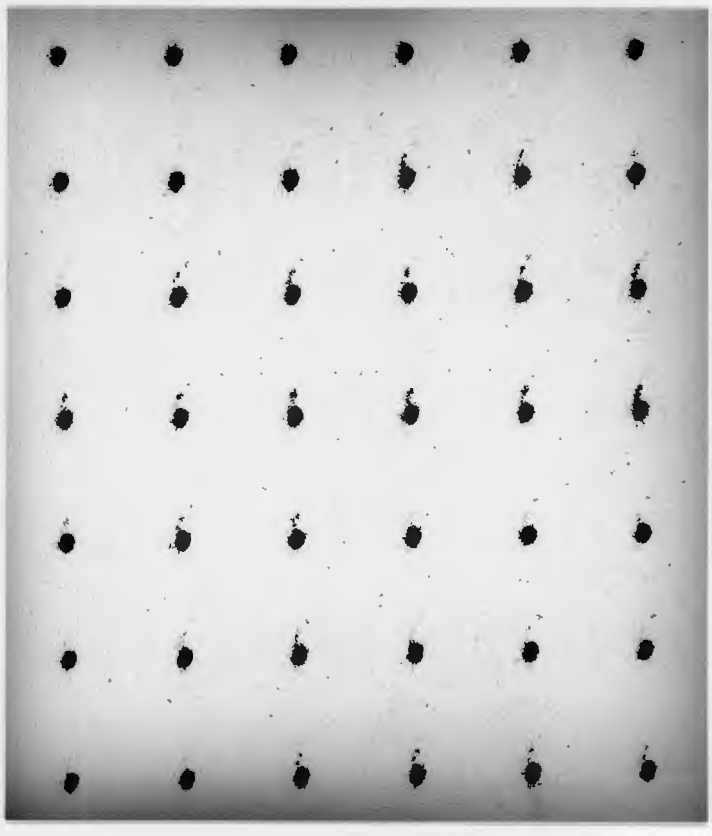


Fig 7,48iii

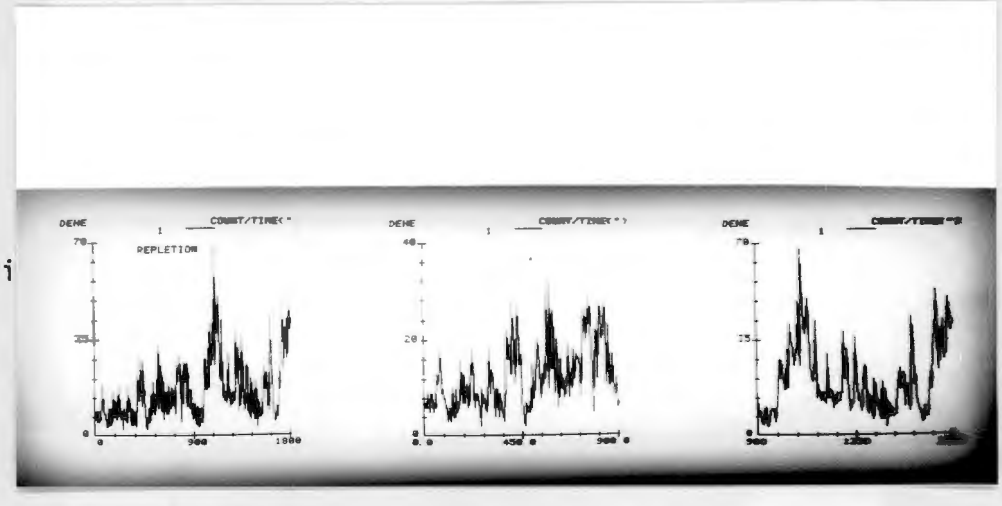


Fig 7,48iv-vi

Gastro Oesophageal Reflux

Fig 7,48i to vi Images from the GOR search of a 30 day old female with very slow gastric emptying (96 and 72% after 30 and 120 min). OTT was normal. She was born at term after a normal pregnancy with Apgars 10 and 10 and mass 2,0 kg. However she had oesophageal atresia type 3 and a subsequent operation at age 2 days. At age 17d she had a haematemesis which was treated conservatively. The GOR search showed pronounced buccal refluxes clearly represented by ciné (Figs 7,48i to iii) and graphical (Figs 7,48iv to vi) means using a ROI in the inferior oesophagus.

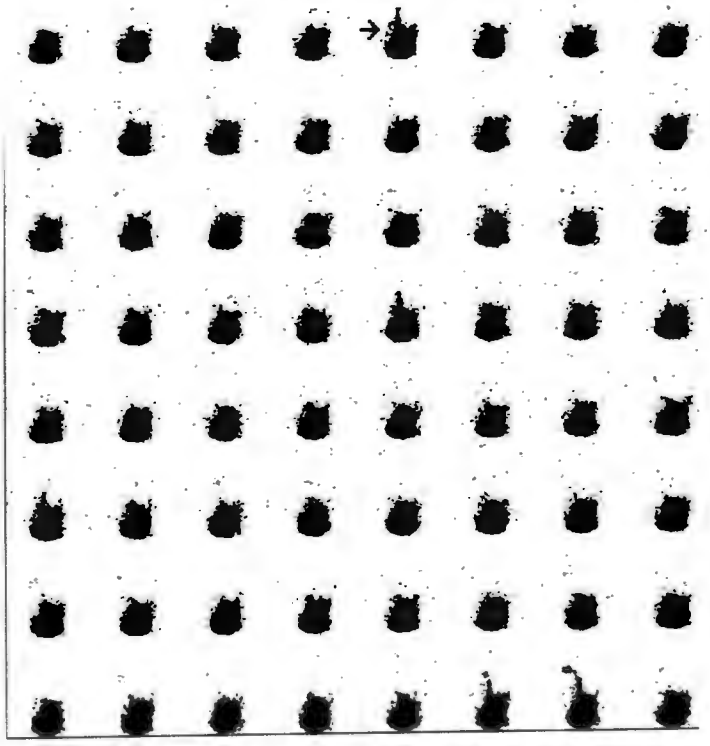


Fig 7,49i

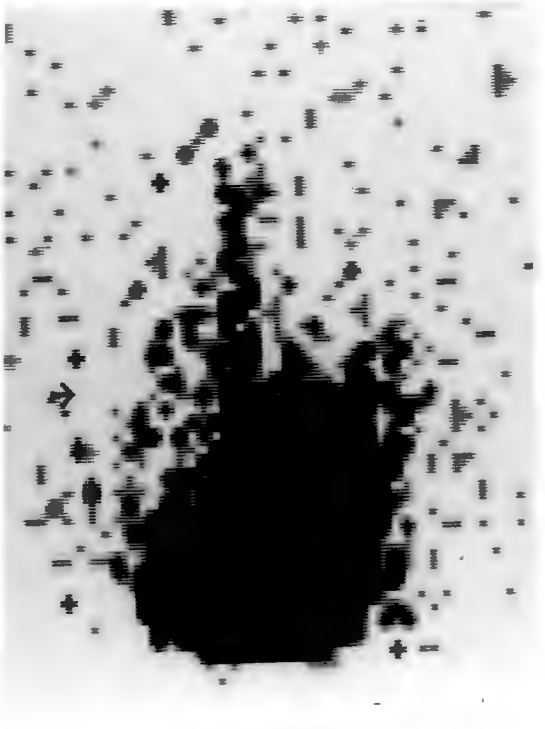


Fig 7,49ii

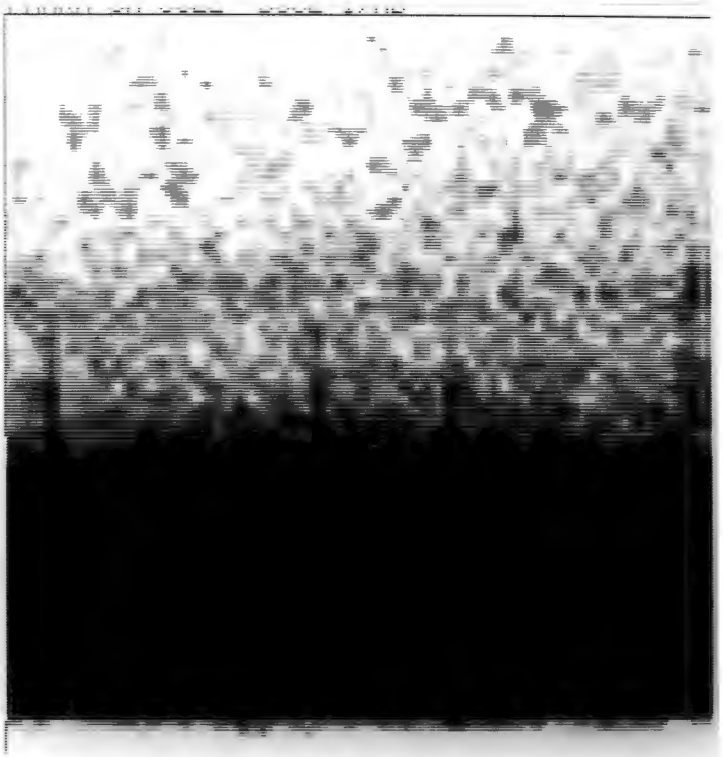


Fig 7,49iii

Fig 7,49i to iii For the previous 3 months this girl aged 7 months at the time of the scintigraphy had repeated respiratory problems including bronchopneumonia and bronchiolitis. This required four hospital admissions and one spell in the intensive care unit. A 24 hour pH study failed to detect reflux. Four clear high GOR are seen in the ciné images of the first 10 min of the search for GOR (Fig 7,49i). The fifth individual ciné image has an arrow at the level of the LOS (Fig 7,49ii) which is reproduced in Fig 7,49i. This arrow was used to determine the level of greatest contrast in the condensed image (Fig 7,49iii) for the selection of the gray scale. If done solely by eye misleading results may be obtained, for small GOR may be missed with the level set too high. This technique to optimise the condensed images for GOR was always used and was devised by the author.

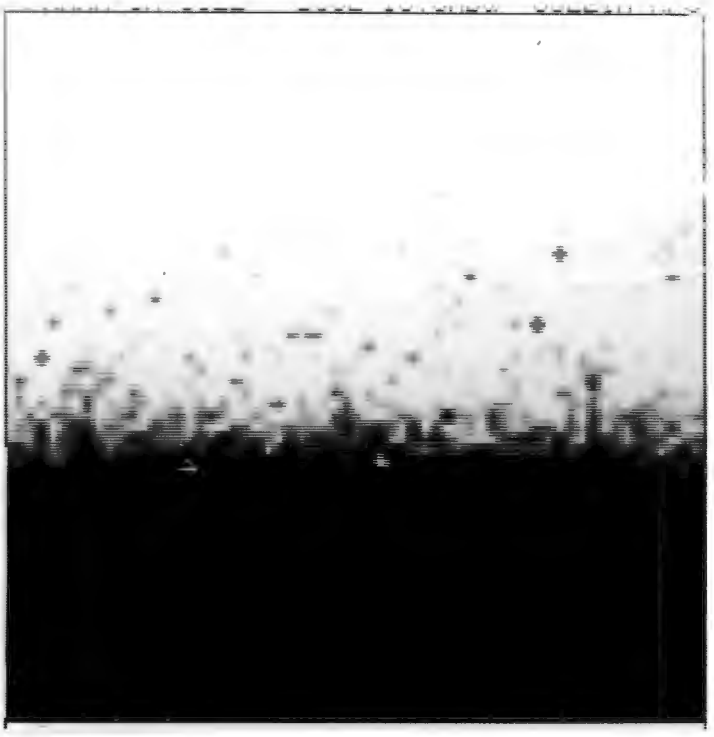


Fig 7,50i

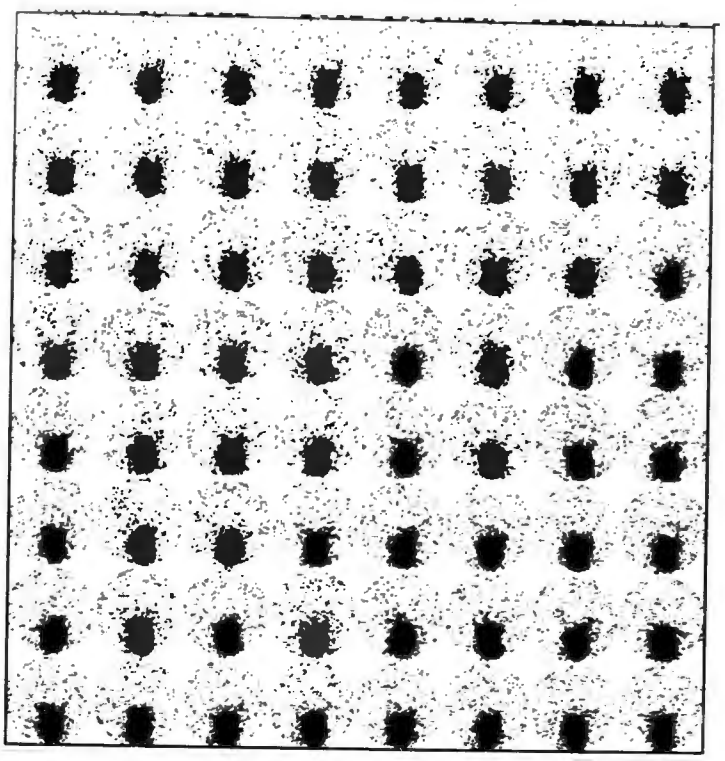


Fig 7,50ii

Fig 7,50i,ii This 8mo old male had two hospital admissions for pneumonia and failed to thrive. He was discovered to have a restrictive ventriculo septal defect with large left to right shunt. pH studies failed to detect significant GOR. However 5 thoracic GOR were observed in this study. The ability of the condensed image (Fig 7,50i) to detect small GOR not clearly identified in the ciné images (Fig 7,50ii) is shown here.

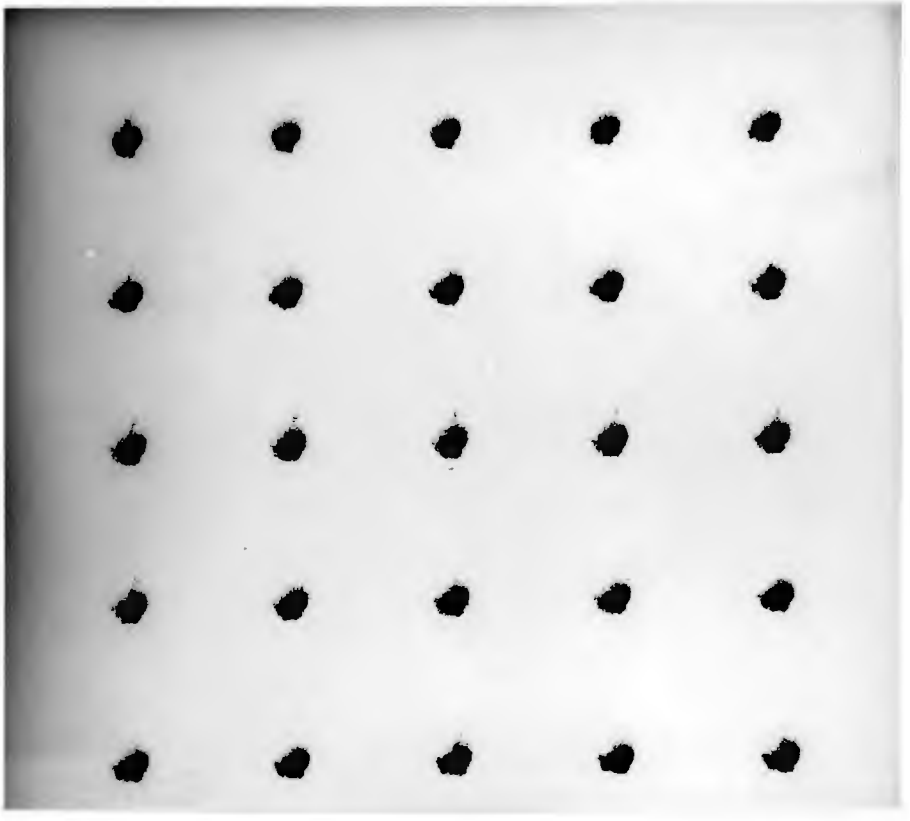


Fig 7,51

Fig 7,51 This 9 day old female was born at term with mass 2,16 kg. She was in good health and was studied because her brother had died of SIDS two years previously aged one month. Five GOR were observed to high thoracic level. Otherwise all tests including the OTT study were normal.

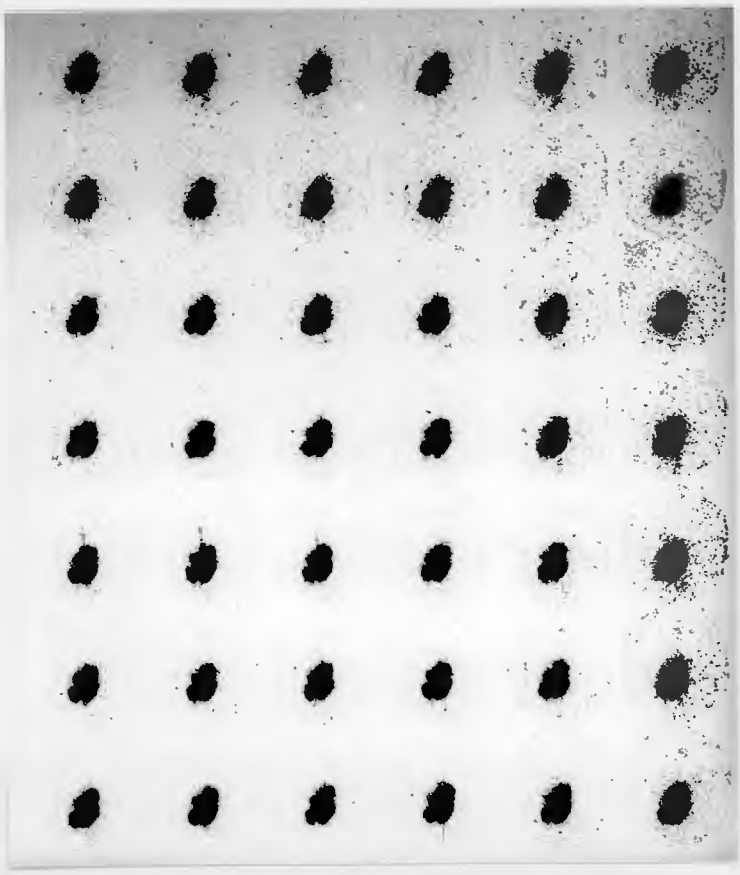


Fig 7,52i

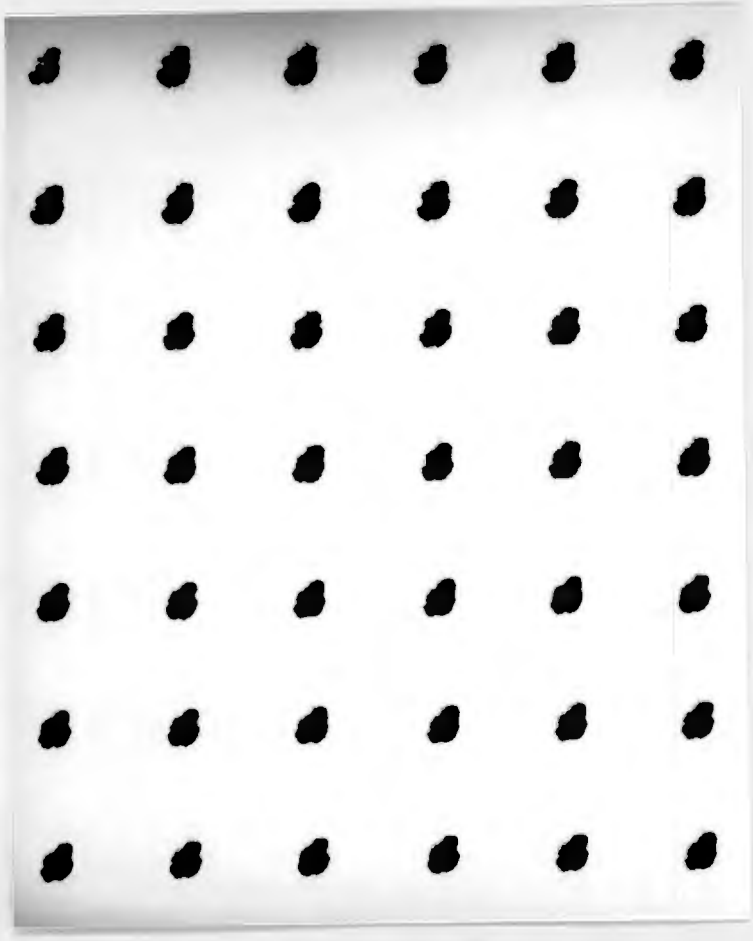


Fig 7,52ii

Fig 7,52iii,iv

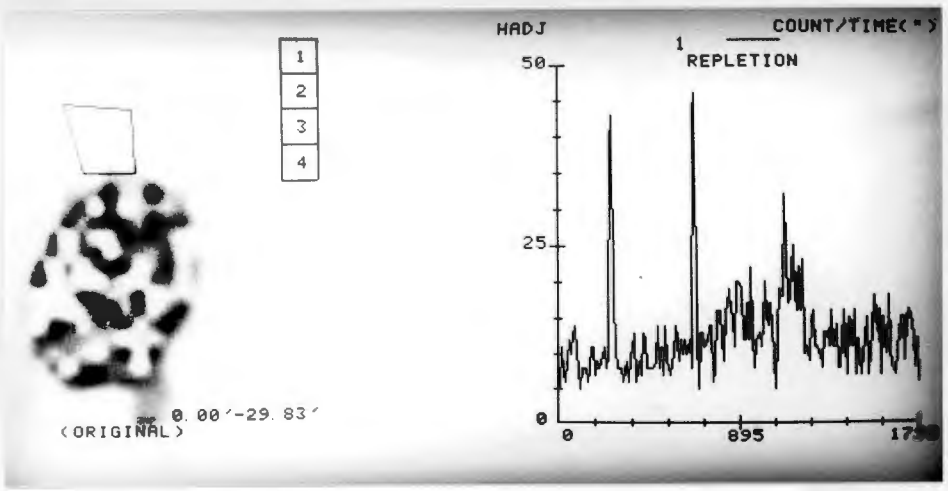


Fig 7,52i to iv Ciné images (Fig 7,52i, ii) of a search for GOR clearly show large refluxes, which are prominent on the graph (Fig 7,52iv) of counts from a ROI, defined in Fig 7,52iii, against time in seconds. These results are for the patient whose swallow is shown in Fig 7,1.

Fig 7,53i

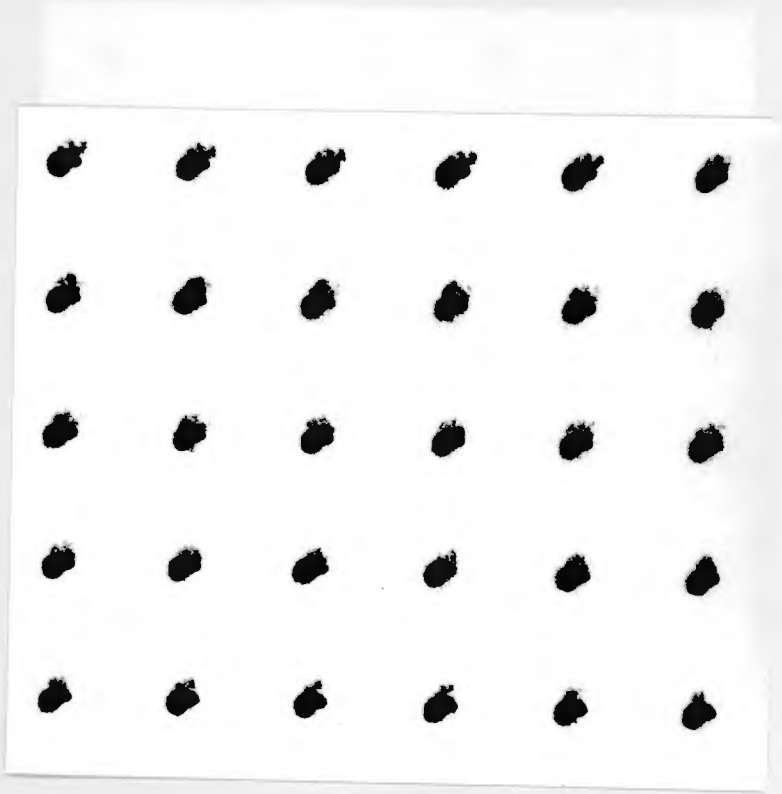


Fig 7,53ii,iii

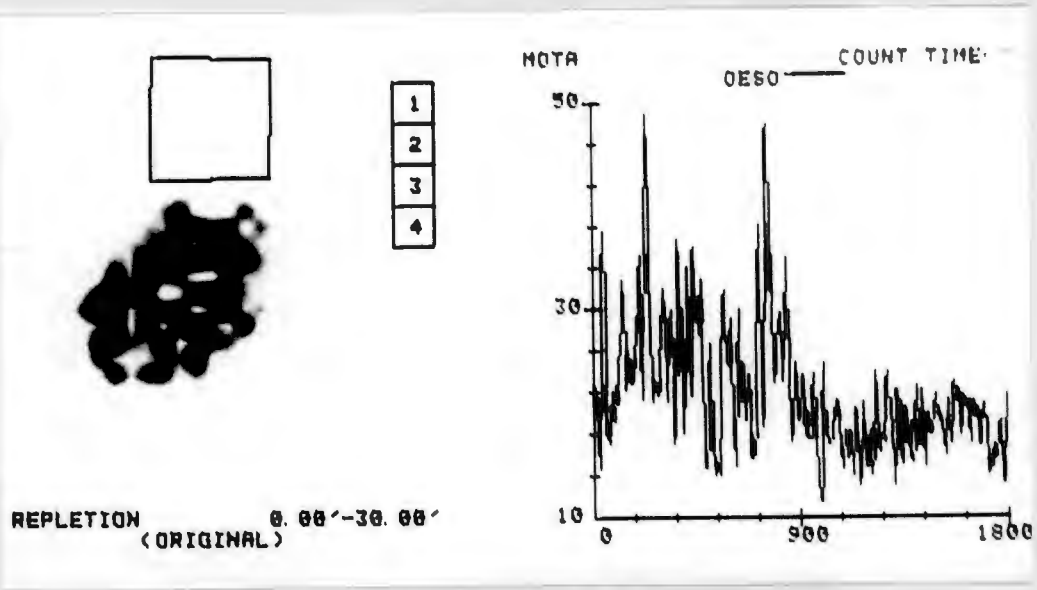


Fig 7,53i to iii Further images from the patient of Fig 7,5. Recognition of GOR is difficult on the ciné images of the first 300s (Fig 7,53i). Yet using the ROI displayed in Fig 7,53ii clear peaks are seen in the resulting activity vs time curve (Fig 7,53iii).

Fig 7,54

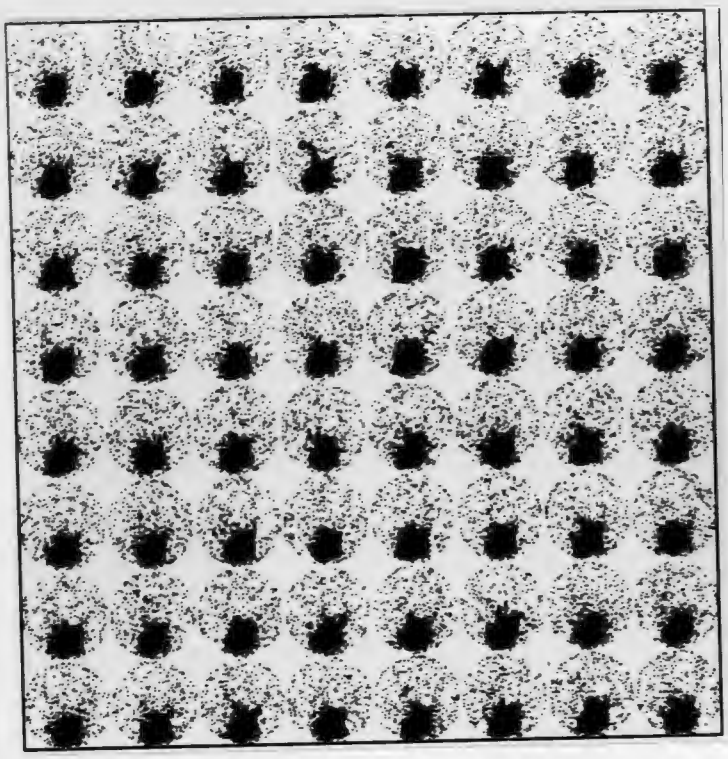


Fig 7,54 This first triplet a preterm (20 weeks) male, suffered brochiolitis and then repeated pneumonia. In this study small GOR were observed and also one which reached buccal level, yet was of duration little more than 10s (in the second row of the ciné images). It is likely this GOR would not have been observed with a radiological study.

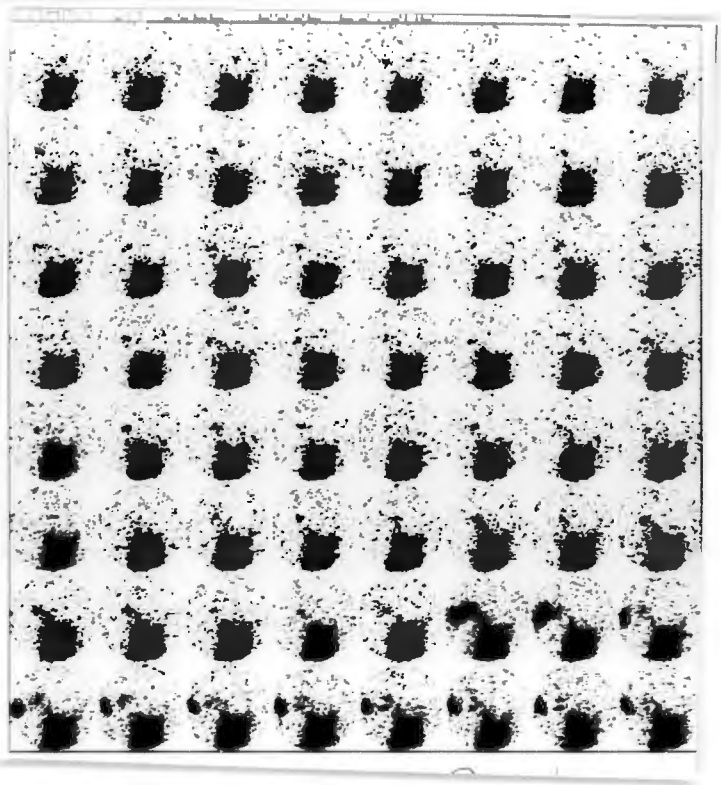


Fig 7,55

Fig 7,55 Barium studies also detected GOR in this 14 month girl, who had recurrent chest infections. In this representation of the first 10 min of the search for GOR several clear refluxes to the buccal level are seen, followed by vomiting.

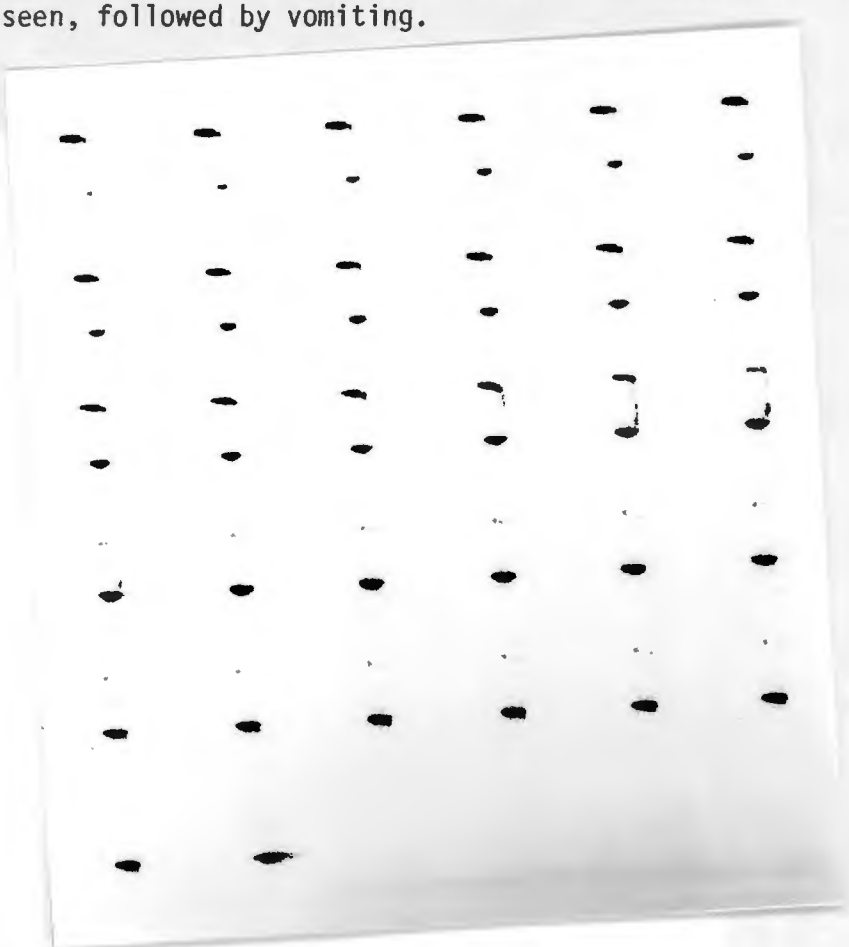


Fig 7,56i

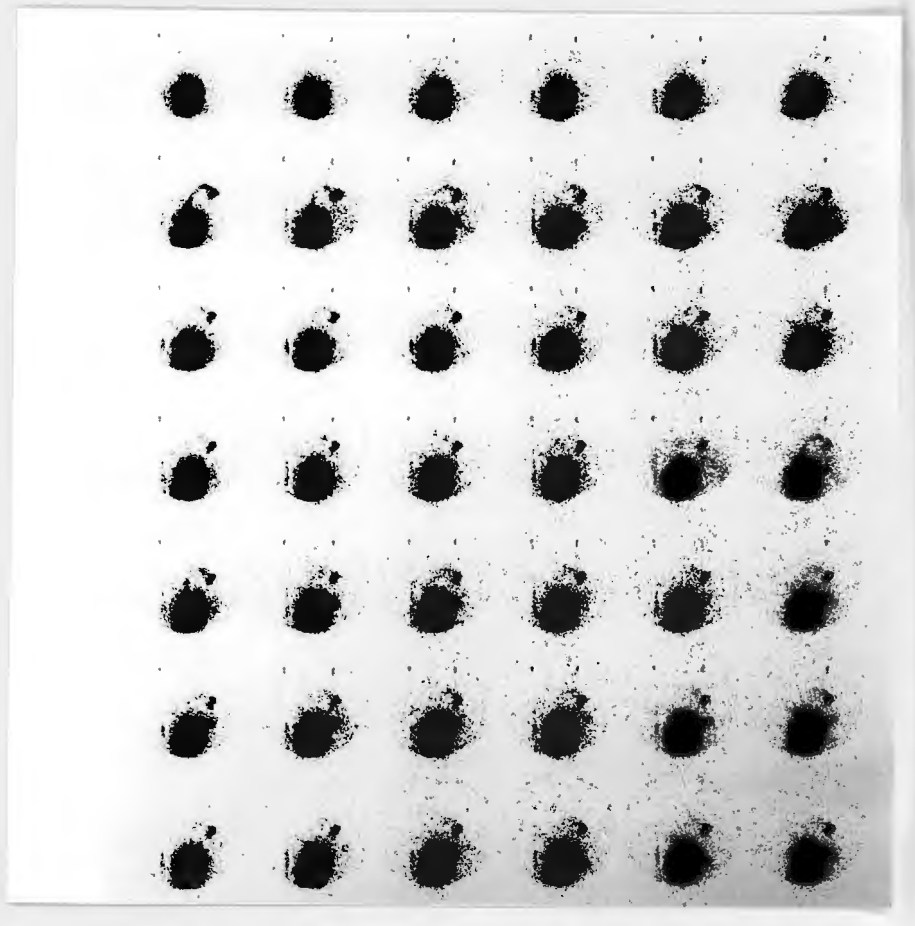


Fig 7,56ii

Fig 7,56i,ii This 17 day old male experienced cyanotic episodes after feeds and excess regurgitation. The swallow (Fig 7,56i) was normal but GOR were observed (Fig 7,56ii) up to buccal level. Slight hold up is seen at the LOS. Radiological and other studies were normal.

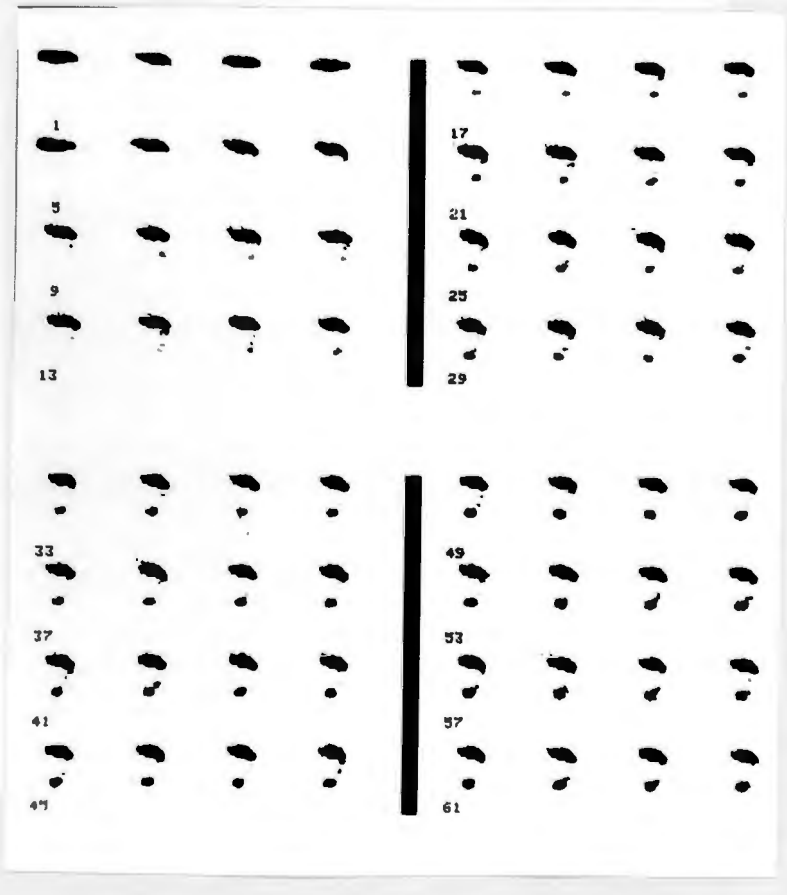


Fig 7,57i

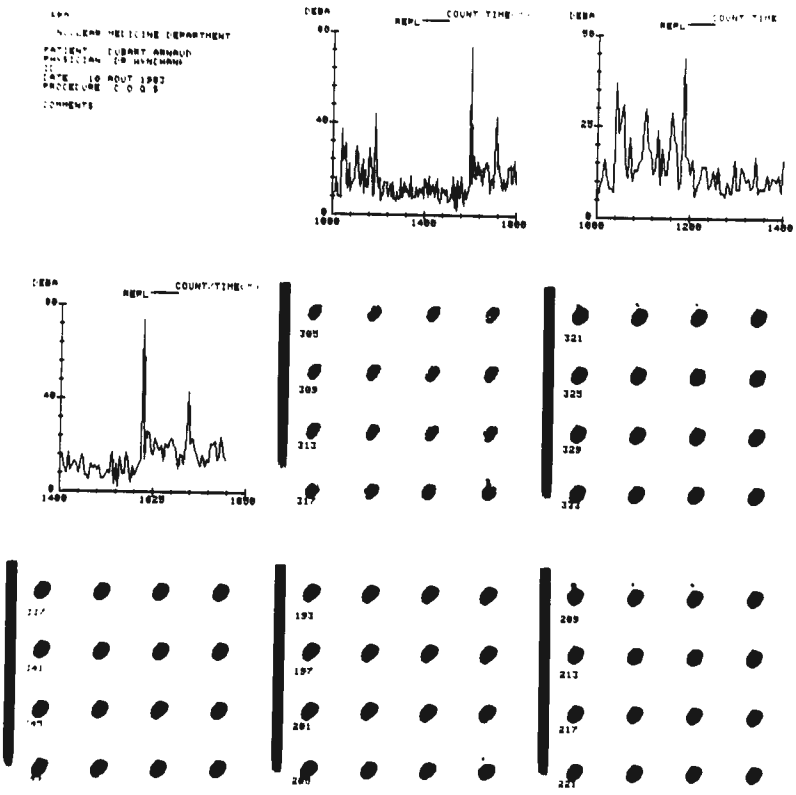


Fig 7,57ii

Fig 7,57i,ii This 14 day male was a twin who had excessive regurgitation. Although his swallow was normal (Fig 7,57i) clear GOR were seen (Fig 7,57ii). Apart from a very slow gastric emptying, although maternal milk was used, (73% remaining at 120 min) no other abnormality was detected. A closed LOS can be deduced from images nos 50 to 60 in the ciné images of the swallow.

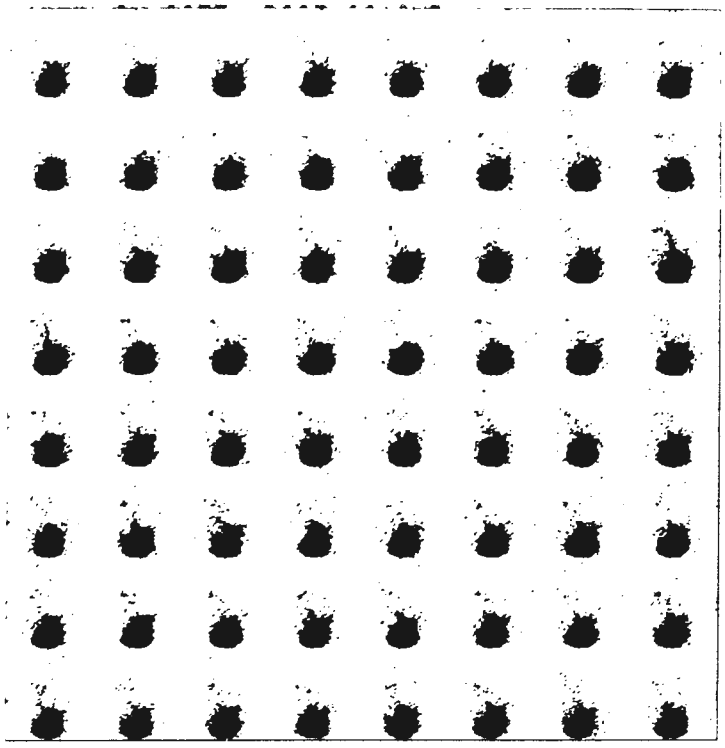


Fig 7,58i

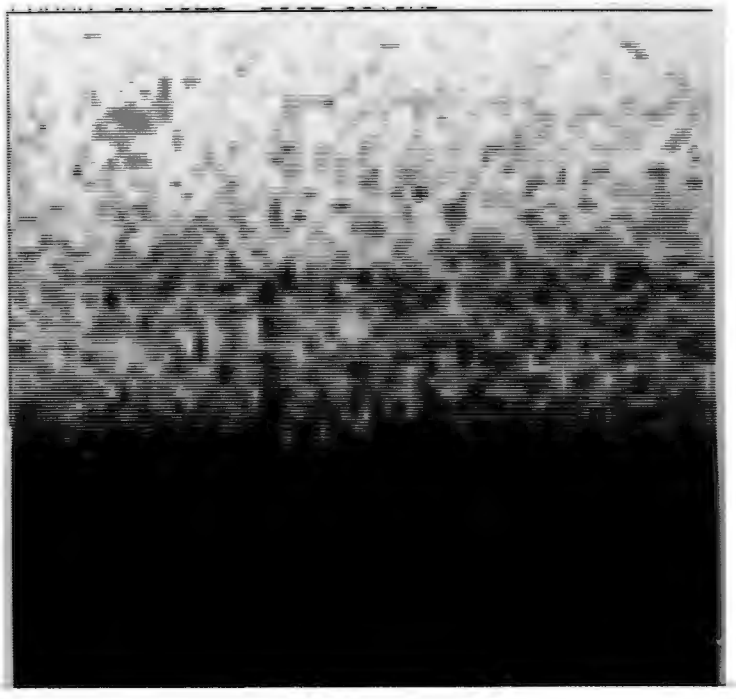


Fig 7,58ii

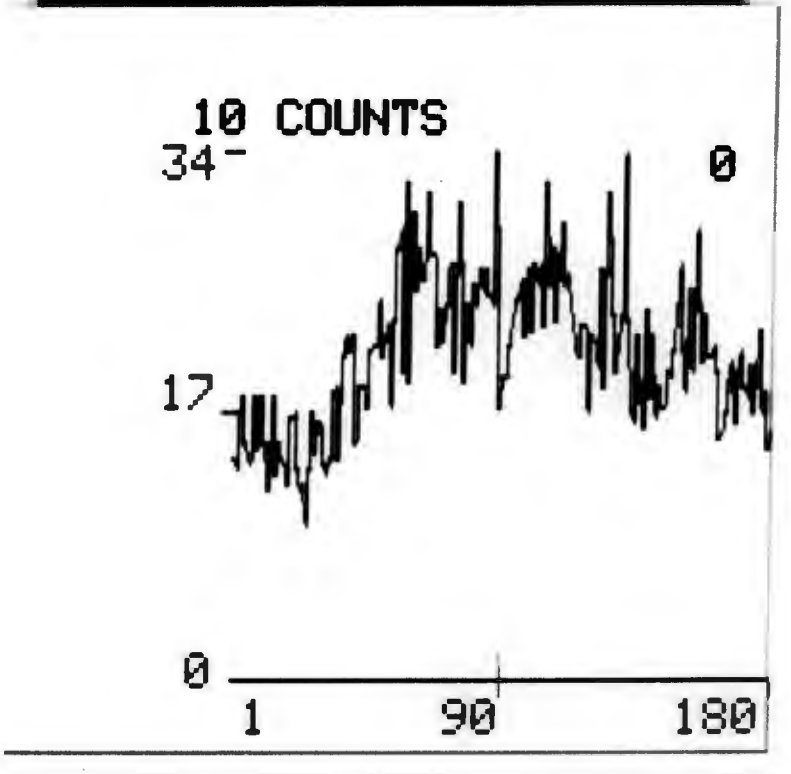


Fig 7,58iii

Fig 7,58i to iii Frequent episodes of brochopneumonia were reported for this 9 month old girl who was also asthmatic and had an allergy to cow's milk. Her gastric emptying was rapid, with 22 and 1% remaining 30 and 120 min respectively after swallowing. Although it was clear from the ciné images (Fig 7,58i) that significant GOR was present, details were not easy to determine from either ciné or condensed images (Fig 7,58ii). However in the activity time curve obtained from a ROI in the inferior oesophagus some GOR not clearly seen by the other means were discernible (Fig 7.58iii).

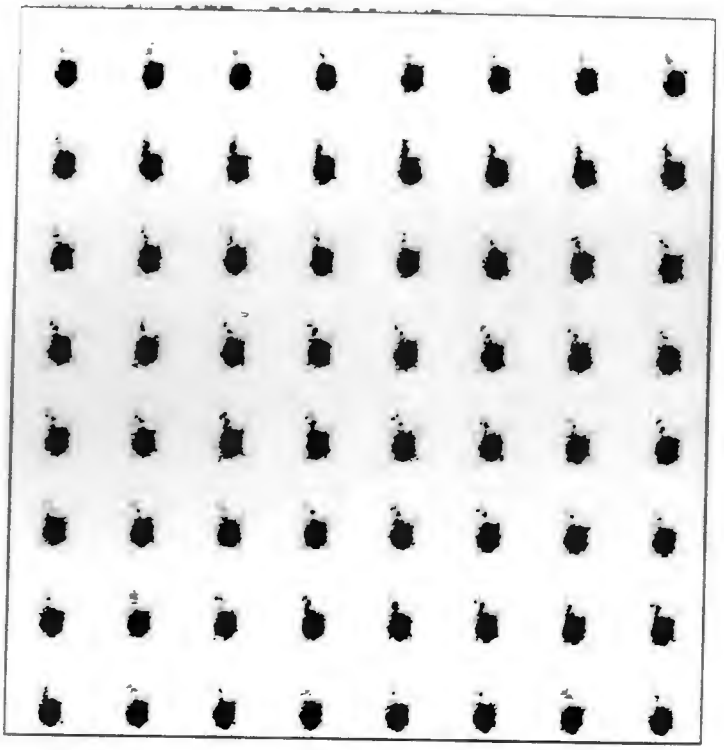


Fig 7,59i

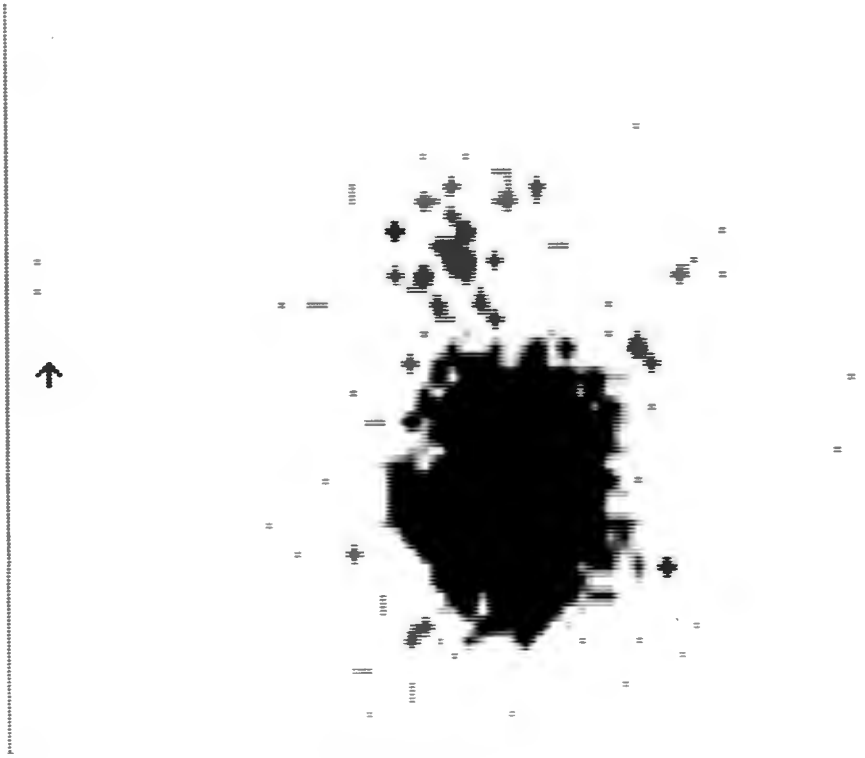


Fig 7,59ii

Fig 7,59iii

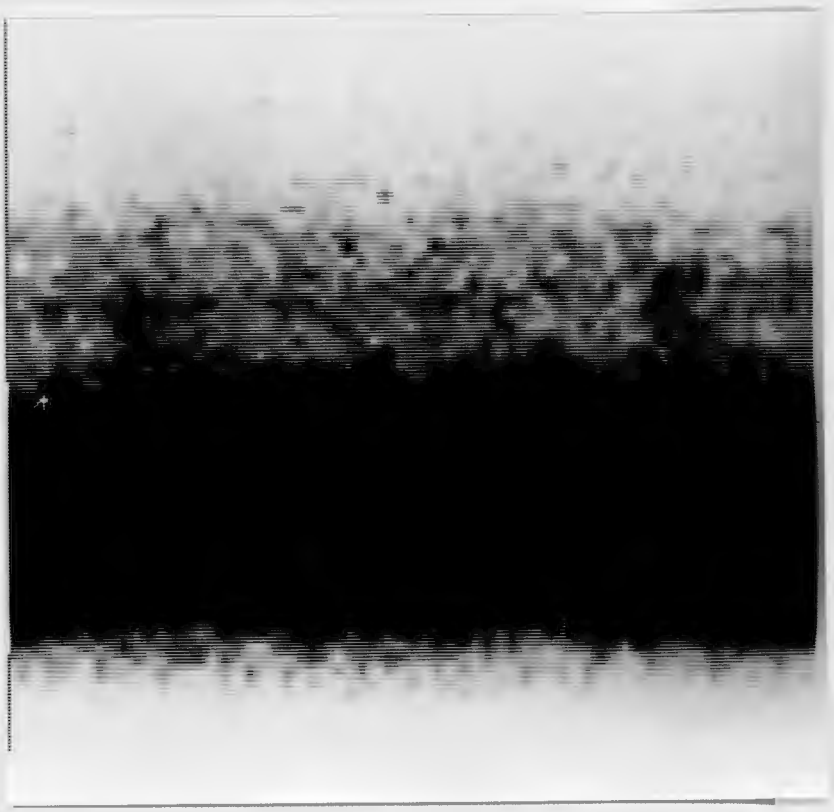


Fig 7,59iv

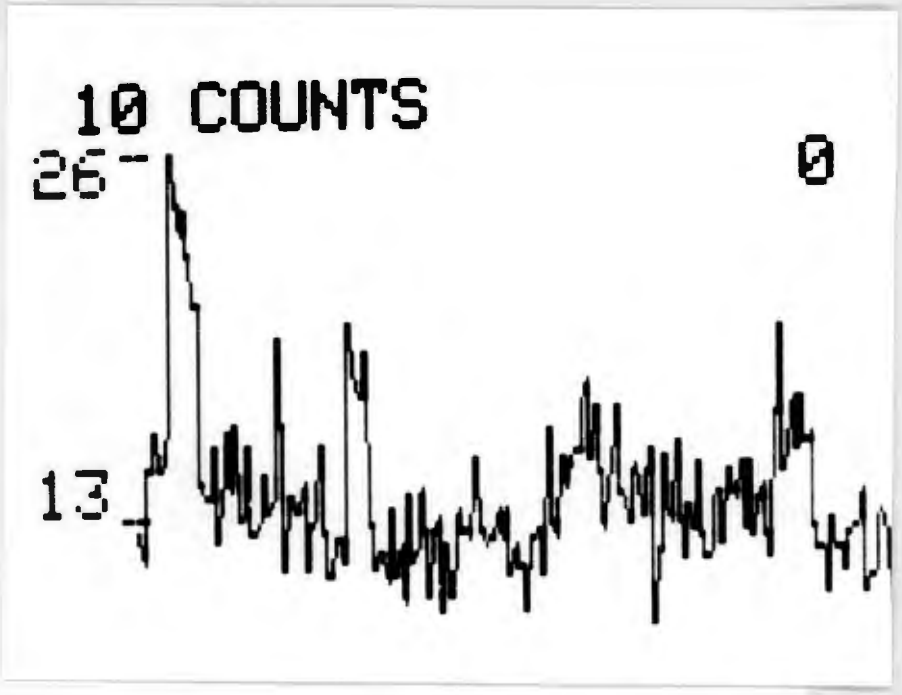


Fig 7,59i to iv Failure to thrive and frequent projectile vomiting (never bile stained, but twice blood stained) since age 1 week, were this 2 month old infant girl's problems. Ciné images (Fig 7,59i) were used with an arrow at the level of the LOS (Fig 7,59ii) to obtain a condensed image (Fig 7,59iii) as described above and some GOR were recognised, but more clearly so with a ROI providing an activity time curve (Fig 7,59iv).

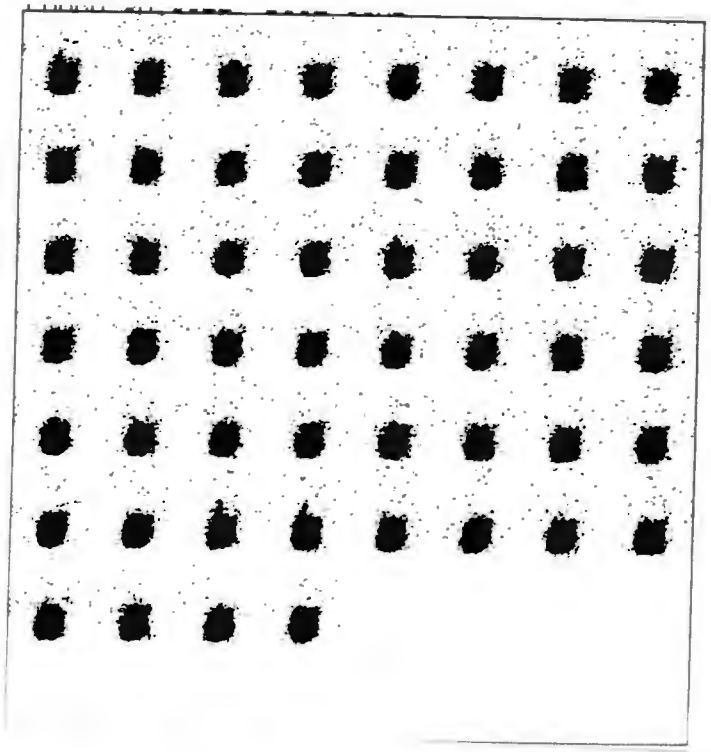


Fig 7,60i

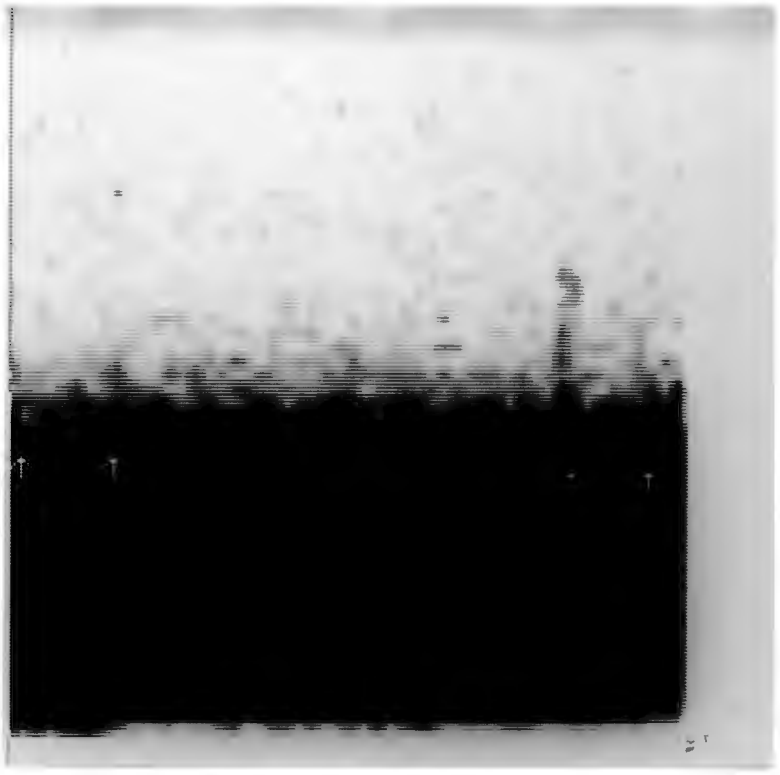


Fig 7,60ii

Fig 7,60i, ii Right sided bronchopneumonia was reported five times for this 2 year old girl during her second year of life and in addition two episodes of wheezy bronchitis. Nasal prong oxygen was required on one occasion. Clear GOR is seen at least twice in the ciné images recorded between 22 and 30 min after swallowing (Fig 7,60i) but GOR (marked with arrows) were recognisable from the condensed image (Fig 7,60ii). This was more than in either ciné images or ROI curves

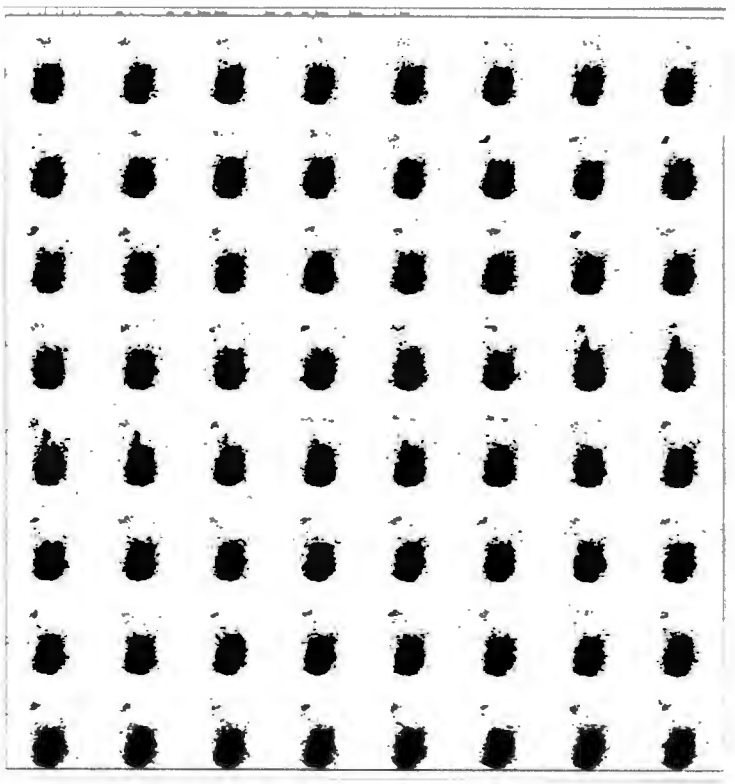


Fig 7,61i

Fig 7,61ii

Fig 7,61i, ii The ability of the condensed image to demonstrate both large and small GOR is shown here. Small refluxes difficult to detect on ciné (Fig 7,61i) and graphical images are indicated with arrows on the condensed image (Fig 7,61ii).

7.2.5 Gastric emptying and dosimetry calculations

In order to have a value for the effective half life for stomach emptying (t_e) in the dosimetry calculation of the next chapter, the values of gastric contents as percentages of swallowed activity at 30 and 120 min (GAST 30 and GAST 120 respectively) after deglutition were used. Results from 163 patients from both hospitals whose studies were normal were considered. Of these 30 patients were aged above 3y. Those 133 results for patients aged below 3y were examined in terms of age. A two way analysis of variance with one covariate was used, this being of course a special case of regression analysis. The covariate was age and no significant variation with age was seen for GAST 30 ($p = 0,80$) or for GAST 120 ($p = 0,84$). Further possible sources of variation of gastric emptying amongst these are sex and the nature of the liquid swallowed.

In order to calculate t_e the following was done. A best fit was obtained for a log/linear plot of gastric contents (%) vs time. This was forced through the point (100%, time zero) and gave mean values of GAST 30 and GAST 120 65,9% (range 50 to 76)% and 23,1% (14 to 38)% for maternal milk (n = 8) and 70,4% (18 to 98)% and 31,7% (1 to 83)% for infant formulae (n = 133). These gave in turn $t_{\frac{1}{2}}$ values of 53,3 and 72,7 min for maternal milk and other milks respectively. In contrast the values of GAST 30 and GAST 120 for those under 3 years whose studies were not adjudged normal were 53,8 (16 to 86) and 21,0 (6 to 73)% after swallowing maternal milk (n = 14) and 65,8 (12 to 96) and 26,9 (1 to 81)% (n = 144) after other liquids had been swallowed. In all cases where mean values of GAST 30 and GAST 120 are given the ranges are very wide, reflecting

natural variation especially in pathological cases when gastric emptying may be slower or faster than average.

In order to contribute to the controversy about the relation, if any, between delayed gastric emptying accompanying GOR (Wynchank et al 1986), mean gastric emptying half life ($t_{\frac{1}{2}}$) is given for patients from both Institutions, together with sex, mean age and the results of a search for GOR (Table 7,25). The differences are not significant (p above 0,05).

7.2.6 Scintigraphy and cisapride

The results from 25 patients of the Children's Hospital who had at least two gastro oesophageal studies with one before and the other after administration of cisapride are listed in Table 7,26. The period between the two studies was six days or more except for six patients (nos 1, 7, 8, 14, 23 and 24). The dose of cisapride used was 1mg/kg per day given orally in equal doses each 8 hours.

For six patients (nos 3, 9, 11, 14, 18 and 25) pulmonary aspiration was only detected in the study before cisapride. In one patient (no 15) pulmonary aspiration was only observed in the study performed during the course of cisapride.

Table 7,1 The indications for the gastro oesophageal study and the numbers of patients in each age range.

	Age range						
	0-1mo	1-4mo	4-12mo	1-4y	4-8y	8-16y	0-16y
Indication for study							
1. Chronic or repeated respiratory problems	3	14	30	81	109	72	309
2. Apnoea/cyanosis/ SIDS susceptibility	58	68	28	4	1		159
3. Oesophago-tracheal fistula/false passage	11	13	6	1			31
4. Frequent vomiting	12	10	6	3	2	1	34
5. Pain	2	1	1	3			7
6. Haematemesis	3	3	2	2	1		11
7. Anorexia/failure to thrive	1	2	1	2			6
8. Prolonged gastric tube feeding		1	1				2
9. Scleroderma						1	1
10. Follow up (medical treatment)	2	8	23	11	2	8	54
After surgical treatment for the following							
11. Hypertrophic pyloric stenosis		1					1
12. Achalasia						2	2
13. Osoephageal atresia	2	3	1				6
14. Oesophagitis				4	1		5
15. Lobar emphysema			1				1
16. Diaphragmatic hernia				1			1
TOTAL	94	124	100	112	116	84	630

Table 7,2 Indications (as for Table 7,1). No GOR is denoted by 0, moderate GOR by + and severe GOR by ++.

	Age range																	
	0-1 mo			1-4 mo			4-12 mo			1-4 y			4-8 y			8-16 y		
Degree of GOR	0	+	++	0	+	++	0	+	++	0	+	++	0	+	++	0	+	++
Indication																		
1	0	0	3	1	2	11	17	2	11	32	10	39	33	18	58	28	6	38
2	20	2	36	17	22	29	17	3	8	2	0	2	0	0	1	1	0	1
3	4	1	6	3	4	6	3	1	2	0	0	1						
4	2	1	9	3	1	6	4	0	2	2	1	0	0	0	2	0	0	1
5	1	0	1	0	0	1	1	0	0	1	0	2						
6	1	0	2	2	0	1	1	0	1	0	0	2	0	0	1			
7	1	0	0	1	0	1	0	0	1	1	1	0						
8				1	0	0	0	0	1									
9																0	0	1
10	2	0	0	6	0	2	20	1	2	10	0	1	1	0	1	6	1	1
11				0	1	0												
12																0	0	2
13	0	0	2	2	0	1	0	1	0									
14										1	0	3	0	0	1			
15							0	0	1									
16										0	0	1						
TOTALS	31	4	59	36	30	58	63	8	29	49	12	51	34	18	64	34	7	43

Table 7,3 Mean ($\bar{t}$) and SD of OTT (in seconds) of patients with no GOR, GOR up to buccal (or cervical) or thoracic level in age groups. (n denotes numbers of patients).

	Age range											
	0 - 1y			1 - 4y			4 - 8y			8 - 16y		
Maximum height of observed GOR	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD
Buccal or cervical	104	4,7	2,0	36	4,0	1,2	31	4,8	1,2	11	6,6	1,0
Thoracic	45	3,4	1,3	24	4,1	1,3	15	5,1	2,3	5	7,5	
No GOR	98	3,0	1,1	39	3,5	1,3	28	4,1	1,1	17	4,4	1,9

Table 7,4 As table 7,3 but for 33 term and 15 preterm neonates aged under 1 month

Maximum height of observed GOR	Term		Preterm	
	n	$\bar{t}$	n	$\bar{t}$
With GOR	26	3,4	9	3,1
(Buccal	17	3,2	4	3,9)
(Cervical	5	4,3	4	2,1)
(Thoracic	4	2,9	1	4,0)
No GOR	7	2,9	6	2,5

Table 7,5 Mean $\bar{t}$ and SD of OTT (in seconds) in patients with neither reflux nor oesophagitis, either, or both, and numbers of patients (n).

	Age range 0-4mo			4-12mo			1 - 4y			4 - 8y			8 - 16y		
	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD
Both GOR and oesophagitis absent	56	2,9	1,0	43	3,1	1,0	33	3,6	1,1	23	4,5	2,1	13	4,4	1,3
Only GOR present	72	3,3	1,4	23	3,9	1,3	34	3,8	1,1	26	4,6	2,2	16	5,6	2,5
Both GOR and oesophagitis present	3	5,6	0,7	9	6,3	2,4	1	6,0		4	10,6	2,8			

Table 7,6 Agreement and disagreement of nuclear medicine (NM) and Xray studies for the detection of GOR in 249 patients.

Age range		0-1mo	1-4mo	4-12mo	1-4y	4-8y	8-16y
Agreement:	GOR present	9	8	14	4	8	5
Agreement:	GOR absent	11	9	11	9	8	6
Disagreement:	GOR present only with NM	21	27	15	14	16	7
Disagreement:	GOR observed as more severe with NM	3	9	6	4	12	6
Disagreement:	GOR seen only with Xrays	1	2	1	2	1	0

Table 7,7 The relationship between severity of GOR in nuclear medicine (NM) and Xray studies and of oesophagitis in 24 patients.

Degree of GOR		Degree of oesophagitis 2	3
Scintigraphy	Radiology		
Severe	Severe	1	7
Severe	Absent	4	10
Moderate	Absent	1	1

Table 7,8 Times of occurrence of first and last GOR in 233 infants and 232 children aged 1 to 16 years are given with numbers of patients in each category.

	Time (min) after ingestion of feed						
	0-2,9	3-5,9	6-9,9	10-14,9	15-19,9	20-24,9	25-30
First GOR (Age below 1y)	93	61	31	22	12	7	5
First GOR (Age 1-16y)	102	54	28	24	9	6	6
Last GOR (Age below 1y)	18	9	25	32	33	31	85
Last GOR (Age 1-16y)	14	16	11	33	35	40	83

Table 7,9 As for Table 7,8 but for 37 neonates (27 term and 10 preterm) aged under 30 days.

	Time (min) after ingestion of feed						
	0-2,9	3-5,9	6-9,9	10-14,9	15-19,9	20-24,9	25-30
First GOR (term)	11	8	4	1	3		
First GOR (preterm)	5	2	1	1	1		
Last GOR (term)	2	2	1	4	6	8	4
Last GOR (preterm)	1		1		4	1	3

Table 7,10 Numbers of episodes of GOR in 233 infants (745 GOR) and 232 children (867 GOR) aged 1 to 16 years are listed with patient numbers in each category.

	Time (min) after ingestion of feed						
	0-2,9	3-5,9	6-9,9	10-14,9	15-19,9	20-24,9	25-30
No of observed GOR (Age below 1y)	95	117	135	131	99	93	75
No of observed GOR (Age 1-16y)	141	142	129	145	118	97	95

Table 7,11 As for Table 7,10 but for 37 neonates (27 term and 10 preterm) aged under 30 days.

	Time (min) after ingestion of feed						
	0-2,9	3-5,9	6-9,9	10-14,9	15-19,9	20-24,9	25-30
No of observed GOR (term)	16	16	14	17	13	14	6
No of observed GOR (preterm)	6	4	8	6	10	6	4

Table 7,12 Mean durations of GOR ($\bar{t}$) in terms of patient numbers (n), ages and maximum height of GOR: $\bar{t}$ is in seconds.

	Age range											
	0 - 1y			1 - 4y			4 - 8y			8 - 16y		
	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD	n	$\bar{t}$	SD
Maximum height of GOR												
Buccal	152	135	294	19	253	285	27	469	678	5	1264	130
Cervical	124	93,4	84,9	35	76,6	110	72	98,8	178	34	135	356
Thoracic	128	43,7	34,0	40	21,2	20,2	43	31,4	40,8	9	355	289

Table 7,13 As Table 7,12 but for 100 GOR in 27 term neonates and 44 GOR in 10 preterm neonates

Maximum height of observed GOR	Term			Preterm		
	n	$\bar{t}$	SD	n	$\bar{t}$	SD
Buccal	43	61,6	98,6	9	233	588
Cervical	22	115	370	24	30,2	19,8
Thoracic	35	124	419	11	87,7	103

Table 7,14 Mean gastric contents (%) at 30 and 120 minutes after ingestion of liquid in terms of maximum height of observed GOR, patient's age and numbers (n).

	Age range											
	0 - 1 year						1 - 16 years					
	Time after ingestion of gastric contents measurement											
	30 min			120 min			30 min			120 min		
Maximum height of observed GOR	n	%	SD	n	%	SD	n	%	SD	n	%	SD
Buccal	70	73,2	15,4	66	37,1	18,9	25	75,5	9,8	25	31,5	20,2
Cervical	58	73,5	13,0	58	41,8	19,4	54	71,2	13,6	55	26,1	21,5
Thoracic	42	74,5	14,6	39	31,9	21,0	32	60,1	16,0	32	27,6	25,0
No GOR	132	73,7	11,4	131	37,3	16,5	64	60,2	13,5	64	20,1	17,0

Table 7,15 As Table 7,14 but for 30 term and 14 preterm neonates aged below 30 days

	Term						Preterm					
	Time after ingestion, for measurement of gastric content											
	30 min			120 min			30 min			120 min		
Maximum height of observed GOR	n	%	SD	n	%	SD	n	%	SD	n	%	SD
GOR present	21	66,8	18,6	21	41,3	22,1	10	55,7	16,9	10	19,5	23,3
(Buccal	15	63,6	20,3	15	29,0	19,9	2	42,5		2	3,0)	
(Cervical	2	74,5		2	46,5		5	65,8		5	29,8)	
(Thoracic	4	74,8		4	42,5		2	43,5		2	7,5)	
No GOR	9	64,0	22,9	9	26,0	13,1	5	62,8		5	18,0	

Table 7,16 Mean gastric contents (%) measured at 30 and 120 minutes after ingestion of liquid in terms of ages, numbers (n) and time of onset of last GOR.

		Time of onset of last GOR after ingestion (min)											
		0 - 9,9			10 - 19,9			20 - 30			No GOR		
Age range	%	n	%	SD	n	%	SD	n	%	SD	n	%	SD
0-1y	(After 30 min	60	72,2	11,2	56	73,4	15,3	65	73,4	15,1	115	73,1	11,5
	(After 120 min	57	38,2	23,1	56	36,4	17,8	64	40,9	21,8	107	37,8	16,7
1-16y	(After 30 min	31	68,6	12,7	27	71,9	13,5	48	69,6	13,2	64	60,2	13,5
	(After 120 min	31	21,8	21,0	31	30,1	19,5	51	32,4	23,2	64	20,1	17,0

Table 7,17 As Table 7,16 but for 27 term and 13 preterm neonates aged under 1 month.

		Time of onset of last GOR after ingestion (min)							
		0 - 9,9		10-19,9		20-29,9		No GOR	
	%	n	%	n	%	n	%	n	%
Term	(After 30 min	5	73,4	6	64,4	8	59,5	9	64,0
	(After 120 min	5	38,5	6	33,3	8	24,5	9	26,0
Preterm	(After 30 min	1	24	3	58,7	4	65,0	5	62,8
	(After 120 min	1	0	3	16,0	4	30,5	5	18,0

Table 7,18 Mean gastric contents (%) for 60 term and 28 preterm infants aged up to 3 months in terms of the liquid swallowed, age, time after swallowing and numbers (n).

Age range		0 - 1 month						1 - 3 months					
		Time after swallowing											
Term or preterm	Liquid	30 min			120 min			30 min			120 min		
		n	%	SD	n	%	SD	n	%	SD	n	%	SD
Term	Maternal milk	11	59,5	17,0	11	18,4	12,1	2	71,5		2	25,0	
	50% maternal 50% formula	1	71		1	41		2	59,5		2	44,0	
	Formula	23	66,8	16,3	23	31,5	20,1	21	72,9	13,7	20	36,3	19,7
Preterm	Maternal milk	5	60,2	27,8	5	27,8							
	50% maternal 50% formula							3	64,0		3	39,3	
	Formula	6	61,7		6	19,5		14	72,7	13,5	14	38,9	16,4

Table 7,19 Indications for 242 studies in 189 patients performed at the Children's Hospital.

Age range	0-1mo	1-4mo	4-12mo	1-4y	4-8y	8-16y	0-16y
Indication							
Chronic respiratory problems	1	18	80	49	3	1	152
Excess vomiting	3	17	22	12	2	1	57
Cyanotic episodes	1	4	9				14
Failure to thrive		1	4	3			8
Oesophageal atresia	1	2	1	1			5
Dysphagia	1		1	2			4
Oesophagitis				1		1	2
TOTAL	7	42	117	68	5	3	242

Table 7,20 Site of aspiration in 25 studies showing pulmonary contamination by Tc-99m sulphur colloid.

	Apex	Mid zone	Lower zone	Totals
Right lung field	8	4	2	14
Left lung field	6	2	3	11
TOTALS	14	6	5	25

Table 7,21 Results of scintigraphy in 32 patients at the Children's Hospital observed to have oesophageal spasm. Sex, age, range of OTT, number and maximum height of GOR (T denotes thoracic level attained, C denotes cervical and B buccal), percentages of gastric contents remaining after 30 and 120 min and indications are given. The latter are repeated respiratory problems (R), repeated pneumonia (P), excess vomiting (V), failure to thrive (F), dysphagia (D), cyanotic episodes (C), hiatal hernia (HH) and oesophagitis (O).

Patient number and sex	Age	OTT or range of OTT (s)	No of GOR	Maximum GOR height	Gastric % 30 min/120 min	Indication
1 F	1mo 21d	8	3	B	74/51	C
2 F	2mo 15d	7 to 11	8	B	53/2	P,HH
3 M	3mo 3d	12,5	14	C	43/5	R
4 M	3mo 5d	9		Nil	66/45	P,V
5 F	3mo 9d	6,5 to 9	10	T	31/16	P,V
6 F	3mo 13d	10		Nil	41/14	R,V
7 M	5mo 4d	8 to 18	6	B	15/4	P
8 M	5mo 6d	10 to 12	4	B	10/5	P
9 F	5mo 15d	6 to 10	11	C	65/8	R
10 M	5mo 20d	2 to 16	2	T	81*/18	F,V
11 M	5mo 21d	4 to 9,5	8	C	72/12	R
12 M	6mo 12d	4 to 11	10	B	75/56	R
13 F	7mo 2d	2 to 13	7	C	69/62	R
14 F	7mo 27d	1,5 to 8	7	T	32/10	P
15 M	8mo 1d	12 to 16		Nil	60/8	D
16 M	8mo 16d	8		Nil	81/60	P
17 F	9mo 12d	7	8	B	61/47	R
18 M	10mo 5d	11	10	B	77/48	P
19 M	1y 1mo	9 to 22		Nil	54/22	F,P
20 M	1y 1mo	3,5 to 14	3	B	23/7	P
21 F	1y 2mo	7 to 10	10	C	12/9	P
22 M	1y 8mo	8 to 19	3	T	52/5	R
23 F	1y 8mo	17	4	B	66/42	R
24 M	2y 1mo	11	3	C	44/30	R
25 F	2y 2mo	6 to 15	3	C	28/8	V
26 F	2y 3mo	12 to 16		Nil	84/13	R
27 F	2y 5mo	4 to 12	continuous	B	87/28	R,O
28 M	2y 6mo	10 to 21	4	C	43/19	R
29 F	2y 8mo	15	6	T	53/38	R
30 M	2y 8mo	25	many		28/6	O
31 F	5y 4mo	30	8	T	75/34	R
32 F	8y 3mo	12,5 to 14	not done**		-	P

* Due to a technical problem this value may be overestimated.
** This patient, who had the Cornelia de Lange syndrome with mental retardation would not cooperate.

Table 7,22 As for Table 7,8 but using data from 80 infants of the Children's Hospital and from 44 patients aged 1-16y.

	Time (min) after ingestion of feed						
	0-2,9	3-5,9	6-9,9	10-14,9	15-19,9	20-24,9	25-30
First GOR (Age below 1y)	41	22	6	3	4	2	
First GOR (Age 1-16y)	19	13	6	3	1	1	1
Last GOR (Age below 1y)	2	5	3	6	7	9	48
Last GOR (Age 1-16y)		3	2	3	3	9	24

Table 7,23 As for Table 7,10 but with 500 GOR observed in 80 infants and 254 GOR seen in 44 patients aged 1-16y.

	Time (min) after ingestion of feed						
	0-2,9	3-5,9	6-9,9	10-14,9	15-19,9	20-24,9	25-30
No observed GOR (Age below 1y)	61	61	63	75	74	80	86
No observed GOR (Age 1-16y)	25	31	38	40	36	43	41

Table 7,24 Results of nuclear medicine (NM) and Xray studies performed at the Children's Hospital to detect GOR in 180 patients.

Age range:	0-1mo	1-4mo	4-12mo	1-4y	4-8y	8-16y
Agreement: GOR absent			4	4		
Agreement: GOR present (same severity)		9	33	14	2	
Disagreement: GOR detected only by NM	1	4	11	12		1
Disagreement: GOR more severe with NM		8	20	19	1	1
Disagreement: GOR more severe with Xrays		3	9	3		
Disagreement: GOR detected only with Xrays		4	11	7		

Table 7,25 Values of $t_{\frac{1}{2}}$ for gastric emptying of patients aged below 36 months from both institutions without and with GOR (designated by N or GOR respectively). Sex, numbers and mean ages are given. The 95% confidence limits are quoted. Liquids swallowed were not maternal milk but other liquids as described in the text.

Number	Sex	Mean age	$t_{\frac{1}{2}}$ (min)	Lower limit (min)	Upper Unit (min)	SD (min)	Result normal (N) or with GOR
81	M	7,5mo	70,8	62,2	79,3	8,7	N
52	F	7,9mo	76,2	65,3	87,0	11,1	N
133	M & F	7,7mo	72,7	66,0	79,5	6,9	N
78	M	8,2mo	60,1	53,8	66,4	6,9	GOR
66	F	8,1mo	65,1	57,6	72,7	7,7	GOR
144	M & F	8,2mo	62,3	57,5	67,1	4,9	GOR

Table 7,26 The efffect of cisapride on various observed quantities. (OTT(s) is mean OTT in seconds, GAST 30 and GAST 120 are gastric contents as % of swallowed amounts at 30 and 120 minutes after deglutition respectively and GOR height and GOR(s) are height and total observed duration of GOR in seconds during the 30 min following deglutition. B, C and T denote buccal, cervical and thoracic levels attained respectively). See text for more details. These results were obtained at the Children's Hospital.

No	Sex	Age	Before or after cisapride	OTT(s)	GAST 30	GAST 120	GOR height	GOR(s)	GOR height	GOR(s)
1	M	1mo25d	before	8,0	74	51	B	45	C	50
			after	7,0	40	1	B	15	C	45
2	F	2mo10d	before	2,8	60	19	T	70		
			after	6,3	76	28	T	20		
3[a]	M	2mo15d	before	3,8	42	23	B	150		
			after	3,5			C	60		
4	M	3mo11d	before	5,3	85	23	B	30	C	50
							T	50		
			after	5,3	17	12	B	80		
5	M	3mo11d	before	9,0	66	45		nil		
			after	12,5				nil		
6	M	3mo12d	before	5,8	41	21	B	240	C	10
							T	20		
			after	5,4	94	72	B	50	C	10
							T	30		
7	F	4mo13d	before	6,5	25	4		nil		
			after	7,0	25	1		nil		
8	M	4mo16d	before	6,0	63	20	C	60	T	60
			after	3,6	72	10	C	40	T	15
9[a]	F	4mo24d	before	4,5	37	7		nil		
			after	8,0		4		nil		
10	F	4mo28d	before	3,0	85	56	C	70	T	80
			after	1,0	55		C	40	T	40
11[a]	M	5mo17d	before	3,0	15	1	B	10	C	20
							T	70		
			after	6,0	56	1	B	20	C	120
							T	60		
12	M	5mo27d	after	4,5	48	1	T	20		

Table 7,26 (continued)

No	Sex	Age	Before or after cisapride	OTT(s)	GAST 30	GAST 120	GOR height	GOR(s)	GOR height	GOR(s)
13	F	6mo17d	before	4,3	71	37	C	10	T	30
			after	3,4	78	1	B	150	C	30
							T	110		
14[a]	M	6mo18d	before	1,9	65	38	T	15		
			after	1,3	76	3	T	45		
15[c]	F	6mo27d	before	3,5	86	49	T	80		
			after	4,7	93	84	C	20		
16	M	7mo18d	before	5,0	55	6	B	10	T	30
			after		63	9	T	40		
17	M	7mo23d	before	11,0	15	4	B	120	C	10
			after	8,0	31	14	T	30		
18[a]	M	8months	before	7,2	72	12	C	70	T	110
			after	5,0	39	5	T	60		
19	F	8mo4d	before	4,0	29	10	B	50	C	70
							T	90		
			after	4,4	55	30	B	40	C	80
							T	40		
20	M	8mo8d	before	4,5	57	24	T	240		
			after	3,5	93	53	T	240		
21	F	9mo16d	before	6,7	68	41	B	20	C	20
							T	60		
			after	5,4	57	14	C	30	T	70
22	F	10mo	before	4,0	44	2	T	100		
			after	7,0			T	30		
23	F	20mo17d	before	17,0	66	42	B	80	C	140
			after	6,6	67	1	C	80	T	400
24[b]	M	21mo20d	before	6,2	66	45	C	60	T	130
			after	2,0	92	86	T	40		
25[a]	F	41mo4d	before	5,0	83	57	T	60		
			after	2,2	83	46	C	20	T	60

a In the pre cisapride study only, pulmonary contamination was seen.

b Patient received cisapride at home, his compliance was uncertain.

c Pulmonary contamination was observed in the post cisapride study.

CHAPTER 8: DOSIMETRY: METHOD AND RESULTS

> ".....he is a foolish physician who cannot cure his patient's disease unless he cast him into another sickness...."
> Thomas More; Utopia, Book 1.

8.1 Dosimetric method

For diagnostic and therapeutic medicine all investigations and procedures must be considered in terms of their potential benefit weighed again any harmful effects. In a recent book describing radiopharmaceutical safety the calculated risk of a typical nuclear medicine examination can be put into perspective by the statement that it is as risky as an average journey of 5 000 km in a modern car, 18 months' work in a typical factory, or one month's work in a modern coal mine (Roedler 1984). Or, expressed as the calculated loss of life expectancy due to a typical nuclear medicine investigation, the patient can expect to live 4 hours less, disregarding any benefit arising from the test. Other common human activities in the Federal Republic of Germany cause far greater diminution of life span e.g. motor vehicle accidents for pedestrians 37 days, for those in the vehicles 207 days, and a 30% excess in body mass 1300 days (Roedler 1986).

For our gastro oesophageal studies, as for virtually all nuclear medicine investigations, the resulting radiation dose is its most noxious effect and so must be carefully evaluated. This can present difficulties (Wooten 1983) and errors if preexisting computer packages are used (Pan et al 1985) and so the calculations described in this work have all been done directly so avoiding these existing errors.

8.1.1 Dosimetric calculations

The theoretical basis of all dosimetric calculations is simple, but resulting calculations are often very complex

(Robertson 1982). An activity, a_1 mCi, is located uniformly in region 1, occupied by an organ of mass m, and we wish to consider its effect on tissue in region 2. The fraction of radiation that is emitted by the source organ and absorbed in region 2 is P_{1to2} and E is the equilibrium dose constant which relates activity in region 1 to dose. The resulting absorbed dose rate in region 2 is d_{1to2}. Thus we have an equation:

$$d_{1to2} = (a_1/m).E.P_{1to2} \quad \text{.....(Eqn 8,1)}$$

These five quantities have units of (rads/hour), mCi, g, (g.rad/mCi.hour) and pure number respectively. If the volume of region 1 is considered the sum of n elements (i = 1,n) and the cumulative activity A_1 results from a time integral of the sum of all the a_i, then:

$$\bar{D}_{1to2} = (A_1/m)\Sigma_i(E_i\ P_{i(1to2)} \quad \text{.....(Eqn 8,2)}$$

The most difficult part of the calculation is usually the determination of cumulated activity (Robertson 1982). A double integration is also needed to derive $\bar{D}$ if the source and target volumes are defined. For ease in calculating $\bar{D}$, the mean absorbed dose rate due to the n elements, it is usual to rewrite the relation:

$$\bar{D}_{1to2} = S_{1to2}.A_1 \quad \text{.....(Eqn 8,3)}$$

This term "S_{1to2}" is written as S below and called the S factor for a source region 1 to a target region 2. Its units are (rad/mCi.hour), while those of $\bar{D}$ and A are rad and mCi.hour. Calculations of S for adults are available for a variety of pairs of organs. These values permit the radiation doses in various regions to be deduced, once the time variation of radioactivity in the source organ is known.

Early calculations for gastro intestinal dosimetry (Eve 1966) used a bolus model but recent work has used a modified bolus model which includes an integral assuming exponential emptying of various parts of the gut (Siegel et al 1983, Wright et al 1981). However this method gives errors quoted by the authors as ranging up to 20%. This was considered, "acceptable compared with doses calculated without considering biological variability, which results in errors of as much as 100 to 200%" (Wright et al 1981).

Physical decay of the isotope is also taken into account. Other reasonable assumptions in this calculation of the dose resulting from swallowed Tc-99m sulphur colloid are that there is no unlabelled activity nor renal clearance, all the activity reaches the stomach immediately on being swallowed and appropriate biological half lives for transit of Tc-99m sulphur colloid in water through stomach, small gut, proximal and distal large gut, obtained from measurements made in 20 normal adults, are used. These half lives are 23 and 168 min, 10 and 17 hours respectively (Siegel et al 1983). Resulting doses are shown in Table 8,1.

8.1.2 Paediatric gastro intestinal dosimetry

Although the figures of Table 8,1 give a useful indication of various adult radiation burdens, they are not directly related to such doses for the smallest paediatric patients. Attempts to obtain S values suitable for paediatric use at different ages have used three different techniques (Roedler 1981). Firstly the standard adult phantom has been subjected to an appropriate geometrical similarity transformation. Next

paediatric phantoms have been constructed and finally the known inter organ relations of paediatric bodies have been used to allow direct calculations of S values. The last approach is used in the NRCP report No 73 (Anon 1983a) where complete tables of S values are given for various ages. These tables have been used for some of the dosimetric calculations done in this work. There are, however, discrepancies (Table 8,2) between the three sets of relevant S values listed in papers describing a standard newborn model (Dirksen et al 1980), in a recently completed detailed table (Stabin 1987) and the NRCP report (Anon 1983a). When the radiotracer is located in a neonate's stomach, the S values which allow calculation of thyroid dose are seen to vary by a factor of 3,2 and for activity located in the upper large intestine irradiating the ovaries, the comparable discrepancy is a factor of 5 (Table 8,2). A further problem in dealing with paediatric dosimetry has been clearly described. It is the variation in the metabolic behaviour of the radionuclide as a function of age. This can cause large uncertainties. For example "the gastrointestinal absorption may be uncertain by a factor of 100" (Henrichs et al 1982). An attempt has been described to allow for varying absorption of GIT contents at different paediatric ages. Both the sloughing of GIT epithelial cells and diffusion into the blood stream were considered as sinks for absorbed swallowed radionuclide (Crawford-Brown 1983). However this problem is not of great concern in the present studies because the colloid is firmly bound to the Tc-99m and in this work there was no observed background to suggest significant absorbed activity in the blood, nor are there other reports to that effect.

8.1.3 Xray and scintigraphic dosimetry

The values of doses from Xrays in Table 8,1 were obtained with LiF:Mg:Ti thermoluminescent dosimeters taped to the testes and skin in the region of the iliac crest. The results for ovaries have an uncertainty factor of 2 mainly due to variation in anatomical position. The doses quoted are a "weighted hospital mean", obtained by averaging results from two hospitals. One uses under and the other over couch tubes. This made little difference to the female gonadal irradiation, but for males there was about a factor of 10 difference and the relevant figures were 0,0036 and 0,032 rads respectively (Tole 1984).

It is not possible to make a detailed comparison between the doses resulting from scintigraphy and Xrays except to note the latter are nearly an order of magnitude greater. However in certain specific studies, not resulting from swallowed non absorbed radionuclide, one report finds, comparing homologous studies, Xray radiation entrance tissue doses larger than radionuclide critical organ dose for a typical 5 year old child (Bushong et al 1978).

There is considerable variability in radiation exposure during Xray fluoroscopic studies as has been described in a recent, extensive report from Manchester, U K, considering over 6 500 studies mainly in adults. Mean radiation exposures resulting from seven different radiologists using given apparatus for the same examinations varied by up to a factor of 2,5. When four of these radiologists used different apparatus, "designed for remote control use, with an undercouch

intensifier", for the same studies, mean radiation exposures were reduced by a factor greater than 2 (Rowley et al 1987). In contrast for a given dose of radiopharmaceutical, for scintigraphy, there are not usually such large variations in absorbed dose, since absorbed dose depends on physiological processes and neither on operator technique nor apparatus.

The irradiation mechanisms of the applied Tc-99m and Xrays for gonads are very different. For the Xray dose to ovaries there are varying proportions of direct and scattered radiation but for testes virtually only scattered radiation. For swallowed radionuclides the radiation, dose depends only on the uptake and source to target organ geometry as described above.

8.1.4 Relevant previous work

Using these principles it is clear that the principal target organ is in, or close to, the GIT and various estimates for its dose in paediatric patients have been made. The difficulty in extrapolating adult to paediatric radiation dose results from the variation in relative organ size and position, the necessity or not of a geometric mean correction (Hardy et al 1985a) and the different biological half lives clearly recognised throughout the range of paediatric ages (Henrichs et al 1982). In the present case where paediatric dosimetry is being investigated, transit through the gut is usually faster in smaller children. Also interorgan distances are smaller, as are organ sizes. But none of these are in direct proportion to age, or to each other. This is clearly demonstrated by considering whole body radiation doses after administration of Tc-99m sulphur colloid by injection (Table 8,3). A few

estimations of dose to various organs have been made for paediatric patients who swallowed Tc-99m sulphur colloid. These are grouped in Tables 8,4 and 8,5.

Although there is much uncertainty in the calculations providing the doses of Table 8,4 it is clear that they are significantly less than those resulting from Xray studies (Tole 1984, Harbert et al 1984), especially for CT and barium studies in neonates (Robinson et al 1983). When older children having CT scans are similarly considered, the dose is also very high, ranging between 1,6 $\pm$ 0,4 and 3,8 $\pm$ 0,3 rads in a recent report (Fearon et al 1985). The barium study also irradiates greatly. A total mean dose of 14,3 rads for data from ten British hospitals (ranging from 5,1 to 26,8 rads) has been reported (Harrison et al 1983). In contrast a recently described low exposure fluoroscopy technique used for children can reduce this significantly, (to about 52 mrad) (Wesenberg et al 1984) although the whole question of accurate dosimetry for fluoroscopy has recently been questioned (Tole 1985).

An attempt has been made to improve the understanding of dosimetry in paediatric nuclear medicine by constructing standard models for different ages. Organs are assumed to be constructed of appropriate numbers of cubes of side 10 mm; for example in a newborn liver the left lobe is made up of 6x4x2 such cubes and the liver right lobe 4x4x5, the bladder 2x2x3 cubes, with the sequence of dimensions lateral x sagittal x longitudinal (Dirksen et al 1980). For those organs with one or more dimensions less than 10 mm (e.g. ovaries, testes and thyroid) or with non cuboid shapes (e.g. brain, lung, adrenals,

gut and spleen) volume elements having dimensions less than 10 mm were included. Relative spacings derived from anatomical investigations are also assumed. Organ tissue is presumed to have unit density, except for bone and lung tissue with densities 1,5 and 0,3 g/mℓ respectively (Dirksen et al 1980). Radionuclide is assumed uniformly distributed within an organ when appropriate. Intra and interorgan deposited dose calculations are made from element of source organ to element of target using the S factor approach described above.

Work using this technique is still in its early stages and few such relevant results have been produced so far, hence the much more complete NRCP report No 73 (Anon 1983a) is used in the present work. The S factor values for small gut contents (source) and liver (target) are $2,82 \times 10^{-5}$ and $1,80 \times 10^{-6}$ for standard new born and standard adult respectively (Dirksen et al 1980). In contrast to this difference of more than a factor of 15, when upper large intestine contents are the source and the ovaries the target, $S = 2,92 \times 10^{-5}$ (neonate) and $1,2 \times 10^{-5}$ (adult), hence they differ by less than a factor of 3. (All these S values are in rads/microCi.hour). Extrapolation from adult to paediatric patients is therefore very difficult and further complicated by the variations in relative organ size with age (Table 8,6).

The relative size of some organs monotonically decreases with age, notably the brain, others such as ovaries increase, the testes show both trends and the lung's relative mass effectively does not change with age. These variations, both relative and absolute, indicate that paediatric scintigraphic

dosimetry is not a straightforward matter. Several publications dealing with paediatric GIT nuclear medicine, including a comprehensive review of nuclear medicine in paediatric GIT problems (Sty et al 1982), have made no mention of dosimetry (Baulieu et al 1984, Rosen et al 1984).

Apart from the first three reports of calculated radiation dose of paediatric gastro intestinal studies after swallowing Tc colloid (Heyman et al 1979, Rudd et al 1979, Savage 1984), there were no such reports (Table 8,4) until that of Castronovo (Castronovo 1986) given in Table 8,5. This previous work has used either a bolus model (Eve 1966) or a modified bolus model (Siegel et al 1983, Behar et al 1978) with exponential emptying of each compartment. From the figures in Table 8,1 it is clear that the large gut is the critical target organ and not the small gut (Heyman et al 1979, Rudd et al 1979) nor stomach (Savage 1984) as many have assumed. Although the physical activity in the large gut is reduced in comparison to that within the stomach and small intestine because of the natural decay of Tc-99m, there is a much longer transit time.

To overcome all these deficiencies, calculations were made as described in the next section using a continuous transport model which assumed exponential emptying of four components of the GIT (stomach, small gut, upper and lower large intestine). The other assumptions mentioned above were also included (Siegel et al 1983). The problems of rate of transfer of radioactivity into and out of the organ which exist for other systems such as the urinary tract, have also been raised (Bice et al 1986), but not solved. The present approach can be used.

The question of assigning effective biological half lives for Tc-99m in the various parts of the GIT is not easy. Correspondence with leaders of different groups working in this field (Professors J Keriakes, J Siegel and H Roedler) has confirmed that no such data exists for children. The procedure therefore followed in this work, as a means to rectify this lack, is described as below. For normal adults the situation is little better. Various estimates have been published, almost entirely in the last two years, and there are considerable differences in quoted values (Table 8,7). This of course reflects the natural variation of individual gut function, fed or fasting state (Kaus et al 1984a), diet etc. Works on gut physiology quote mouth to anus times in normal adults as being in the ranges 40-70h for European and about 35h for high fibre diet (Bell et al 1980), 6,5-98h (Sanford 1982) and finally varying between 3-4h and 3-4 days (Bockhus 1976). It is necessary to consider mean values for transit times of various organs, because rates of travel measured over periods of 30s can vary by a factor of nine (Kaus et al 1984a). The few specific mean measurements which have been published show much less variation, but they employ different mathematical quantities, described as biological and effective half lives, residence and mean transit times. The relations between all these concepts are outlined in Appendix 1 and they have enabled the data of Table 8,7 to be compiled in terms of a single quantity, the effective half life (t_e). Two of the times in Table 8,7 for movement through the upper large gut (Hardy et al 1985b, Davis et al 1986b) were in fact derived from observations made on a radiolabelled capsule. The reason they are included in a table concerned with transits of liquid in

the GIT is because the same authors have shown that in general an observed radiolabelled osmotic tablet travels at the same speed as the surrounding liquid (Wilson et al 1985). Its path can be demonstrated in a striking manner using modern computer graphics (Kaus et al 1986).

Because of the dearth of standard data, an estimate of t_e has been made for infants aged zero or one year using measurements of stomach contents obtained 30 and 120 minutes after swallowing. This is described below.

8.1.5 The present dosimetric model

A new mathematical model was derived which assumed the GIT consists of four compartments in series, the stomach, small gut, upper and lower large intestines (Eve 1966).

The present dosimetry calculation served two purposes.

(i) An attempt to provide detailed dosimetry for paediatric patients allowing for source organs to be all parts of the GIT

and (ii) Derivation of a method with increased accuracy compared with preexisting work, since the previous deduction of small gut as critical organ is being challenged.

The mechanism for the present model is simple. At time zero ($t = 0$), the stomach contains unit activity, designated $y_1(0)$. This activity decays with time t in the form, $y_1(t)$, where:

$$y_1(t) = \exp(-(a + p)t) \quad \text{---------- (Eqn 8,1)}$$

where a and p are time constants which represent removal of Tc-99m from the stomach by passage into the small gut and physical decay respectively. So far we presume removal from compartments by transit is exponential, the Tc-99m appears instantaneously in the stomach on deglutition, all Tc-99m is bound to colloid and there is no renal clearance. The first assumption is clearly closer to reality than a bolus model as the stomach mixes and gradually releases its contents and as shown by observations of distribution of activity in any of the GIT transit studies performed as part of this work. Similarly since the arrival of colloid at the distal end of each compartment is gradual, it is appropriate to use a continuous exponential model in the present calculation with suitable delays for the large gut. Details of the theory and parameters of exponential variations occurring in dosimetric calculation are given in Appendix 1.

Activity in the small intestine (y_2) is that arriving from the stomach less exponential displacement into the upper large gut, with decay constant b, and less physical decay, with decay constant p. The equation describing the time variation of y_2 is:

$$y_2 = (\exp(-at)-\exp(-bt)).\exp(-pt).a/(b-a) \quad \text{------(Eqn 8,2)}$$

and is derived as follows:

For the stomach's colloid contents (y_1), consider its change (dy_1) in time dt. An amount of colloid (ay_1dt) moves into the small gut and an amount (py_1dt) suffers radioactive decay. Hence:

$$dy_1 = -(ay_1 + py_1)dt$$

After integration and use of the initial conditions ($y_1 = 1$ when $t = 0$), the well known solution is Eqn 8,1.

Now the change in small gut contents (dy_2) in time dt is evaluated. An amount (ay_1dt) arrives from the stomach. Losses to the large gut and to physical decay are (by_2dt) and (py_2dt) respectively. Thus:

$$dy_2 = (ay_1 - by_2 - py_2)dt$$

or using Eqn 8,1:

$$dy_2 = (a \exp(-(a+p)t) - by_2 - py_2)dt$$

This can be rewritten as:

$$(dy_2/dt) + (b+p)y_2 = a \exp(-(a+p)t)$$

and is recognised as a linear first order differential equation (Piaggio 1949). The integrating factor is $\exp((b+p)t)$. Thus the above equation becomes:

$$(d/dt).(y_2.\exp((b+p)t) = a \exp(-(a+p)t).\exp((b+p)t)$$

After integration with respect to time t:

$$y_2 \exp((b+p)t) = (a/(b-a)).\exp((b-a)t)+K$$

The initial conditions are $t = 0 = y_2$, hence the constant of integration $K = -(a/(b-a))$. So the equation for y_2 becomes

$$y_2 = (a/(b-a)).(\exp(-(a+p)t)-\exp(-(b+p)t)$$
$$= (\exp(-at)-\exp(-bt)).\exp(-pt).a/(b-a)$$

which is Eqn 8,2.

In a similar fashion the equations describing activity in upper and lower large gut are derived. The decay constants for transit from the upper large and lower large intestine are c and d respectively. Appropriate delays, respectively D and E, are included to allow for initial entry. The equation for activity $y_3(t)$ in the upper large gut is:

$$y_3 = ab.\exp(-pt').(\exp(-at')./(a-b)(a-c) + \exp(-bt')./(b-c)(b-a) + \exp(-ct')./(c-a)(c-b)) \quad \text{-----(Eqn 8,3)}$$

where ($t' = t + D$). The activity $y_4(t)$ in the final compartment is given by:

$$y_4 = ab.\exp(-pt^*).(-\exp(-at^*).c/(a-b)(a-c)(a-d) - \exp(-bt^*).c/(b-c)(b-d)(b-a) - \exp(-ct^*).d/(c-d)(c-a)(c-b) - \exp(-dt^*).d/(d-a)(d-b)(d-c)) \quad \text{(Eqn 8,4)}$$

where ($t^* = t + E$). Derivations follow that of Eqn 8,2, to obtain the differential equations, but are much too long and cumbersome to be included here. However an alternative elegant solution recently given, treats it as an eigenvalue problem and uses matrix manipulation (Gonin 1985) of the differential equations, but it is equally inappropriate to include details here. The functions forming the solutions are plotted against time in Figs 8,1 to 8,6 and the resulting integrals were obtained by a numerical routine. These integrals are used to obtain accumulated activity and hence the radiation dose after forming a product with the S factor.

8.2 Dosimetric results

Mean values of effective half lives for swallowed liquids in various parts of the gut are given in Table 8,7. These are derived from the literature for adults and as explained no such data exists for children. The most recent approach to this problem has calculated a single cumulative activity (activity.time product) for all paediatric ages from 0 to 15y and combined this with different "S" values for different paediatric ages (Castronovo 1986).

A procedure to calculate residence times at different ages was devised which depended on the following assumptions. Gut residence time is proportional to gut length in vivo (Kaus et al 1984a). Cadaveric gut length is proportional to length in vivo and there is no significant difference between gut length of the two sexes. If gut length is plotted against age the relation is a smooth curve which permits interpolation. At the age 18 y gut lengths are those of adulthood and do not change with increasing age (Underhill 1955). Since there was little difference in mean cadaveric small and large gut lengths of 38 infants aged 6 to 12 mo (432,8 and 70,2 cm) and 26 children aged 12 to 24 mo (453,5 and 75,0 cm) respectively (Robbin 1920) an average of all this data can give gut lengths for children aged 12 mo. For 25 infants aged 0 to 6 mo the same author found small and large gut lengths of 303,7 and 50,7 cm (Robbin 1920). Thus our averaging is reasonable for these age groups. The residence times in upper and lower large gut are in the proportion 57:100. This ratio is derived from the means quoted in Table 8,7 and is presumed to hold for all ages. Again since the terms upper and lower large gut, are not clearly defined by those who introduced and also subsequently used the concept, the current proportion is justified. Delay before a segment of gut begins to be filled in this, or any other, model obviously depends on the length of gut proximal to the segment in question, so we assume that the delays, chosen as 2 and 4h for adults' upper and lower large gut, are proportional to the adjacent proximal segment lengths. Some of the above assumptions are derived from the literature and in these cases a reference is given.

All authors who describe gut length emphasise the extreme absolute variability of the normal intestine's length for a "characteristic 100% variation in length of the intestine is in evidence at birth as at all later periods of life" (Bryant 1924). This variation of gut length

relative to body length is also well described, for the large gut length lay between 80 and 130% of body length in 91,3% of 185 infants and the small gut length was between 500 and 900% of body length in 79,9% of small childrens' cadavers measured by the same author (Robbin 1920). The assumptions made above, reasonable it is felt in their own right, are further justified by observed natural variation. Values of small and large gut length obtained from the literature are given in Table 8,8 together with interpolated values and resulting half lives.

As described in chapter 2 gastric emptying function differs significantly from the transit of liquid in the small and large gut. Hence the premises resulting in Table 8,8 cannot be used to describe the stomach's emptying at different ages. Available data for liquids swallowed by adults give gastric $t_{\frac{1}{2}}$ as 41,5 min (Table 8,7). Comparable data for infants obtained from this work and described in chapter 7 gives a mean $t_{\frac{1}{2}}$ of 65,8 min for stomach emptying of liquid by infants. Thus we use an interpolation between these two values which is asymptotic for the infant and adult $t_{\frac{1}{2}}$ to obtain values of $t_{\frac{1}{2}}$ at different ages (Table 8,9). The age associated with the infant $t_{\frac{1}{2}}$ derived in this work is 1,5y. This is the mean age of those whose values of GAST 30 and GAST 120 contributed to the final result. As mentioned above this is justified because of the lack of variation of gastric emptying rates with age up to 3 years. Hence values for gastric $t_{\frac{1}{2}}$ at ages 0 and 1 years are taken to be the same. Again, to deflect any criticism of this method, we note the variation of values in normals of gastric contents of liquid at 30 and 120 min after swallowing is so great that neither this nor any other interpolative method can be unambiguously championed. The obvious extension of this work to other situations where the passage of a radiopharmaceutical from one system or organ to another has been considered. Calculations have already been made of dose in paediatric

patients who receive kidney and urinary tract studies using Tc-99m DMSA and Tc-99m DTPA (Wynchank 1985).

The cumulated activity time products described above which are used to calculate the doses deposited in various organs after swallowing Tc-99m sulphur colloid are listed in Table 8,10. They result from integrations which in effect correspond to normalised areas under curves given in Figures 8,1 to 8,6. The algebraic expressions representing swallowed activity in four compartments of the GIT and their derivations from first principles are given above.

The results of calculations to derive the dose deposited in various organs from swallowed Tc-99m sulphur colloid using the model described in this work are given in Tables 8,11 and 8,12. The calculations assume that 0,1 mCi of radiopharmaceutical were swallowed. S values from two different sources, those of the NCRP report number 73 (Anon 1983a) and Stabin's unpublished compilation (Stabin 1987) are used respectively in deriving the two tables. The latter are derived from the paediatric phantoms of Cristy and Eckerman of Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA, but no details have yet been published (Stabin 1987).

Table 8,1 Radiation doses (rad) for normal adults to various organs and regions resulting from calculations which assume the swallowing of 1mCi of Tc-99m sulphur colloid in water. The last row results from dosimetry measurements made after barium meal examinations. Further details are given in the text.

Stomach	Small gut	Proximal large gut	Distal large gut	Ovaries	Testes	Whole body	Reference
0,094	0,28	0,54	0,32	0,096	0,0068	0,0168	(Siegel et al 1983)
0,140	0,26	0,40	0,38	0,092	0,0048	0,0174	(Wright et al 1981)
0,187	0,315	0,518	0,329	0,102	0,0029	0,0185	(Castronovo 1986)
		0,3				0,1	(Fisher et al 1982)
	0,3 (all GIT)					0,15	(Kjellen et al 1981)
						0,2	(Fisher et al 1976)
			0,4				(Blackwell et al 1983)
				0,29	0,017		(Tole 1984)

Table 8,2 Comparative values of "S", the absorbed dose per unit cumulated activity (rads/mCi.hour) for swallowed Tc-99m in the newborn. Further explanation is given in the text.

Source organ	Target organ	S values (Stabin 1987)	(Dirksen 1980)	(Anon 1983a)
Stomach contents	Thyroid	$2,84 \times 10^{-3}$	$6,66 \times 10^{-3}$	$2,05 \times 10^{-3}$
Small intestine contents	Liver		$2,83 \times 10^{-2}$	$2,51 \times 10^{-2}$
Upper large intestine contents	Ovaries	$7,60 \times 10^{-2}$	$2,92 \times 10^{-2}$	$1,48 \times 10^{-1}$

Table 8,3 Whole body dose (rad) in paediatric patients after injection of 0,5mCi Tc-99m sulphur colloid.

Age (years)	Neonate	1	5	10	15	Ref*
Whole body radiation dose	0,070	0,028	0,019	0,014	0,010	A
			0,02			B

* Ref A is (Sty et al 1983)
Ref B is (Savage 1984)

Table 8,4 Dose in rad deposited in various organs of paediatric patients after swallowing Tc-99m sulphur colloid. * These figures assume 5 mℓ of liquid containing 0,025 mCi of Tc-99m is aspirated and there is no subsequent clearance by ciliary function nor coughing.
** These values are for a child of 5 years. Ages corresponding to other doses are for paediatric patients of unspecified ages.

Swallowed dose (mCi)	Organ	Stomach	Small gut & prox colon	Gonads	Lungs	Whole body	Ref***
0,15-1		0,3-0,5		0,017-0,036	0,11-0,13*	0,033-0,065	C
0,5			0,25			0,063	D
1,0		0,27		0,015-0,020		0,04	E**

*** Ref C is (Heyman et al 1979)
Ref D is (Rudd et al 1979)
Ref E is (Savage 1984)

Table 8,5 As for Table 8,4 but using a swallowed dose of 0,1mCi of Tc-99m sulphur colloid and a bolus model, without intercompartmental transit, but including exponential decay. These results are taken from (Castronovo 1986) modified by (Castronovo 1987).
S values are used from (Stabin 1987).

Target organ	Age:	Doses in mrad/0,1mCi at different ages					
		0y	1y	5y	10y	15y	Adult
Stomach		383	93	50,7	30,8	22,1	18,7
Small gut		372	164	90,1	58,3	36,1	31,5
Upper LI		596	267	164	89,6	53,9	51,8
Lower LI		927	380	194	120	72,1	32,9
Ovaries		99,3	42,0	33,0	22,2	14,9	10,2
Testes		17,6	7,17	3,34	2,09	1,1	0,29
Thyroid		1,64	0,62	0,215	0,07	0,03	0,02
Whole body		20,0	10,7	6,33	4,07	2,68	1,85

Table 8,6 Masses of organs at different ages, expressed as % of body mass at different ages after (Kereiakes et al 1972) and (Spector 1956).

Age (years)	Neonate	1	5	10	15	Adult
Whole body (kg)	3,54	12,1	20,3	33,5	55,0	70,0
Organ as % of body mass						
Brain	9,9	7,8	6,1	3,9	2,5	2,0
Heart	0,56	0,39	0,43	0,42	0,38	0,43
Gut	4,1	3,3	2,7	2,5	2,5	2,4
Kidney	0,65	0,60	0,55	0,56	0,45	0,43
Liver	3,8	2,8	2,9	2,7	2,3	2,4
Lungs	1,5	1,4	1,4	1,6	1,3	1,4
Pancreas	0,079	0,12	0,11	0,090	0,12	0,11
Spleen	0,27	0,26	0,27	0,30	0,25	0,21
Stomach	0,18	0,22	0,28	0,27	0,22	0,23
Thyroid	0,042	0,018	0,023	0,024	0,020	0,023
Testes	0,019	0,012	0,0084	0,0060	0,033	0,040
Ovaries	0,0082	0,0083	0,0099	0,010	0,012	0,012

Table 8,7 Effective half lives (h) of swallowed liquids in various parts of the gut for normal adults. (* Liquid accompanied equal amounts of food. **This result used a ferromagnetic tracer and tea, with some chocolate pudding).

Region of the GIT				Reference
Stomach	Small intestine	Upper large intestine	Lower large intestine	
0,83				(Da Rocha et al 1986)
	2,1			(Davis et al 1986a)
	2,2			(Davis et al 1986b)
	2,3	8,3		(Hardy et al 1985c)
0,43*				(Moore et al 1985)
0,69	2,6	7,6	11,2	(Roedler 1985a)
0,69	2,8	9,0	16,6	(Roedler 1985b)
	3,0			(Wilson et al 1985)
		8,5		(Hardy et al 1985b)
0,75				(Hardy et al 1985a)
0,82				(Kaus et al 1984b)
0,95				(Kaus et al 1984a)
0,38	2,8	10,0	17,0	(Siegel et al 1983)
0,69	2,8	5,5	12,5	(Wright et al 1981)
0,82**				(Benmair et al 1977)
Mean 0,692	2,58	8,15	14,3	

Table 8,8 Gut lengths at different ages measured and interpolated with resulting gut segment half lives obtained as described in the text. (SI and LI denote small and large intestine. ULI and LLI denote upper and lower LI. * Interpolation).

Age (y)	No of subjects	Lengths (cm) SI	LI	Halflives (h) SI	ULI	LLI	Delays (h) ULI	LLI	Ref
0	35	302,6	51,9	1,52	2,73	4,82	1,09	2,37	(Robbin 1920)
1	64	441,2	72,2	2,21	3,80	6,70	1,58	2,87	(Robbin 1920)
5	*	530,2	119,5	2,45	6,32	11,1	1,90	3,10	This work
10	*	550,0	141,0	2,54	7,45	13,1	1,93	3,66	This work
15	*	556,0	152,4	2,57	8,06	14,1	1,99	3,96	This work
Adult	632	558,7	154,1	2,58	8,15	14,3	2,0	4,0	Table 8,7 and (Underhill 1955)

Table 8,9 Values of $t_{\frac{1}{2}}$ in minutes for stomach emptying at different ages obtained from interpolation between values obtained in this work for neonates and from published data for adults. See text for more details.

Age (y)	0	1	5	10	15	Adult
$t_{\frac{1}{2}}$ (min)	65,8	65,8	64,8	54,4	44,4	41,5

Table 8,10 (Activity.time) products in (uCi.h or microcuries.hours) resulting from numerical integrations of the curves of figures 8,1 to 8,6. It is assumed that 100 uCi of Tc-99m colloid was swallowed.

	(Activity.time) in (uCi.h)					
Age (y)	0	1	5	10	15	Adult
Region of GIT						
Stomach	134,0	133,9	132,2	113,8	95,16	89,64
SI	148,1	197,2	213,0	223,9	231,3	233,6
ULI	154,8	162,3	193,3	205,9	205,3	201,8
LLI	139,9	125,8	109,8	99,54	91,23	88,80

Table 8,11 Dose (mrad) deposited in various organs after swallowing 0,1mCi of Tc-99m sulphur colloid using the model described in the text and the S values of the NCRP report No 73 (Anon 1983a).

	Absorbed doses in mrad/0,1mCi		
Target organ	Age: 0y	1y	5y
Stomach	468	122	68,8
Small gut	266	153	82,8
Upper LI	428	180	119
Lower LI	508	157	66,5
Ovaries	55,6	31,8	20,5
Testes	11,2	4,64	1,75
Thyroid	0,357	0,115	0,101
Whole body	14,1	7,15	4,50
Adrenals	7,32	3,27	2,57
Bladder	22,2	16,7	6,82
Gall bladder	30,6	18,7	11,1
Heart	4,70	2,45	1,62
Kidneys	12,0	5,46	4,09
Liver	14,0	6,53	3,77
Lungs	4,38	1,67	0,924
Pancreas	10,6	10,2	5,84
Red marrow	16,6	8,78	6,17
Salivary glands	0,408	0,104	0,094
Skeleton	6,63	2,86	2,13
Skin	9,37	2,71	1,75
Spleen	17,3	1,89	4,30
Thymus	7,83	0,785	0,301
Uterus (non gravid)	51,2	29,9	18,8

Table 8,12 As for Table 8,11 but using the S values of Stabin (Stabin 1987).

Target organ	Age:	Absorbed doses in mrad/0,1mCi					
		0y	1y	5y	10y	15y	Adult
Stomach		289	98,5	51,0	27,2	16,7	15,8
Small gut		201	110	65,5	44,2	27,7	27,8
Upper LI		310	148	91,1	62,0	37,4	36,9
Lower LI		426	160	73,4	42,0	23,5	23,0
Ovaries		49,9	28,1	17,9	12,4	8,25	8,18
Testes		6,90	3,24	1,65	0,947	0,476	0,467
Thyroid		1,04	0,397	0,147	0,053	0,019	0,018
Whole body		11,2	6,02	3,92	2,61	1,58	1,57
Adrenals		8,48	4,91	3,08	1,90	1,13	
Bladder		16,5	9,26	5,70	3,73	2,29	
Brain		0,133	0,0354	0,0142	0,00491	0,00139	
Breast		3,31	1,42	0,788	0,383	0,166	
Kidneys		11,1	6,55	4,52	3,12	2,03	
Liver		13,9	7,45	4,59	2,77	1,42	
Lungs		4,07	2,13	1,16	0,637	0,356	
Muscle		8,02	4,28	2,59	1,71	1,09	
Pancreas		23,3	12,4	7,98	5,29	3,21	
Red marrow		6,34	4,88	4,25	3,57	2,72	
Skeleton		6,96	3,99	2,14	1,42	0,960	
Spleen		13,5	7,51	4,90	3,18	1,99	
Uterus (non gravid)		33,1	19,8	12,9	8,69	6,47	

Figures 8,1 to 8,6

These figures are of calculated GIT activity resulting from 1 unit of Tc-99m activity swallowed at time zero. The computation using the model derived in this work was for the 30 hours following deglutition. The six figures represent calculations made for patients aged 0, 1, 5, 10, 15 years and adults respectively. Results of the corresponding numerical integrations are given in Table 8,10 and further explanation is given in the text.

Fig 8,1

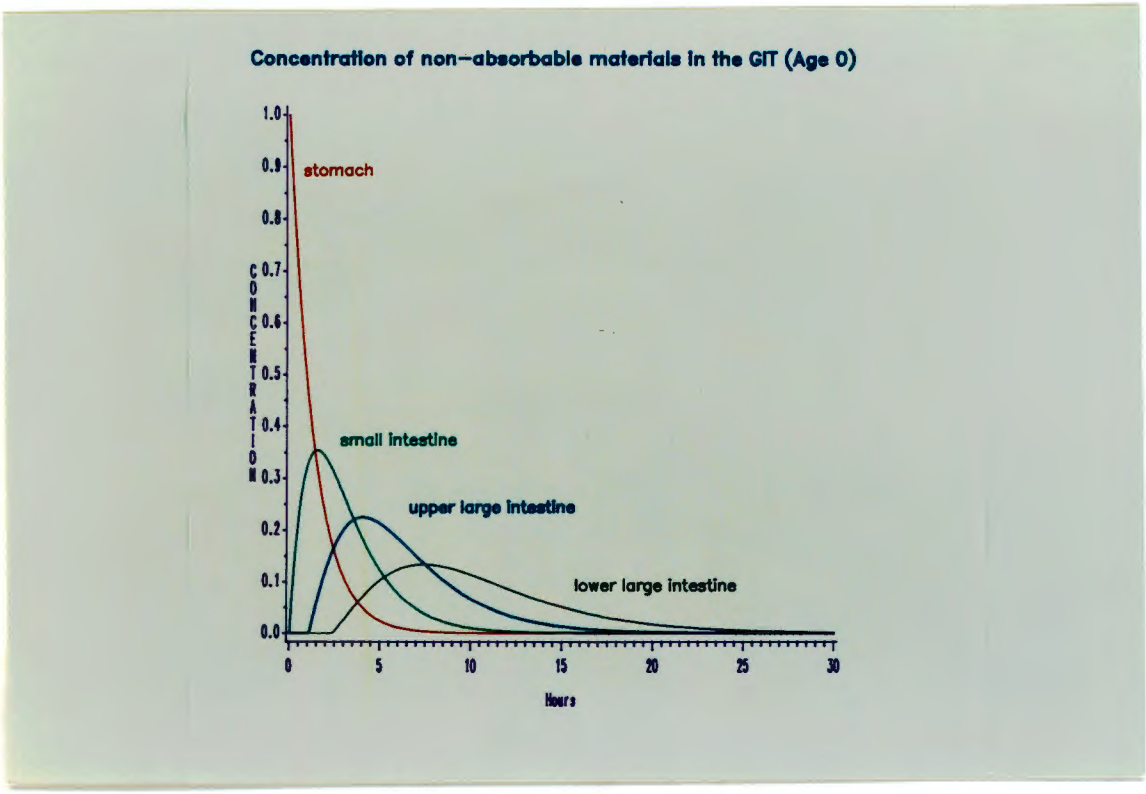

Concentration of non-absorbable materials in the GIT (Age 0)
stomach
small intestine
upper large intestine
lower large intestine
CONCENTRATION
Hours

Fig 8,2

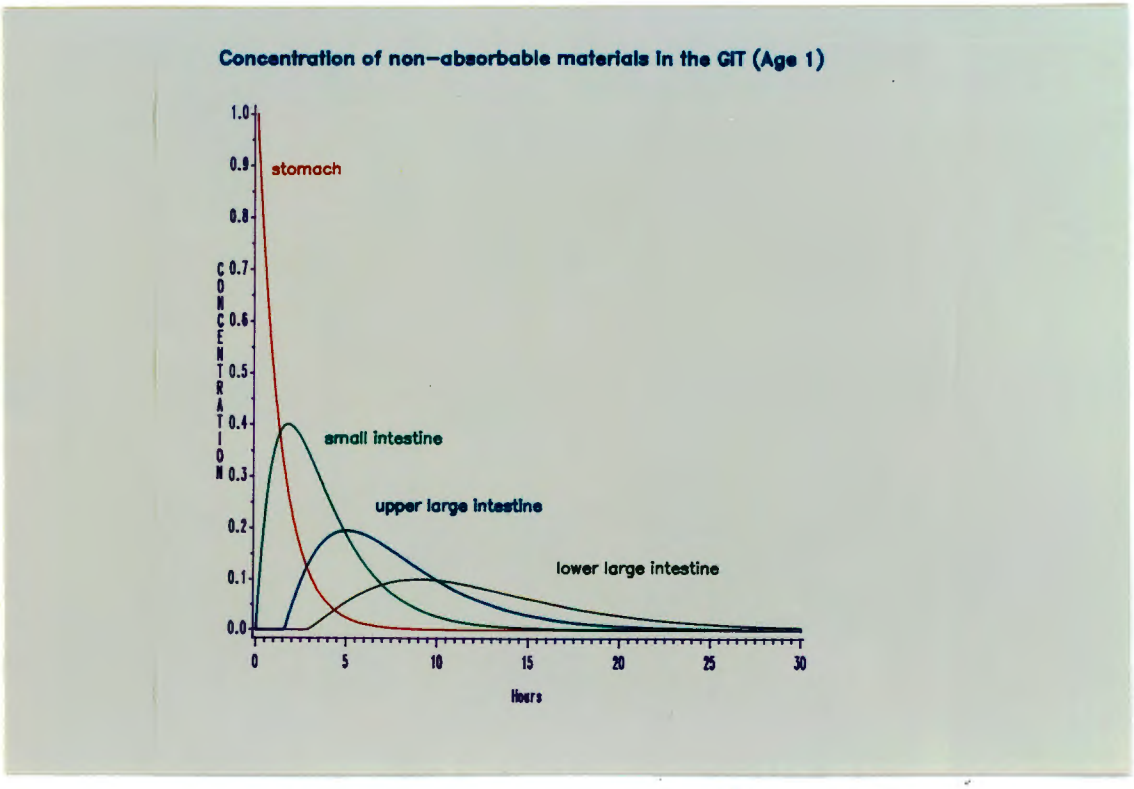

Concentration of non-absorbable materials in the GIT (Age 1)
stomach
small intestine
upper large intestine
lower large intestine
CONCENTRATION
Hours

Fig 8,3

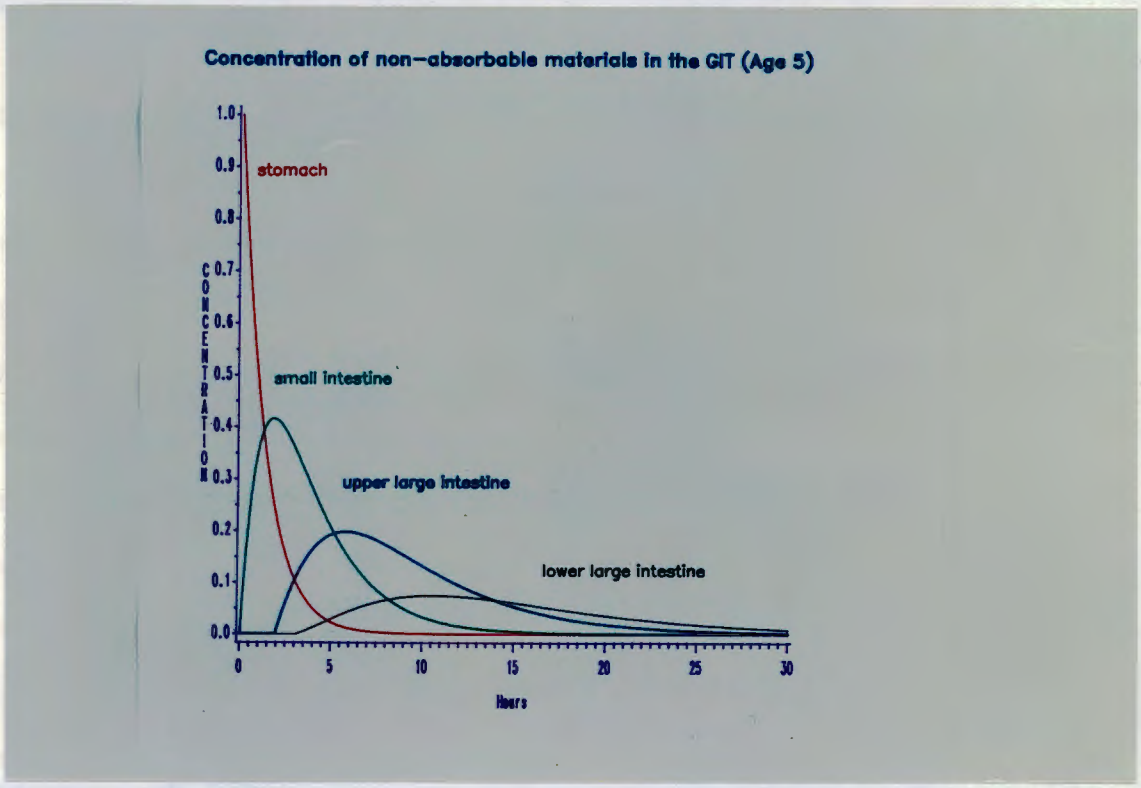

Concentration of non-absorbable materials in the GIT (Age 5)
stomach
small intestine
upper large intestine
lower large intestine
CONCENTRATION
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
Hours

Fig 8,4

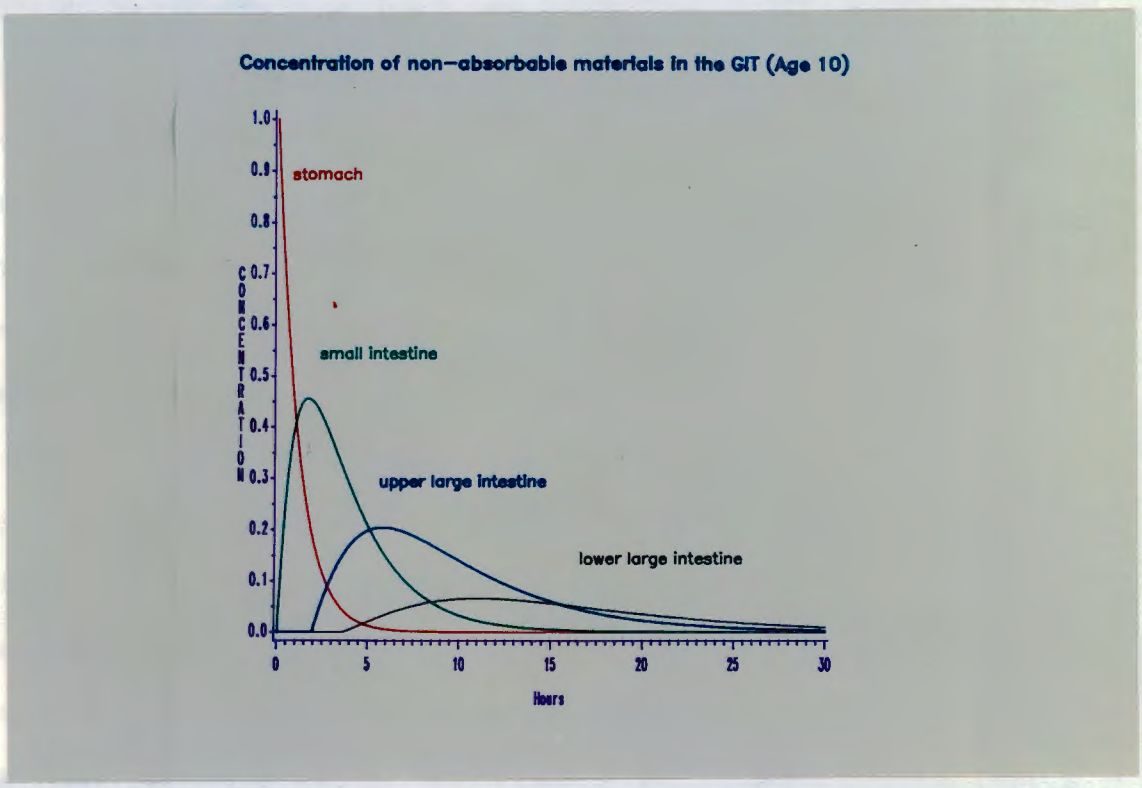

Concentration of non-absorbable materials in the GIT (Age 10)
stomach
small intestine
upper large intestine
lower large intestine
CONCENTRATION
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
Hours

Fig 8,5

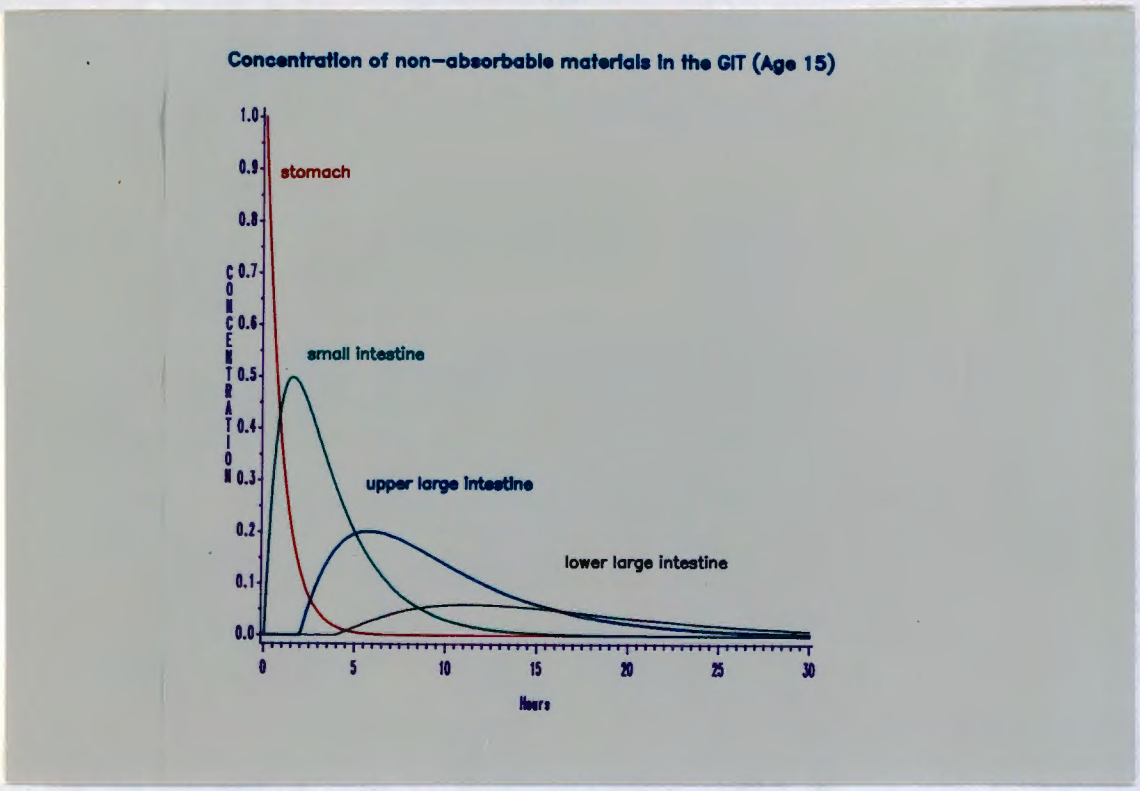
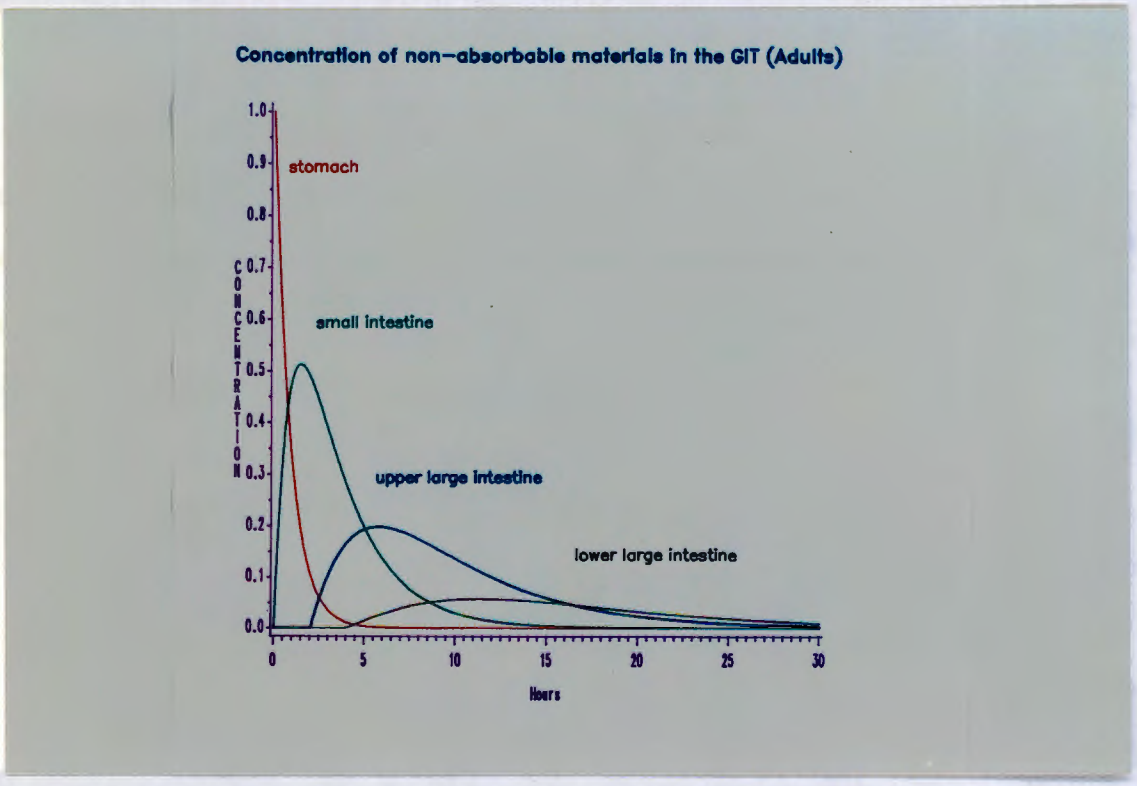

Concentration of non-absorbable materials in the GIT (Age 15)
stomach
small intestine
upper large intestine
lower large intestine
CONCENTRATION
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
Hours

Fig 8,6


Concentration of non-absorbable materials in the GIT (Adults)
stomach
small intestine
upper large intestine
lower large intestine
CONCENTRATION
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5
10
15
20
25
30
Hours

CHAPTER 9: DISCUSSION

"If the faculty of understanding is common to us all, reason also, through which we are rational beings, is common."
Marcus Aurelius; Meditations.

9.1 Introduction

The details of the scintigraphic examination finally adopted for this work have been given without detailed comment. The justification for the form of the study chosen rests in the study's advantages, the results obtained and their significance, which are discussed in this chapter.

The scintigraphic study described here and used in over 900 examinations is relatively easy to perform and it provides information not available from other commonly practised methods of investigating the relevant problems. The modality which is the closest contender for study of the paediatric disorders studied by this scintigraphic examination, especially when GOR or an anatomical abnormality of the foregut is suspected, is radiology. Numbers of images which can be recorded using Xrays are far fewer than those obtainable with scintigraphy, because of dosimetric considerations. Barium compounds are non physiological and their use does not allow reflux and stomach contents to be quantified. As has been explained, other examinations are invasive, or otherwise unsuitable, and cannot supply all the information available from the scintigraphic study. Neither swallowing nor stomach contents are usually investigated in practice with the pH electrode or oesophagoscopy (with or without biopsy) and manometry cannot easily give direct information about reflux or gastric emptying. Thus in theory scintigraphy is unequalled in the range of information it can offer.

9.2 Scintigraphic method

The present scintigraphic study requires apparatus commonly found in all Departments of Nuclear Medicine and no special skills, unusual apparatus nor uncommon radiopharmaceuticals. Tc-99m sulphur colloid is easy to prepare and to administer. The infant patient is ready for a meal at the time of the study and so there are virtually never any problems in persuading the patients to drink next to the camera. Similarly when supine and being replete, the patient is likely to sleep during the next part of the examination. Lack of cooperation from the patient for the search for GOR is a very rare occurrence. For older children explanation and pointing out there is no need for injection usually overcome all fears. Typically the time required for radiopharmaceutical preparation and the patient to be imaged totals up to about 60 min. Subsequent data reduction and developing of film necessitate a further 10 or 15 min, so the complete study is suitable as a routine paediatric examination. Scintigraphy, as described here, does not require invasive procedures, excessive length for the examination, unusual skills, dedicated complicated apparatus nor non physiological manoeuvres. Apart from its theoretical benefits, scintigraphy has practical advantages too. The range of deductions possible will be described below and in addition scintigraphy has clearly proved a valuable and practical method of studying the effects of pharmacological intervention upon foregut function.

9.3 Information provided by scintigraphy

The information resulting from the study is varied. Details of oesophageal transit, number, height, duration, time of occurrence and degree of severity of GOR, gastric contents 30 and 120 min after swallowing and localisation and amount of aspired gastric contents are all routinely available from the study. On occasions other items of

diagnostic importance can be gleaned, for example presence of oesophagitis, anatomical abnormalities and temporary entry of swallowed material into the trachea during deglutition. Examples of such findings have been presented.

The analytical techniques required to treat the acquired scintigraphic data and so provide the required information, are not complicated and use of regions of interest and condensed images is within the ability of technical personnel in average nuclear medicine departments.

9.4 Indications for the study

The relative numbers of different indications for the gastro oesophageal studies in terms of age are seen to vary between the two institutions (Tables 7,1 and 7,19). For this reason, also because at present the referring paediatricians probably have different attitudes towards the studies, since fewer of these examinations have been performed at the Children's Hospital on a different type of patient and for other reasons given below, the results are analysed separately except where noted. However for a young infant with apparent GOR yet who is thriving and whose clinical examination and chest Xray are normal, there are no compelling reasons for further investigations, unless an additional pathological process is suspected (Fisher 1987).

The most frequent indications for the gastro oesophageal scintigraphic study are the investigation of repetitive or chronic respiratory problems, for which no clear diagnosis is available, and SIDS susceptibility including apnoeic or cyanotic episodes. Siblings of those who succumbed to SIDS and others susceptible to it were found to have GOR in 100/154 of those aged under one year. So preventive measures after

this discovery are likely to reduce morbidity and mortality in these infants. In fact during these studies the moment of an observed GOR was associated with respiratory irregularity in eleven infants and in ten others with pulmonary contamination. This study provides a direct connection between GOR and SIDS, for 4% of these considered in danger of SIDS had pulmonary contamination. Thus in essence with these indications scintigraphy was able to provide information not readily obtainable otherwise. This could aid subsequent management.

For patients over one year of age respiratory problems are the most likely indication (Table 7,1) although at the Children's Hospital the age range 4 months to 4 years provided most patients (Table 7,19). This is due to the interest of the referring pulmonary physicians. Repeated respiratory problems can often cause diagnostic difficulties and the two thirds incidence of GOR detection in these patients, which is frequently severe (Table 7,2), can identify an unexpected malfunction, capable of being treated.

The knowledge of availability of this study for clinical colleagues also explains why follow up of medical treatment for GOR is the third commonest indication. The sensitivity and low irradiation of the nuclear medicine study are good reasons for its use in monitoring treatment for GOR. In this way a reproducible quantitative means of following patients' progress became available. In the opinion of the clinicians it confirmed their more subjective assessments of the patients' course. In contrast the South African use of this examination to investigate excess vomiting is not reflected in Bordeaux. It should be emphasised that one most useful indication for the study which remains to be fully exploited is the monitoring of pharmacological intervention. Its power has been demonstrated in this work by the evaluation of the effect of casapride

administration. In a similar fashion in the youngest patients an improvement with age can be observed and this may be associated with a natural maturation process in the foregut. Thus therapeutic measures and their duration can be more effectively planned.

9.5 Scintigraphic findings and resulting deductions

The results discussed in the text and numerical data given in the tables are obtained from scintigraphic and radiological studies performed in Bordeaux unless otherwise stated. The nature of the Department of Nuclear Medicine there, its throughput, relative number of studies performed and type of patient for whom the examination is requested all differed so much between the two Departments that for statistical and medical reasons it seems appropriate to separate the results in this account. The phenomena being demonstrated here can be succinctly described as manifestations of the differences between appropriate paediatric problems of the foregut and their scintigraphic investigation in the first and third worlds. The clear disparity between the relative numbers of different indications, the numbers, times of occurrence and severity of GOR observed and the relative merits of scintigraphy and Xrays in detecting GOR in the two settings, all point towards a large majority of the Bordeaux patients being much less ill in general than their South African counterparts. Thus it is gratifying to deduce that a useful contribution to the management of all these children can be offered by scintigraphy, whether they form part of the first or third world. Further, the results will be considered in terms of mean values and standard deviations. This allows deductions to begin to crystallise and the resulting hypotheses can be analysed in greater detail where appropriate by more sophisticated statistical methods.

9.5.1 Oesophageal transit

The relation of OTT to the maximum height of observed GOR is given in Table 7,3. It is clear from the standard deviations that there is a wide spread of OTT in each category. However in all cases mean OTT is shortest when there is no GOR detected. Also in this situation OTT is seen to increase with age as is expected from simplistic anatomical considerations. Numbers are far smaller for the neonates similarly examined (Table 7,4) but a similar conclusion is possible after comparison between OTT of those with and without GOR. When this comparison is taken further to consider those with endoscopically confirmed oesophagitis (Table 7,5), an additional increase in OTT is clearly demonstrated. When OTT is considered in terms of age for the different degrees of GOR, in all cases p values are below 0,02 after both correlation and variance analysis. The correlation between OTT and degree of GOR is significant (p = below 10^{-4}) for absent GOR ($n = 122$), GOR not rising above thoracic level ($n = 45$) and for highest GOR reaching cervical and buccal regions $p = 0{,}019$ and $0{,}004$ respectively with $n = 63$ and 69. In a similar fashion when GOR and OTT are compared the correlation is significant ($p = 0{,}01$) with $n = 312$. Thus the clear trend of $\bar{t}$ in table 7,3 in terms of maximum height of observed GOR is confirmed by more sophisticated analysis. The known anatomical fact that OTT increases with age is also corroborated here and an assertion that OTT also independently increases with greater excursion of GOR can be relied upon.

An excessively long OTT, say exceeding the duration of the

observation, is an indication of an oesophageal mucosal lesion trapping the colloid and most commonly this is oesophagitis and not reflux. Such a deduction can usually be confirmed by a subsequent failure of the unmarked liquid to rinse the oesophageal mucosa and to remove adherent colloid. However if the mucosa is rinsed clear of colloid, the nature of the oesophageal transit can be studied without a superimposed persisting activity and different deglutitions compared by examination of the ciné images and resulting condensed images and graphs. In this way oesophageal spasms, achalasia, scleroderma, oesophagitis or other abnormalities may be recognised. In contrast, a greatly prolonged OTT is not usually an indication of prolonged, high GOR. This can readily be confirmed again by viewing the images acquired during the swallows in the ciné mode, even if activity persists in the oesophagus, and also by inspection of the results of the scintigraphic search for GOR. Together with the failure of unmarked liquid to remove radiotracer remaining on the oesophageal mucosa, it can be deduced there is a mucosal lesion. These checks will prevent any undeserved direct association between excessively long OTT and GOR from being made.

Movement of swallowed radioactive material towards and into the trachea, even if only during about 0,5s or less, was recognisable during the part of the study observing deglutition. In this way swallowing incoordination could be identified as a possible cause of repeated respiratory problems, even if no GOR could be detected. If there was either entry into the trachea before the first deglutition, or

large amounts entered the laryngeal region for at least 0,5s, then there was clear detection of these happenings from examination of the ciné images or the condensed images formed from the complete region viewed by the gamma camera (Figs 7,37 and 7,38). However if pharyngeal incoordination is suspected, passage of this misdirected liquid was recorded simultaneously with a swallow and it proved difficult or impossible to distinguish between each of these two motions in the ciné and condensed images, additional condensed images, just of the region anterior to the hypopharynx, can be formed and hence visualisation of only the misdirected descent is possible (Fig 7,47). A similar approach was used to eliminate the activity due to a feeding bottle which although inadvertently recorded in ciné images was removed from the associated condensed images (Fig 7,9). It is believed that this technique has not been previously described.

In adults a condition known as diffuse oesophageal spasm is well known, having been first described in 1889 (Moersch et al 1934) and characterised by repetitive non progressive contraction in the distal two thirds of the oesophagus. This may be of greater pressure than peristaltic components (Waters et al 1981). A common clinical feature is pain which in adults may be confused with pain of cardiac origin (Wynchank et al 1986,). From observations in this work it appears that this condition is found in paediatric patients (Figs 7,32 to 7,36). Results for 32 patients from the Children's Hospital in whom oesophageal spasm was observed are given in Table 7,21. Of the six who had no GOR, three emptied their stomachs faster than average and patient no 16 with slower emptying had repeated

pneumonia. This illustrates the complex relation between oesophageal spasm, length of OTT, GOR and severe recurrent respiratory problems. In part because of the assistance given to management of the youngest patients by our results, more requests for studies with neonates and young infants were made in France than in South Africa.

9.5.2 Gastro oesophageal reflux

The time of occurrence and length of GOR are considered in Tables 7,8 to 7,11. The incidence of GOR at various times after deglutition in Tables 7,8 and 7,9 shows a drop for times longer than about 10 min after swallowing which implies that the search time chosen as 30 min is likely to be adequate. This adequacy is confirmed when the time variation of the observed time of the first GOR is tabulated. In all cases about 10% of first GOR are detected in the last 15 min of the 30 min allocated to a search for GOR. If the search were shortened to 25 min under 3% of first GOR would be missed and a reduction to 20 min results in a loss of below 5% of first GOR. Thus over 95% of first GOR occur within the first 20 min and so the 30 min employed has been confirmed as a most appropriate compromise between needs for efficient detection of GOR and satisfactory throughput. It should be noted that this finding indicates a possible shortcoming of the oesophageal pH electrode method for detecting GOR. Buffering of a normal feed is considerable, hence those GOR occurring soon after the feed may not be registered as a drop in pH. This can of course be overcome by using apple juice in place of the feed, but this is not common practice.

The variation of occurrence of first GOR with time is in effect a monotonic decrease from a prominent peak at earliest times. When the gastric contents are considered at different times, this early occurrence for first GOR may in part be explained. At later times there is usually significantly less liquid remaining in the stomach, hence assuming a continuously malfunctioning LOS allowing GOR, fewer GOR occur at later times. Also over a time scale using increments greater than the typical duration of a GOR, there is monotonic decrease of gastric radionuclide content. This too implies lessening amounts of activity are available for reflux as time increases. As is expected after inspection of the numbers of GORs occurring in the last 5 min of the relevant part of the study, the time distribution of last GOR is seen to be very strongly peaked after 25 min. A small local minimum which occurs between 3 and 6 min is not significant. The differences between results for neonates (Tables 7,9 and 7,11) and all patients reflect the statistical paucity of results for neonates, for in all the groups there are similar mean numbers of GOR per patient, ranging from 3,2 to 4,4. The points made in the above discussion of the temporal distribution of GOR (Tables 7,8 to 7,11) apply to analagous data obtained from patients at the Children's Hospital (Tables 7,22 and 7,23) with one exception. The mean number of GOR per patient is higher being about 6. This is yet another manifestation of their generally sicker state.

The mean duration of GOR is apparently directly related to the maximum height attained by the GOR (Table 7,12) for patients grouped by age in 4 ranges up to 16 years. However

examination of the standard deviations indicate the considerable variation which was observed. In the neonates' population (Table 7,13) this relation between duration and height of maximum GOR is inapparent due to small numbers. Twenty-three GOR were observed of length over 20 min. However over three quarters of the longest GOR observed in a given study are under 3 min duration, usually below 1 min. This illustrates well the rapid nature of these pathophysiological events being observed.

9.5.3 Gastric emptying

When the relation of mean gastric contents at different times to GOR is examined (Tables 7,14 to 7,17) for the patients grouped in the range 0 to 1 year there is no significant difference between stomach contents in patients with GOR rising to different heights and no GOR (Tables 7,14 and 7,15). (This lack of concordance has also been reported in children between gastric emptying of liquids and presence or not of Crohn's disease, irrespective of nutritional state (Grill et al 1985)). When the mean gastric contents for this age group are considered in terms of the time of onset of the last GOR (Table 7,16) again there is no correlation. However for the children aged 1 to 16 y the mean gastric contents tend to decrease compared with those aged below 1 y having equivalent GOR. This is of course implicit in the values of Table 8,9. For neonates there are too few data for the same degree of confidence in the results, but in all categories except one, preterm infants are seen to empty their stomachs more rapidly than those born at term (Table 7,17).

It is clear that there are patients with GOR having normal or even accelerated gastric emptying . An instructive investigation in them would be pH and pressure studies, for it seems probable that abnormal peristalsis can be the cause in association with reduced LOSP. These findings confirm the complicated nature of various processes contributing to the observed foregut malfunctions.

When the emptying of different liquids is considered in term infants up to 3 months of age (Table 7,18) maternal milk is emptied more rapidly than infant formula. For those aged over one month mean gastric contents after 30 min are similar but statistical significance is low for those who drank maternal milk. Similarly when the results for preterm infants are considered the few examinations in the younger group prevent any clear cut deductions. The effect of a thicker feed upon gastric emptying and certain behavioural characteristics has recently been reported for 20 infants, using a scintigraphic technique (Orenstein et al 1987). The results confirmed expectations and showed less emesis and crying and increased sleeping and gastric emptying.

The relation between gastric emptying and other characteristics was examined in closer detail in the present work. In particular there is some controversy in the literature about its relation with presence of GOR. One study (Hillemeier et al 1981)) found that 7 infants with severe vomiting and failure to thrive and 6 with repeated respiratory symptoms and severe GOR symptoms had significantly slower gastric emptying (p below 0,05) for cow's milk than 10 infants

with histories suggesting only mild to moderate GOR. A similar conclusion was reached by another group after 57 children were examined with swallowed Tc-99m colloid (Baulieu et al 1984). Gastric emptying measured after 60 min was faster in those with less than 1% reflux than those with more than 3% refluxed (p below 0,01) and those with pulmonary aspiration (p below 0,001). However those with and without oesophagitis refluxed similarly. Several aspects of this work require comment. Firstly the figure of 1% of gastric contents in GOR is too high to be considered insignificant. This point was conceded by the authors (Baulieu et al 1985) in response to published criticism of their work (Cosgriff et al 1985) when they agreed that a refluxed quantity of 0,3% was significant. However no corresponding values of gastric emptying were given when this admission was published. Next the apparent lack of difference in gastric emptying rates with and without oesophagitis implies a similar lack of correlation with persistent GOR, which is usually associated with oesophagitis. This point was not discussed by the authors and a reasonable conclusion is that all deductions from this reported data are not necessarily those quoted by the authors.

Another report (Rosen et al 1984) found in 126 children aged 0-16 y there was no significant difference in gastric contents of 5% dextrose water 60 min after ingestion between those with and without GOR defined scintigraphically (42 ± 25 and 46 ± 28% respectively). However when age groups 0-2 y and 2-16 y were considered separately the same conclusions were reached, although an age related difference was observed with p below 10^{-4}. A further study of 4 infants

and 8 children with mean ages 5,7 months and 9,1 years "did not find a high correlation between reflux and delayed gastric emptying" (Seibert et al 1983). This has been confirmed in a recent preliminary study (Valdés Osmos et al 1986) which used 97 children of all ages. A very recent publication quoted results from 477 children and infants, who were studied with oesophagoscopy, LOSP measurement, pHmetry and gastric emptying determination, and came to a conclusion similar to the present work, that for children under the age of 6 y there was no correlation between gastric emptying and any of LOSP values, presence of oesophagitis or GOR (Di Lorenzo et al 1987).

It is hoped that this controversy is settled by the current results. Results in 306 patients below the age of 3y from both hospitals were considered (Table 7,25). Values of gastric contents at 30 and 120 min after ingestion and the percentage emptied between 30 and 120 min in the four groups ((males or females) and (normal results or GOR observed)) were compared. When this was done for the two sexes and presence or not of GOR was considered there was no significant difference (p below 0,008 for Bonferroni's test), noting there are 6 (= 4!/(2! x 2!)) pairwise comparisons possible. However one comparison of subgroups (normal males and those with GOR) alone had different values of gastric contents after 30 min. These were (73,2 $\pm$ 15,9) and (64,7 $\pm$ 21,8)%, for n = 85 and 87 respectively. (The percentages are mean $\pm$ SD). It is clear from the SD values that the variations observed in percentages were considerable and this must be borne in mind when considering the Bonferroni test p value of 0,004. To examine the data further the effects of age were eliminated by a two

way analysis of variance with one covariate which was age. When two groups were selected from this data (those normal and those with GOR) no significance for age as covariate was seen since p = 0,80 and 0,84 for gastric contents after 30 and 120 min respectively. There are three implications from this result for paediatric patients below three years in age. Firstly there is no effect of sex on the lack of difference in gastric emptying with and without GOR. Next there is no effect of age. Finally one can deduce the gastric emptying rate in normal neonates and infants of age 12 months can be considered the same. We use this fact in deciding the values to adopt biological half life for stomach contents when calculating radiation doses.

There have been few studies of gastric emptying in normal infants. Cavell of Lund University, Sweden (Cavell 1981) who compared gastric emptying of maternal milk and infant formula found

$t_{\frac{1}{2}}$ = (48 ± 15) min (n = 8) and (78 ± 14) min (n = 9)

respectively for each liquid. This work used a non radionuclide dilution marker technique and repeated sampling through a nasogastric tube. The Yale group investigated 10 children aged 2 to 14 months with normal growth and histories suggesting mild to moderate regurgitation (Hillemeier et al 1981). After 15, 30, 45 and 60 min gastric contents were 87,9 ± 3,9, 69,3 ± 4,3, 64,7 ± 5,8 and 55,7 ± 6,0%. This implies a value for $t_{\frac{1}{2}}$ of (69,5 ± 5,0) min. These measurements used a cow's milk formula and Tc-99m sulphur colloid. Thus the present results for infant gastric emptying of $t_{\frac{1}{2}}$ = (56,2 ± 4,5) min (n = 8) for maternal milk and (72,7 ± 3,4) min (n =

133) for other liquids correlate satisfactorily with those previously obtained. The reason for this difference in gastric emptying rate of the two liquids has been suggested as being due to their fat and protein contents, for there is little difference in their osmolality and lactose concentration. Also this difference is independent of the patient's age (Cavell 1981). When measurements of stomach and small gut activity are made in adults the suggestion has been made that a correction may be necessary to allow for self absorption (Tole 1985, Christian et al 1983, Christian et al 1984). However many authors, for example those who published in 1984, 1985 and 1987, consider it unnecessary (Mannell et al 1984, Maddern 1984, Feldman et al 1984, Jordaan et al 1984, Sutton et al 1985, Jonderko 1987). Hence when one considers the much lesser amount of tissue present in paediatric patients one appreciates there is no need for this correction. One very recent report found that gastric emptying in 35 normal adults depended on stomach shape and presence, or not, of duodenal ulcer (Jonderko 1987). The resolution of the present data and the absence of these ulcers in paediatric patients reduce the relevance of these findings to this work.

The relation of pulmonary problems to aspiration of gastric contents is clear and this relation has been clearly demonstrated as described above. In those infants suspected of being liable to the SIDS the moment of GOR was associated with respiratory irregularity in seven although no aspired radiotracer was recognised, in spite of a careful search. Thus the discovery of GOR even without pulmonary aspiration is a significant finding and an aid to management in these infants.

If a detectable quantity of regurgitated colloid is inhaled then in principle the mucociliary function can be estimated by noting the rate of its removal from proximal airways.

9.5.4 Some surgical problems and scintigraphy

Some patients at the Children's Hospital with alleged GOR and resulting pulmonary aspiration were found to have no improvement in respiratory system disease after surgery to the region of the LOS (Nissen fundoplication), intended to prevent reflux (Rode 1985). These patients had received surgery without any prior gastro oesophageal scintigraphy but having had clinical and radiological examinations. They were then referred to the Nuclear Medicine Department for an investigation to detect putative continuing GOR, for GOR had been the indication for their surgery. After the scintigraphic study something totally different was found. No GOR was discovered but a very abnormal oesophageal transit was apparent, with irregular spasms and sequential swallows showing the bolus held up at varying sites and different resulting values of OTT (Figs 7,19 to 7,21 show similar results). The apparent hold up due to a fragmented bolus can be recognised by the absence of a single peak in the ROI curves (Sand et al 1986). Thus an explanation for the lack of success after surgery became apparent. Hence all patients later considered for such surgery were then examined with the scintigraphic study before a decision to operate was made. If alleged GOR caused repeated problems but only grossly abnormal oesophageal transit was discovered, surgery to the LOS was therefore not attempted. Thus one indication for the study, the detection of GOR correctable by surgery to the LOS, evolved into another

indication, the confirmation of absence of a severe oesophageal transit abnormality. This was a necessary and sufficient condition before the proposed surgery could be attempted and such sieving as part of a pre surgical evaluation resulted in success for all Nissen fundoplications after the introduction of the radioisotopic study (Rode 1987).

There are other surgical procedures which can also be used to correct GOR (Hecker 1985, Menardi et al 1985, Bernhard et al 1985) for there is some controversy concerning use of the Nissen procedure (Schärli 1985b, Guggenbichler et al 1985), although it continues to have its enthusiasts (Davidson 1987). One such is use of the Angelchik prosthesis. A recent prospective study comparing it with the Nissen fundoplication in 25 paediatric patients and 13 paediatric sized adults found they had similar degrees of improvement and long term results over 12-30 months, using oesophageal pH measurements and manometry (Gourley et al 1986). All these patients were developmentally disabled and mentally retarded. It is likely that scintigraphy could also evaluate the use of the Angelchik prosthesis and other surgical procedures, which so far have not been used in the hospitals where the present work has been done. When the results of pyloroplasty in infancy and childhood are reported for gastric outlet obstruction or antral dysmotility, the results are very satisfactory even without repeated scintigraphic studies (Franco et al 1986). Others who discuss the results of fundoplication with or without pyloroplasty obtained over a 14 year period in children with GOR, assert that 24 hour oesophageal monitoring is the most accurate test to detect GOR. However radionuclide studies were

only used to measure gastric emptying (Fonkalsrud et al 1985). No attempt was made by these workers to study deglutition scintigraphically. A very recent publication by the same group advocates a manometric LOSP measurement and oesophageal motility studies in addition, before attempting surgery and that as a result states fundoplication with or without pyloroplasty, "should be used early in the management of infants and children with symptomatic GOR" (Fonkalsrud et al 1987). This report was based on results from 352 patients under the age of 18 y and adds confirmation to the present work.

9.5.5 Scintigraphy and cisapride

In the 25 patients to whom cisapride was administered (Table 7,26), aged from 53 days to 41 months, mean OTT was reduced in 14 (mean reduction 2,3 s) and increased in 8 (mean increase 2,2 s). GOR was reduced in either duration or maximum height attained or both in 15. It was unchanged in 4 and increased in duration in 5. In order to compare different durations and heights of GOR and to quantitate the effect of cisapride on GOR, a simple arbitrary weighting system was devised. This allows quantitative comparison of any observed reduction (or increase) in height of GOR after cisapride. Relative weights of 1,0, 0,5 and 0,25 were assigned respectively to buccal, cervical and thoracic GOR. This weighting is conservative and possibly gives too little importance to buccal GOR. Even with this conservative choice it is evident that cisapride causes a mean reduction of 46 s in observed GOR duration in 15 patients, no change in 4 (3 of the 4 had no observed GOR but one (patient no 9) of the 3 had

observed pulmonary aspiration in the right mid zone in the pre-cisapride study only) and a mean increase of 54 s in measured GOR for 5 patients. (All durations of GOR given in this paragraph are in terms of buccal GOR equivalent using the weighting system described above).

Gastric contents 30 min after swallowing were decreased in 5 patients (a mean decrease of 35,2%), unchanged in two and increased in 13 (mean increase 17,0) after cisapride. The situation is little different for gastric contents two hours after deglutition. This has of course practical significance, since delayed gastric emptying for 2 hours can therefore permit more opportunity for GOR to occur with all the resulting complications. This two hours includes a long period beyond that in which our measurements of GOR were made. In 11 patients there was significant reduction of gastric contents 120 min after swallowing with mean reduction 21,5%, in 9 patients there was an increase (mean value 21,9%) and in one no change.

Thus it seems evident that cisapride has an effect on reducing amount and degree of GOR. (This has been confirmed by a very recent report from the Children's Hospital which related pH determinations of GOR to cisapride administration (Rode et al 1987)). When further analysis of the present findings was undertaken using the Wilcoxon signed rank test, this impression was confirmed ($p = 0,042$). Apart from the comparisons mentioned above it is of significance that for 6 patients pulmonary aspiration was detected in the pre-cisapride images recorded after 2 hours, but none in the post cisapride studies.

However one other patient (no 15) had pulmonary aspiration detected in the post cisapride study only, when significantly slowed gastric emptying was also observed. So it can be seen that cisapride has a beneficial effect upon degree and duration of GOR and pulmonary contamination but little effect upon the other quantities measured.

9.6 Contributions to physiology and anatomy

Observations of data obtained during deglutition have aided our knowledge of oesophageal physiology for there still exist aspects of paediatric oesophageal function that are poorly understood. The neonatal LOS is thought incapable of fully contracting during feeding. In a reference work on clinical paediatric physiology (Godfrey et al 1979) the following statement is made concerning neonates. "Peristalsis is poor in the lower third and the LOS never closes completely between swallows". Present observations of frequent lack of progression of swallowed boluses beyond the inferior limit of the oesophagus until a series of swallows is complete disproves the above assertion (Figs 7,29, 7,30, 7,56 and 7,57). In fact this has been already described in adults as a variation of normal (Ham et al 1985b) when a peristaltic wave causes all of its predecessors to stop. If swallows of a series follow in rapid succession the LOS may remain closed until the last deglutition reaches it. A further feature is recognisable in images of infants who have successive swallows during which the LOS remains closed until the series of swallows ends (Figs 7,7, 7,10, 7,12 and 7,13). The first deglutition after this series has a greatly increased transit time (Figs 7,14 to 7,16 and 7,31). This can be considered a "tired oesophagus". (I am indebted to Professor M D Mann for this term). If this is interpreted in terms of the mechanism which controls the orderly progression of an oesophageal peristaltic wave it may supply evidence which helps to contribute to the

understanding of oesophageal peristalsis. Its mechanism is programmed in the muscle or in the nervous system. If the latter, from experiments with a cut vagus and other evidence (Baron et al 1981), it seems clear that the peripheral nervous system and not the central nervous system may establish the progressive contractions of oesophageal muscle which follow on swallowing. Hence the programming occurs within the myenteric plexuses or within the smooth muscle itself. The smooth muscle is considered the more likely candidate since there is a monotonic gradient of latency between arrival of a stimulation pulse and smooth muscle contraction. This latency increases with distal movement along the oesophagus. A gradient of intracellular ionic potassium content along the oesophagus, causing a similar gradient in electrophysiological properties of muscle cell sarcolemmae, has been postulated as the basic physiological mechanism for these observations (Decktor et al 1980), in a similar way to embryonic differentiation, which is thought to take place along the cranio-caudal axis as the result of a protein concentration gradient (MacDonald et al 1986). The slower steady descent through the inferior oesophagus observed after a series of rapid deglutitions may also be explained by an intramuscular origin of the peristaltic contraction programming, due to a refractory period arising from properties of the muscle itself (Meyer et al 1981). By analogy with the autonomic control of myocardial function and consideration of the tired oesophagus it therefore seems more likely that inferior oesophageal peristalsis is controlled by a muscular rather than neurological mechanism.

Although scintigraphy's greatest power resides in its ability to provide information about function, it may also give useful details of morphology or anatomy, which are not readily available from other sources. For example a hiatus hernia, unsuccessfully sought in an adult

with Ba Xray studies and endoscopy, has been unequivocally demonstrated in images of swallowed Tc-99m sulphur colloid (Wynchank et al 1986). An abnormal oesophagus, which was unsuspected after radiological and other studies, was clearly shown in a 16 month old male as part of the work presented here (Fig 7,17).

9.7 GOR: Scintigraphy and Xrays

A comparison between Xrays and our nuclear medicine study for detecting GOR is shown in Table 7,6. For all age groups, in only 7 patients was GOR detected with Xrays alone and not with scintigraphy. In contrast there was agreement between the two methods, or superiority demonstrated by nuclear medicine in 242 patients. Of the seven negative scintigraphic studies two were subject to technical problems and in one of the positive Xray studies the Trendelenberg position was used by the radiologists. It must be stressed that GOR is frequently an episodic function and also that the Bordeaux radiologists usually employed no unphysiological procedures in searching for GOR. The two studies cannot be performed simultaneously but the time interval between them was never more than a week and frequently only one day. A highly significant difference between the abilities of scintigraphy and Xrays to recognise the presence of GOR is confirmed by application of McNemar's version of the chi squared test to the symmetry of this data. The resulting p value is below 10^{-4}. Similar results are obtained with Pearson and Yates' corrected chi squared tests. When the same data is considered in age groups below and above 1 year the McNemar test shows identical results. Hence there is no doubt that the scintigraphic method is to be preferred over Xrays for detection of GOR. When a search for GOR was made with both studies in patients who were known to have oesophagitis (Table 7,7) again the unequivocal superiority of nuclear medicine is demonstrated. In no cases were GOR detected by Xrays and not by scintigraphy in

patients with oesophagitis. Yet there remains at least one author who believes that the two modalities are of comparable worth (Savage 1984). In spite of the clear advantages of scintigraphy over Xrays in demonstrating GOR both in sensitivity and evaluation of the degree of severity, there remains a continuing need for Xray examinations. If the GOR is shown to be resistant to treatment, anatomical abnormalities can be best investigated with barium studies. Similar conclusions after studies in 34 patients have also been reported (Le Luyer et al 1983).

The comparable results from the Children's Hospital comparing both modalities (Table 7,24) are less easy to interpret for two main reasons. Firstly total numbers are much smaller (hence their statistical significance is much less) and any advantage of scintigraphy over Ba Xray studies is less clear cut in terms of relative numbers in each group. Where there is a disagreement between results of the two modalities, scintigraphy can either detect GOR in more patients or show it is more severe than that demonstrated by Xray studies. However there are fewer Children's Hospital patients overall and even with all age groups combined, the totals for the detection of GOR are 78 with disagreement between the two methods in favour of nuclear medicine over Xrays and 37 with disagreement but vice versa. Another explanation of the Children's Hospital results is that the French patients were in general less ill than their South African counterparts and certainly they had fewer episodes of GOR per patient in whom reflux was detected, as Tables 7,8 to 7,11, 7,22 and 7,23 show. Since the ability of Ba Xray studies to detect GOR increases with severity of the reflux, it can follow logically that there is less difference between the results of the two modalities when applied to the South African patients described in this work. This was confirmed by considering the data of Tables 7,6 and 7,24 as two way tables and using the Kappa statistic (Fleiss 1981).

9.8 Relations between observations

The complexity of relations between the physiological processes which contribute to the mechanisms observed in this study is now apparent. However in spite of this there are some relations which can be understood. A search was made for relations amongst the data available for patients associated with this work which so far had not yielded any correlation. The data included in this analysis, if available, were; sex, type of liquid swallowed, age, presence of GOR, OTT, whether term or preterm, Apgar values at 1 and 5 min, GAST 30, GAST 120, (GAST 30 - GAST 120) and results of a radiological search for GOR. A log/linear model of contingency table analysis (Everitt 1977) was used to identify possible associations between the variables mentioned above, for which no correlation have already been described, taken two and three at a time. The only significant associations were between the two Apgar values ($p = 0,018$), the Apgar at 5 min and whether term or preterm ($p = 0,025$). GAST 30 and GAST 120 ($p = 0,0002$) and the three variables (OTT, GAST 30 and GAST 120) ($p = 0,046$). The latter correlation between the triad is of marginal significance. It follows that if GAST 30 is reduced then GAST 120 is likely to be low. As stomach contractions and gastric emptying rarely stop suddenly this is not unexpected. Otherwise these findings give no cause for surprise, for a low Apgar at birth is often followed by a low value at 5 min. Similarly for a preterm neonate the Apgar is more likely to be low than for a term neonate (Van der Elst 1987). The lack of association between the other variables is a further indication of the complexity of all the physiological and pathophysiological processes involved.

Oesophageal spasm is an entity which has been observed in this work. The importance of the recognition of oesophageal malfunction in the care of children with apparent foregut problems has been made clear. In

contrast it has been demonstrated that the presence of GOR is not generally associated with abnormal gastric emptying. There is no obvious subdivision of types of GOR into those with and without accompanying slow stomach emptying. Pathological foregut function may be therefore more or less extensive involving both organs, or one, in the patients studied. On the other hand GOR and OTT have been shown to be interdependent. The anatomical implication, that the oesophagus is involved in both processes, is reasonable. A previous misconception concerning neonatal oesophageal physiology has been explained and some possible insight into the control mechanism has resulted. The place of the scintigraphic study described here in the paediatricians' armamentarium is clearer after the results of a comparison described above with the only other commonly practised study to detect GOR, using the Xray detection of swallowed Ba. Further, the radiation dose to the patient has been calculated by means of a new model which bears a closer relation to the physiological passage of a swallowed unabsorbed radiopharmaceutical.

The range of problems that can be studied, with scintigraphic examination described here, is large. Various pathological features can be clearly recognised from the images and the associated analytical methods recounted here. Malfunction of oesophageal transit, stomach emptying and their detection have been described in detail, but also recognition of presence of pulmonary aspiration, laryngo tracheal incoordination resulting in entry of swallowed material into the trachea, oesophagitis and the effects of drugs upon various foregut functions are possible. In all it is hoped the present work has been of some use for the care of infants and children.

9.9 Dosimetry: an overview

There is no controversy about the need to reduce to a practical

minimum the amount of radiopharmaceutical administered to paediatric patients. However the means whereby this minimal quantity of activity can be determined are more contentious. There are two main uncertainties associated with this determination. They are how to choose the quantity of radiotracers to be administered and then consideration of the resulting energy absorbed in tissue (i.e. the radiation absorbed dose); its quantitation, nature and effect. In this work calculations of certain radiation absorbed doses are made for swallowed Tc-99m sulphur colloid at various paediatric ages. This is therefore an essential step in the chain of three stages lying between the choice of a quantity of gamma emitting liquid to be swallowed and any resulting noxious radiobiological sequelae. The other aspects of the problem of administering radioactive substances to a patient will also be briefly considered to complete the picture. The three stages are (1) choice of administered dose, (2) the determination of resulting energy deposited in various tissues and organs and (3) the radiobiological sequelae, sub-divided into stages 3a-3d.

An overriding principle concerning the administration of radioactive substances for diagnostic investigations (stage 1) is that an adequate clinical result is required and the least quantity that can be given to achieve this aim is the most appropriate dose. For adults much empirical work has been described to determine suitable quantities of radiopharmaceuticals based on this principle, but much more remains to be done (Shore et al 1986). However the scaling of these doses administered to adults for paediatric use at different ages is much less consistent. A survey of administered doses used for paediatric patients in selected institutions of the USA found variations with up to tenfold differences in some of these doses (Treves 1985). Scaling of doses administered to adults for paediatric use can be done using several techniques. These

include ratios determined from patient height, body surface area, mass (Shore et al 1986) and an empirical formula depending on age (Webster et al 1984). The latter two methods closely approximate each other. If the organs being visualised with static images can be characterised as thin or thick, then it has been shown that optimal scaling factors should depend on two or three linear dimensions of the patient respectively (i.e. surface area or mass). For some dynamic studies, notably renograms, adjustment of adult administered dose for paediatric use should depend upon one dimension, or the patient's height. Such logic cannot be directly applied to gastro oesophageal scintigraphic studies for several reasons. There is far less published material available on the rational determination of administered doses for the adult GIT, than for other systems and organs studied with radiolabelled compounds. The studies are initially dynamic but as the radionuclide travels more distally, its passage slows until it is virtually a static study. Also the relative depth of the parts of the adult GIT containing the activity varies so that corrections for attenuation are not straightforward.

9.10 Deposited dose and sequelae

The quantity of radiation absorbed dose deposited in various organs and tissues after swallowing given amounts of Tc-99m sulphur colloid (stage 2) is a main concern of this work. However the nature and effects of this radiation (stage 3) are equally important. Gamma rays of energy 140keV are emitted from Tc-99m and their interactions with individual atoms (stage 3a) have been well described in terms of the two interaction mechanisms known to have non zero cross sections at this energy, which are the photo electric and Compton effects. The consequent effects of the 140 keV photons from Tc-99m upon biochemical compounds and living structures are very much more complex and the whole science of radiobiology is devoted to the study of such interactions. In addition

to the encounter between photon and atom, there are three other sequential types of event (the physico-chemical, chemical and biological), described for radiobiological interactions.

The rapid physico-chemical stage, which involves unstable molecular excitations and ionisations, is next (stage 3b). The following chemical stage involves the breaking of bonds (stage 3c). A chain of events may follow leading to changes in nucleic acids, macromolecules within membranes, enzymes and other cellular constituents. This is the direct action of ionising radiation. The incident photons can also interact with atoms and molecules to produce free radicals which can diffuse far enough to reach critical targets. The most studied of such species arise from the radiolysis of ubiquitous cell water and include the dissociative free radicals $H^{\cdot}$ and $OH^{\cdot}$. These can initiate reactions with themselves, their own reaction products and tissue water to form hydrogen peroxide (H_2O_2) and further highly reactive compounds such as hydroperoxy and singlet oxygen radicals ($HO_2^{\cdot}$ and O_2^{1*}). The final stage 3d is the biological and can last from seconds to many years, ranging between complete repair, metabolic change, genetic alteration and cell death. Thus between deciding upon the dose of radiotracer to be administered and trying to evaluate the final damage it causes, there exists the necessary step of calculating how much energy is deposited in the target tissues and organs (stage 2). Details of the principles involved in such calculations have already been described in detail.

In spite of the present discussion of deposited radiation dose it must be emphasised that nuclear medicine procedures typically cause lower exposures than the unavoidable natural radioactive background and "the degree of risk from low level exposures is generally thought to be very low" (Sorenson 1986).

9.11 Dosimetry and children

When children are to be examined by scintigraphy one can find arguments for both increasing and decreasing the amount of radiopharmaceutical given, in comparison to accepted adult quantities, when they exist. This in turn implies similar relative increases and decreases in the radiation energy deposited in various tissues and organs. It is well known that some tissues are intrinsically more radiosensitive than others, for example the gonads. Further it is clear that developing tissues are more sensitive than their fully grown equivalent (Anon 1980). Children of course have greater life expectancy than adults and hence more opportunity for sequelae of radiation to be expressed. These arguments provide good reasons for reducing relative energy deposition in paediatric patients compared to adults. However in contrast, the dimensions of a paediatric abnormality detected by scintigraphy may be smaller than the corresponding adult lesion. This implies a greater absolute spatial resolution is required for the paediatric examination which can result from a higher resolution collimator than that used for adults. Also a shorter imaging time may be necessary for small children to reduce the possibility of patient movements. These latter arguments imply a greater relative deposited dose is needed for paediatric patients than adults. If single photon emission computed tomography is considered necessary for a particular scintigraphic study, this too usually causes the quantity of administered radiotracer to escalate. The present work so far has not required this refinement, although the facility was installed in Bordeaux in 1982 and has been available at the Children's Hospital since January 1985.

The number of detected counts per unit area is directly related to the contrast resolution in the scintigraphic image. This can be expressed as an information density and it is the final quantity to which

in principle administered dose and resulting irradiations are subordinate. The adequacy of the information density in this work can be deduced from the detailed nature of the results obtained and the wide range of information made available. When a comparison is possible with another modality in this work, nuclear medicine is shown to be more adept at recognising GOR. Apart from all the other advantages of scintigraphic methods over their radiological homologues, discussed in detail above, it must be emphasised here that the deposited radiation dose from radionuclides is less than that from Xrays. Little work has been reported on the long term effects of diagnostic doses of the swallowed radiopharmaceutical used in this work, or any other radiotracer used for imaging, because of the difficulty involved. This difficulty arises because the assessment must be predictive, rather than based on recorded experience, since it depends on such low absorbed dose rates. Thus the statistical problems associated with a derivation of any reliable risk estimation for these low exposures are considerable, but an extrapolation from known effects of higher doses implies there is no significant danger (Pochin 1987). For example it has been shown that if a comparison is to be made between those exposed to 1 rad of low LET radiation and controls to determine the increase in tumour induction above the rate of spontaneous cases, about 10^7 persons would be required for each group (Roedler 1986).

Having described the calculation of dose deposited after the swallowing of non absorbed Tc-99m and the calculation's relevance to the diagnostic use of radionuclides, numerical results of the present work will be considered. Previously published dosimetric values relating to swallowed Tc-99m sulphur colloid in paediatric patients are presented in Tables 8,4 and 8,5. The results of Castronovo for seven organs and the whole body were obtained from a bolus model with four compartments in the

GIT. Monoexponential decay for activity in each compartment was used to obtain effective residence times (Castronovo 1986). It is clear that at any given age absorbed dose for each compartment increases with distal movement of the radiotracer through the GIT, with one minor exception, that of neonatal stomach and small gut where deposited doses are very similar (383 and 370 mrad/0,1 mCi respectively). The apparent monotonic decrease of dose with increasing age for each GIT compartment in the results of Stabin and the present work, must of course be reconsidered after allowance has been made for the different doses administered at different ages. In the work described here, the swallowed doses ranged between 0,1 and 0,6 mCi. The current discussion assumes administration of a typical swallowed quantity of Tc-99m as described above, but when considering these (or any other) dosimetric results in a particular patient, it is always wise to reflect if there are any special circumstances relevant to the patient, which alter the assumptions made when the dosimetric model was derived. If such conditions exist then there may be cause to modify the administered dose of radioisotope, in terms of the guidelines described in Chapter 7.

The swallowed quantities of Tc-99m used in this work (0,1 to 0,6 mCi) were comparable to, or more conservative than, those reported by other workers which ranged between 0,15 mCi (Tolin et al 1979, Heyman 1982) and 1 mCi (Malmud et al 1982). When the different administered doses (typically 0,1 , 0,3 , 0,5 , 0,6 and 0,6 mCi for neonates and patients aged 1, 5, 10, 15 y and adults respectively) at different ages are incorporated into the dosimetric calculations the maximum absorbed dose from the present work is found in the large gut for a one year old patient. From Table 9,1 this is so whether the S values of Stabin (Stabin 1987) or the NCRP report No 73 (Anon 1983a) are used. These greatest deposited doses are 480 and 540 mrad respectively. The

predictions of Castronovo's model (which to be directly compared with the present work must be based on identical swallowed doses, as has been done in compiling Table 9,1) give the maximum absorbed dose in the lower large gut of a one year old patient. However this dose is 1,14 rad. This is about twice that of the present model. Such a discrepancy is interpreted to reflect the more realistic nature of a compartmental model which allows serially for both filling and emptying, as in fact happens in the relevant regions of the human GIT.

However the same anatomical information and its variation with age between the neonate and 15 year old are presumably equally available to the present writer and previous calculators of absorbed dose after a swallowed radioactive liquid passes through the GIT. Thus the changes of deposited dose with age, when allowance is made for the different swallowed amounts of Tc-99m, follow the same general trends. For all three calculations with results in (mrad per 0,1 mCi) given in Tables 8,5, 8,11 and 8,12 the following are observed. The maximum total absorbed dose in the stomach is for the neonate followed in order by ages 1, 5 and where available 10, 15 y and adult, except for the calculations using Stabin's S values, where the one year old has a slightly higher absorbed dose than the neonate, but the difference is only about 2%. For small and upper large gut all three compilations indicate there is maximum absorbed dose at age 1 y. This is followed by age 5 y in the present work and for the upper large gut in Castronovo's calculation by 0 y (Table 9,1). When the lower large gut is considered with the model derived here, the deposited radiation is greatest in patients of ages 0 and 1 y and these doses are little different (508 and 480 mrad respectively). Then follow other ages in chronological order with a bigger gap occurring below 5 y than above this age (Table 9,1).

As there is passage of the radiotracer distally through the gut, the differences between the results of the model presented here and others are likely to become more apparent and this is indeed seen. An explanation for this probably arises from the effects of multiple filling and emptying of all four compartments in series, which are accumulative as the gut contents move onward, since the only tracer motion postulated is prograde, there being no reason to consider any retrograde movement within the time scale under consideration. However the overall agreement otherwise implies that the general anatomical considerations mentioned above are reflected in results of all three calculations.

The relative importance of absorbed dose from swallowed Tc-99m in the distal gut was not fully appreciated by the first persons who considered the matter and whose results are given in Table 8,4. Although enough time has elapsed between deglutition of the radiotracer and its appearance in the distal gut for physical decay of the Tc-99m ($t_{\frac{1}{2}}$ = 6,02 hours) to be significant, the relative effect of the competing processes depends on an integral of activity with respect of time. When Figures 8,1 to 8,6 are examined it is clear that the large gut transit time contributes significantly to this integral and hence to the relevant absorbed dose. This is an illustration of how a detailed calculation can sometimes modify an intuitive, but incorrect, opinion which in this case is that radiation from swallowed non absorbed radiotracer with a physical life of a few hours is most likely to deposit more energy in the foregut than hindgut. The first report which considered paediatric dosimetry resulting from swallowed Tc-99m sulphur colloid described only effects upon stomach, gonads, thyroid and whole body. Lungs too were of concern if significant amounts of activity were aspired (Heyman et al 1979). Other work, contemporary with that report, presented the radiation dose to "small gut and proximal colon" as a single unit and also the whole

body (Rudd et al 1979). As late as 1984 in a compilation of paediatric absorbed radiation doses after a variety of diagnostic procedures using radionuclides, when swallowed Tc-99m sulphur colloid was considered, deposited doses were quoted for a 5 y old child and a statement was made that the stomach was the critical organ. Absorbed doses were only quoted for stomach, ovary, testes and whole body (Savage 1984). Now that this question has been considered in greater detail in the present work, the relative doses absorbed by different parts of the gut at different ages can be given. But it must be kept in mind that although these doses in GIT compartments are within acceptable limits, especially in comparison with radiological procedures, no effort must be spared to reduce these doses wherever possible, without detriment to acquired information density. This desired end may be accomplished by use of improved computer techniques, electronic or radiation detection apparatus, or more appropriate radionuclides and radiopharmaceuticals, whenever any of these advances become available.

The application of the present dosimetric model has been to the GIT only in this thesis. However it is clear that it can be applied to other situations where there is emptying and filling of radiotracer into and out of regions, organs etc. Calculations have already been made for injected Tc-99m DTPA within the blood, kidneys and urinary tract and preliminary results give absorbed doses comparable to those of other models. Further refinements and applications to other radiopharmaceuticals and organs are planned. It should be noted the present dosimetric model is independent of the details of any S values or physiological information used to obtain the results quoted here. Thus if improvements to any of these items are reported in the future, the revised data can easily be incorporated into the necessary calculations

and modified values of the absorbed radiation doses can readily be obtained.

In summary it is suggested here that a more realistic and hence accurate calculation of absorbed radiation dose after swallowing non absorbed Tc-99m, has been described. In particular the results of calculation of deposited radiation in the distal gut and in the youngest patients have been discussed. Where agreements can be found with previous detailed work (trends of absorbed dose with variation in age and anatomical site) there are reasons for such agreement. Where increasing differences with previous work are found (absolute values of calculations, most especially in distal regions) again this can be explained and leads one to hope that the differences are understood in terms of the previous discussion and that a useful improvement in the comprehension of this matter has been presented. The variation of absorbed dose with age shows that infants and young children suffer the greatest absorbed dose, but it is less than had been previously believed. However a fuller understanding of the relevant dosimetry does not absolve the practitioners and users of paediatric nuclear medicine from continuing to ensure it is used so the greatest benefit may result for the patient.

Table 9,1 The absorbed radiation dose (mrad) for each anatomical compartment of the GIT with adjustments made for the typical swallowed dose of Tc-99m sulphur colloid at different ages. These swallowed quantities were 0,1 , 0,3 , 0,4 , 0,5 and 0,6 mCi respectively for patients aged 0, 1, 5, 10 and 15 y. The resulting absorbed doses are listed in descending order and followed in brackets by the ages of the patient in years. Sources for this material are as follows:

A: Castronovo's calculation (Castronovo 1986) (Table 8,5).

B: The present model using S values from the NCRP report No 73 (Anon 1983a) (Table 8,11), and

C: The present model using S values from Stabin (Stabin 1987) (Table 8,12).

Target organ	Absorbed dose in mrad (Age in y)					Source
Stomach	383 (0)	279 (1)	203 (5)	154 (10)	133 (15)	A
	468 (0)	366 (1)	275 (5)			B
	295 (1)	289 (0)	204 (5)	163 (10)	100 (15)	C
Small gut	492 (1)	372 (0)	336 (5)	292 (10)	217 (15)	A
	459 (1)	331 (5)	266 (0)			B
	330 (1)	262 (5)	221 (10)	201 (0)	166 (15)	C
ULI	801 (1)	656 (5)	596 (0)	448 (10)	323 (15)	A
	540 (1)	476 (5)	428 (0)			B
	444 (1)	364 (5)	310 (0)	310 (10)	224 (15)	C
LLI	1140 (1)	927 (0)	776 (5)	600 (10)	433 (15)	A
	508 (0)	471 (1)	266 (5)			B
	480 (1)	426 (0)	293 (5)	210 (10)	141 (15)	C

CHAPTER 10: CONCLUSIONS

"Not from the stars do I my judgement pluck".
William Shakespeare; Sonnet XIV.

The main conclusion presented is that a scintigraphic study of infant and childhood oesophageal and gastric function as devised and practised in the work described here can readily provide important and unique results. Hopefully a valuable addition to the paediatrician's diagnostic armamentarium results.

A syndrome, of an oesophageal dysmotility analagous to the diffuse oesophageal spasm syndrome of adulthood, previously unrecognised, has been described and its diagnostic features clearly recognised by scintigraphy, especially when used in association with a condensed image of oesophageal transit data. The recognition of oesophageal dysmotility has important practical consequences in the work up of patients being considered for a Nissen fundoplication as described. Similarly the use of the examination described here for investigation of repeated respiratory problems, apnoeic or cyanotic episodes, SIDS etc can result in detection of GOR or other abnormalities and so allow appropriate treatment which otherwise may not be offered. Also recognition of the passage of swallowed liquid into the larynx or trachea has been shown to be possible by means of a newly described technique, even in the presence of simultaneous normal deglutitions. Hence this work has important practical consequences in terms of management. It also provides theoretical insights into the understanding of paediatric gastro oesophageal physiology and pathology. The dogmatic statement that the neonatal LOS never closes completely between deglutitions is shown to be untrue. The situation where a tired oesophagus is observed can be interpreted as suggestive of muscular control of inferior oesophageal peristaltic action.

A controversy in the literature concerning the relation between GOR and rapidity of gastric emptying is settled in this work by the statistical significance of the present results, which is believed to be a great improvement on previously published work. In essence there is no relation between increased emptying rate and lack of GOR.

In contrast the presence of GOR is related to OTT, the mean value increasing with the severity of GOR. In a similar way oesophagitis is related to OTT. Unlike gastric emptying, OTT is age related. This can be readily explained by the increasing length of the oesophagus with growth. In patients up to the age of 3 years there is no effect of age, sex and upon gastric emptying rate in normals. Also values for gastric $t_{\frac{1}{2}}$ in normal infants (53,3 $\pm$ 9,7) and (72,7 $\pm$ 6,9)min for maternal milk (n = 8) and other liquids (n = 133) respectively were obtained from greatly increased numbers than the very few previous determinations. Correlations between various characteristics of GOR, OTT, oesophageal spasm and age were examined and the relation was found to be very complex.

Since the current situation concerning absorbed radiation dose in patients of any age after deglutition of a non absorbed radionuclide depends on an unrealistic model, a new model was devised which allowed continual exponential removals distally of the tracer from each of four compartments representing part of the gut. Both physical decay and transit to the distal compartment are included in this calculation. This model although mathematically more involved than previous ones is believed to be a closer approximation to the truth.

In all, a paediatric scintigraphic examination has been derived with a combination of characteristics believed to be unique, described and adequately tested, which confirms its ready availability as a routine study in a normally

equipped and staffed nuclear medicine department, whether situated in the first or third world. A large variety of paediatric disorders can profitably be investigated, information be derived non invasively that is both not readily obtainable by other methods and which permits considerable assistance for subsequent management. For example the great majority of GOR are of duration much less than 60 s and so are unlikely to be detected by Xrays or routine non invasive means. The scintigraphic study is practical in terms of the time it requires, and hence the patient throughput, and also in its recognition rate for abnormalities. Such studies deserve to be better known and are not generally practised in the comprehensive form described here, hence it is hoped some advantage will result for paediatric diagnosis and care from this work, in terms of cost benefit, risk benefit and most importantly of all, information benefit.

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"He who learns from his fellow a single chapter, a single rule, a single verse, a single expression, or even a single letter, ought to pay him honour." R Meir, Ethics of the Fathers, Chapter 6.

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APPENDIX 1: EXPONENTIALS, SWALLOWED RADIONUCLIDES AND GASTRO INTESTINAL DOSIMETRY

> "Again the sciences that deal with first principles are the most exact of all, for those employ few principles, like arithmetic, are more exact than those that employ more.. And the things best to know are first principles and causes". Aristotle; Metaphysics, Chap 2.

Exponential variations occur throughout nature and are characterised by a variation between two variables, say y and t, of the form:

$$(dy) = -ky(dt)$$

where k is a constant called the decay constant.

Integration gives: $y(t) = Y_0 \exp(-kt)$

where Y_0 is a constant of integration being the value of y when t = 0 or y(0). The value of t at which $y = 0{,}5\ Y_0$ is called the half life for obvious reasons and is designated here by $t_{\frac{1}{2}}$ or $t_{0,5}$. Decay of activity in a given organ or region may be due to physical or biological processes. Each process can have its own half life denoted here by t_p and t_b respectively. Simultaneous variation due to these two exponential decays results in a third exponential described by t_e, the effective half life. Now:

$$(1/t_e) = (1/t_p) + (1/t_b)$$

The relation between half life and decay constant k is:

$$k = (\ln 2)/(t_{0,5})$$

Thus an effective decay constant is also related to physical and biological decays by:

$$k_e = k_p + k_b$$

with suffices having the same meaning as for half lives.

In dosimetry the effective residence time (r_e, the reciprocal of k_e) of a radionuclide in an organ or region is often used. Thus:

$$r_e = 1/(k_e)$$

A calculation of absorbed radiation dose requires the cumulated activity A_c. This is simply related to the initial activity A_0 and r_e. For:

$A_c(mCi.hour)/(A_o(mCi)) = r_e(hour)$

When a bolus model is used its transit time t_t is related to t_b if excretion is exponential thus:

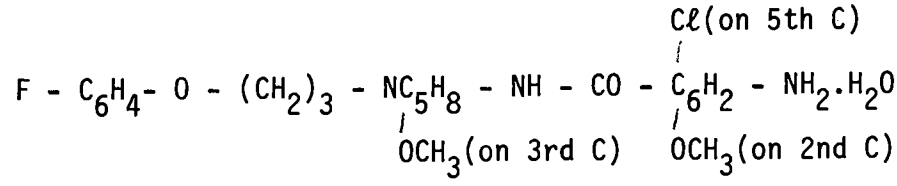
t_t = Integral of $(\exp(-0{,}6931.t/t_b).dt$

All these relations are necessary when an attempt is made to obtain data for use in our dosimetry model, to permit correlation of different values quoted in the literature.

APPENDIX 2: PROPERTIES OF CISAPRIDE

"The old order changeth, yielding place to new".
Alfred Tennyson; Morte d'Arthur.

Recently a new experimental drug for use in patients with disturbed gastro intestinal motility has been produced by Janssen Pharmaceutica, Beerse, Belgium and made available through Professor H Rode of the Department of Surgery of the Children's Hospital. Its structural formula is:



and it differs from comparable drugs in the following ways. Cisapride increases release of acetylcholine in stomach, duodenum, ileum and colon of guinea pig in vitro. In vivo it quickens gastric emptying of solids and liquids in rats and dogs (Schuurkes et al 1983) and in the latter causes increased small and large gut contractility. Also it has dopaminic and muscarinic properties. However most importantly there is an absence of central, cardiovascular and endocrine effects (Anon 1985). Independent observations confirm that it increases acetylcholine release within the rat small gut (Hardcastle et al 1984). In normal adult humans there is an increase in LOSP (though some authors maintain this is true in the fasting, but not postprandial state (Smout et al 1985)), gastric emptying rate for liquids (Corazziari et al 1983, Jian et al 1985), increased flatus after GIT operations (Reyntjens et al 1984a), increased small gut transit rate (Baeyens et al 1984, Van Daele et al 1984) and colon motility (Reboa et al 1984, Lee et al 1984). In dyspeptic adults gastric emptying is similarly quickened by cisapride (Urbain et al 1985). However there is disagreement regarding its effect on the normal adult oesophagus. After administration of similar doses, some report increased peristalsis pressure (Corazziari et al 1983) and others no change (Smout et al 1985). Other drugs used to treat foregut dysmotility

are acetylcholine analogues or cholinesterase inhibitors which have marked effects on secretion, or such drugs as dopamine antagonists which affect dopamine activity away from the gastro intestinal tract. Hence it is believed that all these disadvantages may be avoided by use of cisapride.

In toxicity tests (Anon 1985) the LD_{50} values (for rats and dogs) ranged between 28 and 37 mg/kg for intra venous administration and above 1280 mg/kg for oral and subcutaneous administration. In examining side effects in dogs and rats the lowest oral dose to produce any observed acute effect was 320 mg/kg which produced diarrhoea, ataxia and tremors in the dog. Subacute toxicity was sought after 3 months of oral dosage and for 10 mg/kg traces of urine acetone were found in male rats and no other effects below a dose of 160 mg/kg. In dogs the only effect at 10 mg/kg was a terminal increase in serum cholesterol after 3 months. When chronic toxicity effects were sought in rats after 3 months of 40 mg/kg oral dose of cisapride, none were found. Chronic toxicity after 10 mg/kg in rats showed only a decrease of white blood cell numbers in females and 160 mg/kg caused marginal serum cholesterol increase and lower weight gain. A variety of searches for mutagenesis in Salmonella typhimurium, Drosophilia, mice and rats was negative. Similarly after 18 months of doses of cisapride ranging from 2,5 to 40 mg/100g of food no carcinogenic potential was found in mice (Anon 1985).

In man maximal plasma levels were obtained between 1 and 2 hours after an oral dose of 10 mg with a subsequent monoexponential plasma level decay having half life about 10 hours (Anon 1985). After considering all this information, the total daily dose in the patients discussed in this work of 1 mg/kg administered orally in three equal parts is seen to be justified.

Cisapride has been administered to 1600 human adults and adverse reactions noted were diarrhoea and abdominal cramps. For both the incidence

was below 2%. Very rarely transient light headedness was experienced. Absolute bioavailabilities after various forms of oral preparation range from 40 to 50%. The unavailable cisapride is likely to be metabolised during its first passage through gut wall and liver. Absorption is unaffected by the presence of food and by achlorhydria. Elimination is shared approximately equally by faeces and urine with 5% and under 3% respectively eliminated in the unchanged form by each route. About three quarters is norcisapride, the major metabolite.

Specific actions of cisapride on the human foregut have been reported as follows for normal adults. It increases LOSP by between 30 and 95% (n = 43). Oesophageal contraction pressure was increased in 28 subjects by more than 26%, but unchanged in 6. GOR observed by a pH probe was reduced by 60% (n = 10). Gastric emptying of saline in 6 normal males and of solid and liquid in 10 with symptoms of gastroparesis was measured after administration of cisapride. In the normals mean measured $t_{0,5}$ for liquid decreased from 22,5 to 12,2 min (p below 0,01). In the symptomatic patients liquid emptying was unaffected but, "cisapride significantly enchanced gastric emptying of solids" (Anon 1983b). Other results were similar $t_{0,5}$ = 22,2 and 10,1 min for placebo and cisapride but other drugs caused faster emptying (Walters et al 1986). Cisapride is also effective for post operative gastro paresis (Cullen et al 1987). Stomach and small gut transit times of Ba sulphate were similarly decreased by cisapride (n = 230) with p below 0,01. Stomach and duodenal motility (product of amplitude and duration of contraction) also increased. Gastric secretion (n = 15) and prolactin levels (n = 28) are unaffected by cisapride. Finally discomfort due to upper GIT malfunction was significantly relieved (with p below 0,01 and n = 63). All these results were obtained from double blind trials using placebo (Reyntjens et al 1984b).

Cisapride was used in paediatric patients at the Children's Hospital who had established foregut problems manifesting as oesophageal dysmotility, delayed gastric emptying or GOR. It exerts a marked effect within 7 minutes of its oral administration for when it has been administered with an oesophageal pH probe in situ recording a flat trace, significantly decreased readings are seen denoting GOR within seven minutes in contrast to placebo administered under similar conditions (Rode 1985). A possible explanation for this effect is that absorption of cisapride increases stomach contractions and so causes GOR (Rode 1985).

The only published work on paediatric use of cisapride known to the author has been in neonates with a short gut remaining after extensive resection (Puntis et al 1986), its use to correct absent postprandial motility in a child with cystic fibrosis (Hyman 1986), to demonstrate improvement in GOR in 14 infants and children who had repeated respiratory problems (Saye et al 1987) and the use of pHmetry at the Children's Hospital to confirm the beneficial effect on 40 infants of cisapride used to treat GOR (Rode et al 1987). In the latter two studies GOR was monitored with pH measurements. However it has been administered for 4 weeks (0,1 to 0,3 mg/kg tds) to 137 infants with excessive regurgitation and resulted in improvement in 81%. (Placebo gave improvement in about 60%). However 8 out of the 14 patients followed up relapsed (Van Eygen 1986).