

THE ONTOGENY OF SMALL INTESTINAL MOTOR ACTIVITY

IN THE HUMAN PRETERM INFANT

by

W. MICHAEL BISSET BSc, MB ChB, DCH, MRCP, MSc

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Department of Child Health,
Institute of Child Health,
30, Guilford Street,
London WC1N 1EH.

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Name of Candidate WILLIAM MICHAEL BISSET

Address

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In the preterm infant immaturity of intestinal motor function is a major limiting factor in the ability to introduce enteral feeding. Very little is presently known about the development of this activity.

Small intestinal motor activity is characterised by a fasting cyclical pattern of activity which is disrupted by food and is replaced by a continuous pattern. Using continuously perfused multilumen nasojejunal catheters the development of fasting small intestinal motor activity has been studied longitudinally in 12 preterm infants on 28 occasions, from 28 to 42 weeks gestation, and in 9 of these infants the motor response to milk feeds has also been defined.

With increasing gestational age well defined maturational changes in fasting motor activity occur. In the fasting state four patterns of activity were seen with increasing gestational age, ranging from random activity at 28 weeks gestation to clustered phasic, persistent phasic and eventually an organised motor complex pattern near term. Associated with these changes smooth muscle contractility [gastric antral pressure ($p < 0.005$), average duodenal pressure ($p < 0.001$)], propagated activity index ($p < 0.01$) and slow wave frequency ($p = 0.005$) all increased in a highly significant fashion.

When given a bolus feed appropriate to the infants age, in the very preterm infant (28-30wks) a fed pattern did not occur but with increasing gestational age ($p = 0.005$), increasing feed volume ($p < 0.0001$), and particularly with increased time fed enterally ($p < 0.0001$) the fasting pattern of activity was disrupted and replaced by an increasing length of post prandial activity.

The development of fasting motor activity is largely gestationally dependant and relies on the maturation of enteric neural connections while in the fed state the early exposure of the gut to enteral feed enhances the humorally mediated post prandial motor response.

A knowledge of these developmental patterns and the response of the intestine to enteral nutrition should provide a guide to determining the timing and frequency of enteral feeds that will best facilitate enteral feed tolerance and infant growth.

DECLARATION

The work presented in this thesis was performed over two and a half years while working as a research fellow at the Institute of Child Health, London and as an honorary registrar at The Hospital for Sick Children, London and St. Mary's Hospital, London.

All the experiments were carried out by myself. Dr J. B. Watt (Winicott Baby Unit, St. Mary's Hospital) helped with the recruitment of subjects for the study and with the collection of patients details.

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PART I
INTRODUCTION

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CHAPTER 1

GENERAL INTRODUCTION

1 GENERAL INTRODUCTION

With recent improvements in the care of the very preterm neonate it is now common for infants of less than 28 weeks gestation and of less than 1000 grams weight to survive. These changes have been brought about largely by improvements in the obstetric management of the preterm delivery and by major advances in the care of respiratory disorders in such preterm infants.

Having to a large extent overcome the problem of the respiratory distress syndrome, a major problem that remains unsolved is that of nutrition. The preterm infant requires a steady balanced input of nutrients to meet its own very rapid growth potential and the additional requirements from neonatal stress whether they be thermal, infective or metabolic. Where nutritional intake is inadequate, growth and development fail to occur and morbidity and mortality from a wide range of neonatal insults increases. (Fanaroff,1979) It is therefore quite clear that adequate nutrition is a major determinant of the ultimate survival of the preterm infant.

Normally all nutritional requirements are met by the enteral route. In the preterm infant however the immaturity of gastrointestinal function is a limiting factor and the intravenous route, with all the problems of venous access and sepsis that this entails, is frequently used. While gastrointestinal absorptive

(McNeish et al, 1979) and secretory function (Grand, Watkins and Torti, 1976) is moderately well developed by 28 weeks gestation the development of adequate motor function lags many weeks behind. (McLain, 1963) As a consequence , the early introduction of enteral nutrition, particularly in the ill preterm infant, may result in the intolerance of feeds. (Dunn, 1963) The resulting abdominal distension and increased risk of gastro-oesophageal reflux are both liable to affect the delicate respiratory balance in these infants.

The reasons for the delay in motor maturation and the factors which control and influence the maturation of gastrointestinal motor function are at present very poorly understood. While a little is known about the motor activity of the oesophagus (Gryboski, 1965) and the factors which determine the rate of emptying of fluids from the stomach (Siegel, 1983) in the preterm infant, very little is known about the motor activity of the small intestine. Failure of small intestinal motor function will delay gastric emptying and seriously compromise the nutrition of the preterm infant. Without a better understanding of small intestinal motor development, our ability to accurately time the introduction of enteral feeding and to determine the most appropriate mode and frequency of delivery will remain limited. At present feeding regimes in preterm nurseries are based more on local dogma than on sound physiological reasoning. The great variation in feeding

regimes from one unit to the next testifies to this.

An improved understanding of neonatal gastrointestinal physiology may therefore lead to improved neonatal nutrition and increased neonatal survival.

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CHAPTER 2
THE SMALL INTESTINE:
FUNCTION AND MOTOR CONTROL

2 THE SMALL INTESTINE: FUNCTION AND MOTOR CONTROL

2.1 The Function of the Small Intestine

Food is moved by the co-ordinated activity of intestinal smooth muscle from one specialised region of the gut forward to the next. The oesophagus acts as a conduit for the transfer of food from the mouth to the stomach where it is stored and mixed prior to its controlled passage into the small intestine. In the small intestine the food is digested and absorbed with subsequent transit into the large intestine where salt and water are conserved prior to excretion.

This simplified view of gastrointestinal function disguises the very complex nature of the many systems which interact to give normal intestinal function. (Table 2.1)(Chadwick and Phillips, 1982)*

Normal small intestinal function requires the combined action of each of these systems and if any one should break down intestinal function will be compromised. The break down of absorptive function in glucose-galactose malabsorption results in chronic diarrhoea, the loss of pancreatic secretion in cystic fibrosis results in maldigestion, the excess of hormonal secretion that occurs in pancreatic tumours results in severe secretory diarrhoea and the loss of normal gut immune defences results in recurrent enteric infection and an enteropathy. Similarly in patients with pseudo-obstructive disorders (Maldonado et al, 1970) or

TABLE 2.1

Small intestinal functional systems.

DIGESTION - LUMINAL
- MUCOSAL

TRANSPORT

METABOLISM

ENDOCRINE

MOTILITY

MUCOUS

IMMUNOLOGICAL

in preterm infants where small intestinal motility is poorly developed intolerance to enteral feeds occurs.

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2.2 The Gross Structure of the Small Intestine

In man the small intestine occupies the major length of the gastrointestinal tract and is the major organ of digestion and absorption. In the adult the small intestine varies in length from 3-5 metres depending on the state of contraction, while in the term infant the length is probably nearer 1.5 metre. The small intestine is divided into the duodenum which extends from the pylorus to the duodenal-jejunal flexure at the level of the ligament of Treitz. The remaining small intestine is arbitrarily divided into the jejunum and ileum which represent the proximal two-fifths and distal three-fifths respectively.

In cross section the structure of the small intestine is grossly similar throughout. The inner circular lumen is lined by a highly convoluted mucosa which exposes a large surface area for the absorption of nutrients. Within the submucosa lies the muscularis mucosa. This thin muscular structure plays a role in the movement of the mucosa during digestion but takes no part in the bulk movement of nutrients along the small intestine. (Wyburn, 1972) The muscularis propria comprising an inner circular and an outer longitudinal layer provide this function.

Two distinct neural plexuses lie within the small intestine. The submucosal or Meissner's plexus is located between the muscularis mucosa and the circular

muscle layer, in the submucosa, while the myenteric or Auerbach's plexus lies between the circular and longitudinal muscle layers. Nerve fibres freely travel between these plexuses with extensions distally into the mucosa and proximally through afferent and efferent fibres which project both to and from the brain stem and cerebral cortex. (Gershon and Erde, 1981)

2.3 Motor Control

Normal small intestinal motor function is controlled by a combination of neurogenic, myogenic and humoral mechanisms. As a result of the activity of these systems the gut is able to coordinate a number of complex functions, including the control of motor activity over the whole length of the intestine, and the ability to sense the presence of intraluminal nutrients and respond appropriately. The understanding of how each of these factors interrelates to bring about this overall control still however remains unclear. Information obtained from patients with pseudo-obstructive disorders (Tanner, Smith and Lloyd, 1976., Milla et al, 1983a) shows quite clearly that the breakdown of any one of the three controlling systems results in a loss of normal intestinal motility. (Weisbrodt, 1981)

By studying the ontogeny of intestinal motor function in the preterm infant we have an opportunity to observe the development of these controlling systems.

2.3.1 Intestinal Smooth Muscle

The smooth muscle of the small intestine is arranged in two layers, an inner circular and an outer longitudinal layer. The co-ordinated activity of these two layers is responsible for the orderly intraluminal movement of food. The muscle layers extend the whole length of the small intestine and because the fibres in each layer lie at right angles to one another, contraction and relaxation of the smooth muscle can result in either shortening or lengthening of the intestine when the longitudinal muscles are involved and in constriction or relaxation of the lumen with the circular muscle layer. It is the co-ordinated action of these muscle layers which cause the characteristic peristaltic and segmenting motor activity that is seen in the small intestine.

Structure

Under the light microscope the orientation of the two muscle layers can be seen clearly. Within each layer the cells lie approximately parallel to each other forming a sheet-like structure. The smooth muscle cells are small mononucleate cells of approximately 500um in length and 5um in diameter. Unlike skeletal muscle the cells are not striated and their small size results in a very large surface area/ mass ratio. This leads to difficulty in the maintenance of intracellular ion concentration, which is overcome by increased membrane

resistance. (Gabella, 1981)

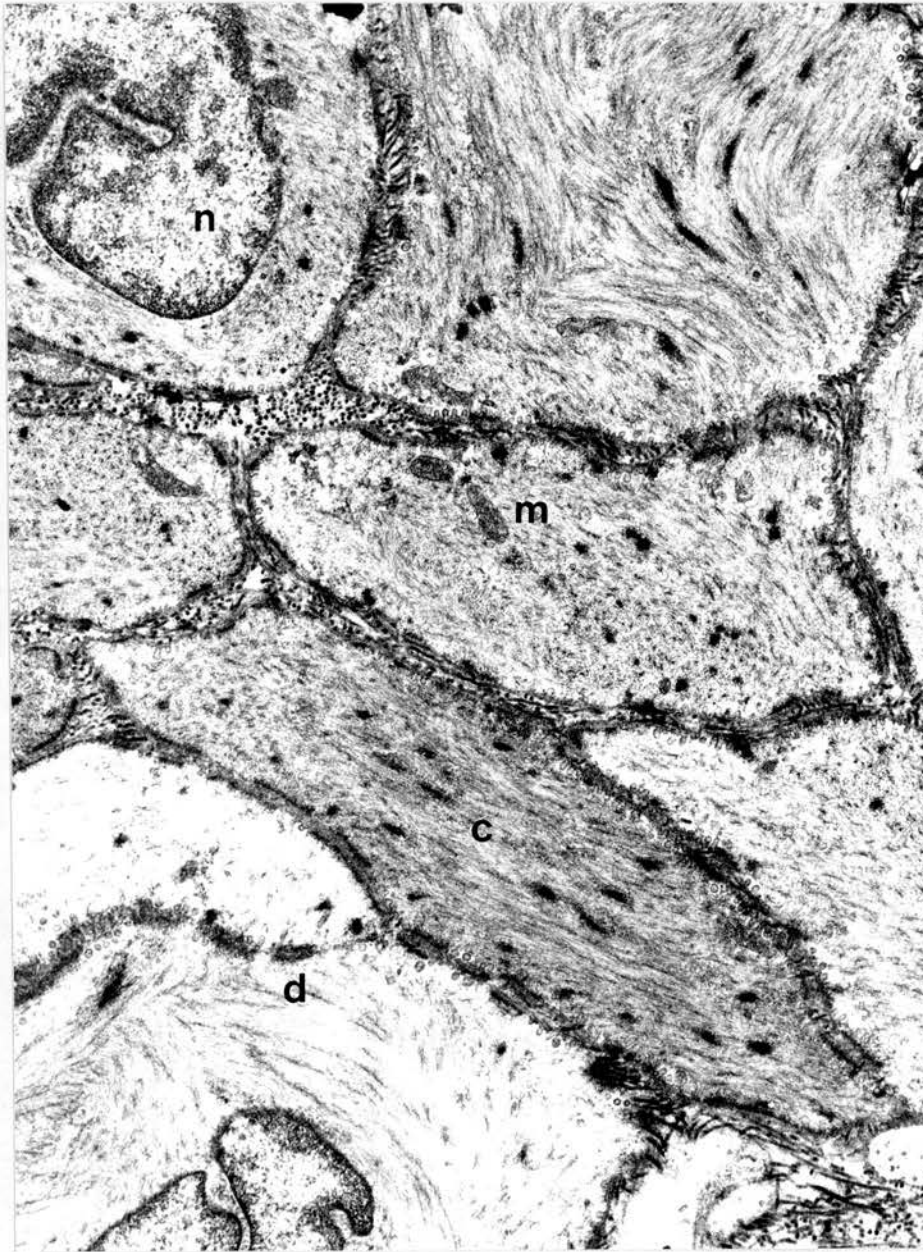
When examined under the electron microscope up to 50% of the smooth muscle membrane is covered by electron dense bands which anchor the contractile protein actin to the cell membrane. Because of the random positioning of these dense bands the cells lack the ordered striated appearance of skeletal muscle. (Fig. 2.1) Frequently dense bands on adjacent cells are closely approximated forming a structure known as an intermediate junction. At this point the cells are held together by an electron dense intercellular cement. The connection of the contractile apparatus from one cell to the next thus allows the transmission of motor activity throughout the muscular syncytium. (Gabella, 1981b)*

While each skeletal muscle cell is innervated by a motor nerve, the nerve to muscle cell ratio is very much less than one to one in smooth muscle. Therefore electrical signals must be transmitted from one cell to the next and this occurs by the gap junctions. Gap junctions are areas where the plasma membrane of 2 cells is in close proximity and small channels allow the passage of ions between these cells and thus allows the coupling of a large number of cells. Coupling is greatest in the direction of the long axis of the cell, and is greater in the circular layer compared to the longitudinal layer where very few gap junctions are present.

Between the layers of smooth muscle the interstitial cells of Cajal are found. It has been suggested that

Fig. 2.1

An electron micrograph of intestinal smooth muscle.
(x 12,400)



—
1 micron

n = nucleus, m = mitochondria, d = dense bands
c = contractile fibres

these cells represent modified sympathetic neurons but, electron microscopic studies suggest that they more closely resemble modified fibroblasts. The cells of Cajal do however frequently lie very close to enteric nerve endings and occasionally form gap junctions with smooth muscle cells. It has been proposed that they provide electrical coupling between the circular and longitudinal muscle layers and that the rate of regular depolarisation and repolarisation of the plasma membrane of smooth muscle cells, the electrical control activity (ECA), is controlled by these cells. (Hara, Kubota and Szurszewski, 1986)

Contractility

The main contractile proteins found in smooth muscle are actin and myosin. The contractile process is activated by an increase in intracellular Ca^{++} concentration from 10^{-7}mol/l to 10^{-5}mol/l which is triggered by depolarisation of the cell membrane. The increase in Ca^{++} concentration results from the movement of Ca^{++} out of mitochondrial stores and an increased inward flux of Ca^{++} from the extracellular space. The Ca^{++} binds to calmodulin which activates a myosin cross bridge phosphorylase with the formation of links between actin and myosin which, with the repeated hydrolysis of ATP, move over each other resulting in the contraction of the smooth muscle cell. The cell can contract to 1/4th of its original length when maximally contracted which

results in extensive convolutions of the cell membrane. The contractile activity is terminated by the removal of Ca^{++} from the cell and the restoration of the pre-contraction Ca^{++} level. (Grundy, 1985a) (Hartshorne, 1981)*

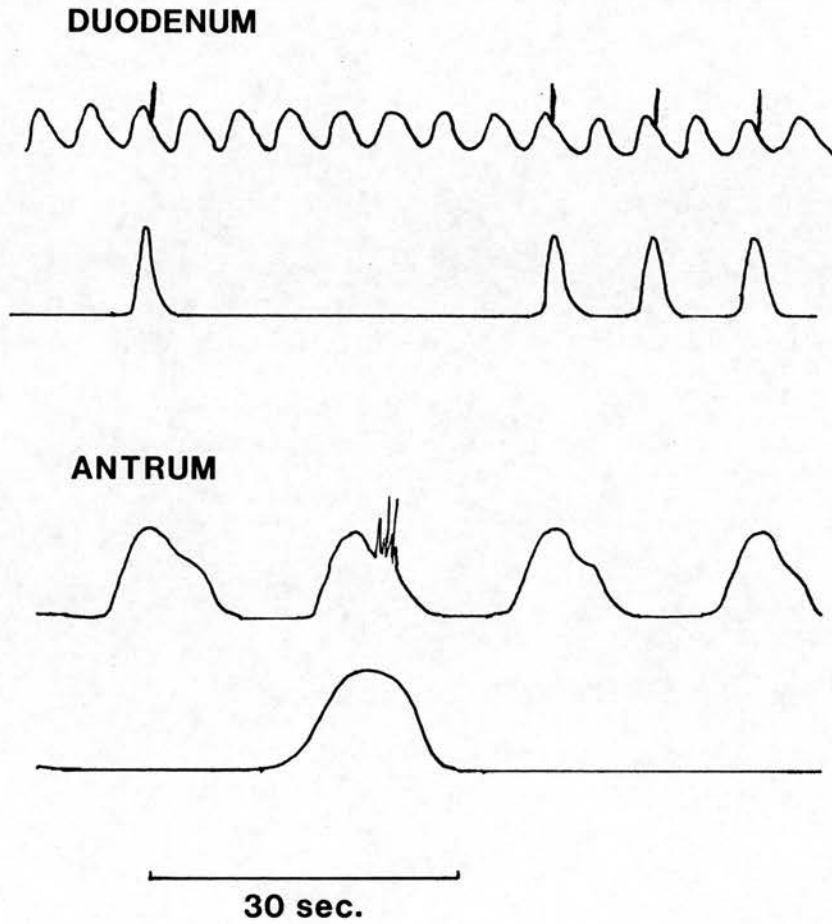
Myoelectric Activity

Intestinal smooth muscle, like smooth muscle elsewhere in the body, exhibits an inherent rhythmicity of its membrane potential. (Grundy, 1985a) This inherent rhythmicity or slow wave activity which is present at all times is perhaps best referred to as the electrical control activity (ECA). These fluctuations may be due to changes in the activity of the plasma membrane Na^{+}/K^{+} ATPase as they can be inhibited by the glycoside ouabain and by metabolic inhibitors such as 2-4 dinitrophenol. The frequency of the ECA varies from species to species and from one part of the gut to another. (Fig. 2.2) In the human a rate of 3 cycles per minute (cpm) in the stomach, 12 cpm in the duodenum, and 9 cpm in the ileum is seen. (Mangel, Connor and Prosser, 1982)*

The ECA results in fluctuations in smooth muscle excitability which determines the timing of action potentials or electrical response activity (ERA) and thus the generation of contractile activity. During the depolarisation phase of the ECA a threshold voltage may be reached which triggers the opening of voltage dependent channels and initiates the action potential. Excitatory stimuli will reduce the resting membrane

Fig. 2.2

A diagram of the electromyographic and manometric activity from the human duodenum (12 cpm) and gastric antrum (3cpm). Motor activity (shown below) occurs when electrical response activity is superimposed on the electrical control activity.



potential increasing the likelihood that the threshold voltage will be reached while inhibitory stimuli will increase the membrane potential.

The depolarisation of the membrane is due to the slow inward movement of calcium. Removal of Ca^{++} from the external environment abolishes the action potential, while the sodium channel blocking agent tetrodotoxin which blocks neural action potential has no effect on smooth muscle. Repolarisation is due to the fast outward movement of K^+ ions and as this occurs shortly after the action potential the degree of depolarisation or electrical response activity is limited by this efflux. Simultaneous myoelectric and motor recordings from intestinal smooth muscle have shown clearly that electrical response activity coincides with motor activity (Bozler, 1939)(Fig. 2.2) and that the degree of response activity determines the extent of smooth muscle contraction. While the ECA controls the timing of electrical response activity (ERA) and thus acts as an intrinsic pacemaker the frequency of ERA is controlled by the excitatory and inhibitory influences of the enteric nervous system and of circulating neurohumoral compounds. (Tomita, 1981)

As a result of the low electrical resistance between smooth muscle cells, a single action potential would soon be dissipated throughout the syncytium. The contraction of the smooth muscle therefore relies on the simultaneous activation of many smooth muscle cells. The

use of Ca^{++} as the ion that initiates both the action potential and the activation of calmodulin results in the efficient integration of smooth muscle electrical and contractile activity.

Where a gradient in the frequency of ECA exists, as occurs in the smooth muscle of the small intestine, (Diamant and Bortoff, 1969a & b) the fastest frequency activity can capture similar but slightly slower more distal activity. Such coupling of smooth muscle cells may be responsible for the formation of the duodenal pacemaker (Hermon-Taylor and Code, 1971)* and for facilitating the aboral propagation of motor activity.

An understanding of the influence of neurotransmitter and neurohumoral substances on smooth muscle excitability is essential if we are to better understand enteric neurophysiological function.

2.3.2 Enteric Neural Mechanisms

The wide spectrum of intestinal motor function relies on the presence of intact neural controls for normal enteric function. The drastic effect of the loss of these controls can be seen in Hirschsprungs disease, where there is aganglionosis of the distal large bowel, and in gut treated in vitro with the Na⁺ channel blocking drug tetrodotoxin. In both cases the loss of intrinsic neural control results in the contraction of circular smooth muscle with loss of propagated activity and a functional enteric obstruction. (Wood, 1972)

The neural control mechanisms lie at three distinct levels. At the first level lies the enteric nervous system, at the second the autonomic nervous system, and at the third the central nervous system. For some time it was felt that the enteric nervous system was purely an extension of the autonomic nervous system but it is now quite clear that this is not the case. While the abdominal vagus carries fewer than 2×10^3 efferent fibres (Hoffman and Schnitzlein, 1961), the enteric nervous system contains more than 10^8 cells (Furness and Costa, 1980) and it seems unlikely that vagal innervation has more than a modulatory role in intestinal motility.

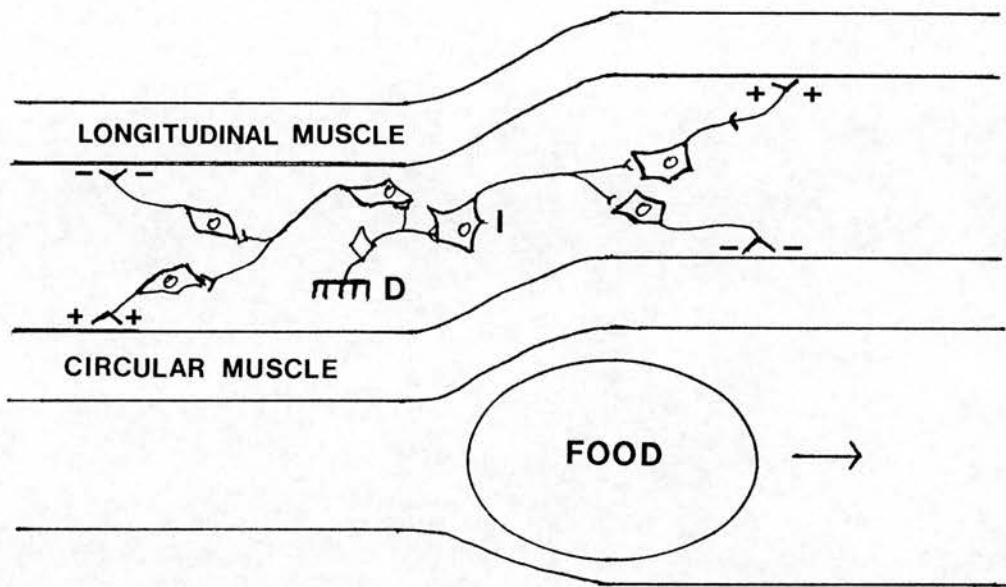
Enteric Nervous System

The enteric nervous system is composed of two distinct layers, the submucosal and myenteric plexuses. Within each layer there are a large number of nerves, some with (Gershon and Erde, 1981)

their cell bodies outside the intestine but the vast majority are intramural throughout their entire course. From the turn of the century it was realised (Bayliss and Starling, 1899) that the small intestine had a repertoire of movement that depended on the integrity of the enteric nervous system. It is only in the last 20 years that the extent of these controls and their underlying physiology has been more fully understood. Even today our understanding remains incomplete due largely to the great complexity of the enteric neural connections. Bayliss and Starling defined the peristaltic reflex, with distension of the intestinal lumen causing a propagated band of distal relaxation and proximal contraction of the intestinal smooth muscle. The peristaltic waves were independent of external neural control but were disrupted by enteric paralysis. Like other reflex pathways a sensory arm, a modulatory unit and an effector arm is present within the enteric nervous system. Stretch sensitive sensory neurones lie within the neural plexuses with intermediate neurones modulating this signal and sending simultaneous aboral inhibitory signals to the circular muscle and excitatory signals to the longitudinal muscles. Reciprocal control of the circular and longitudinal muscle layers results in the synchronous relaxation of one layer and the contraction of another. (Wood, 1981) A diagrammatic view of this reflex is shown in Fig. 2.3.

Fig. 2.3

The peristaltic reflex. In response to distension of the intestinal lumen, the reciprocal excitation and inhibition of the smooth muscle layers results in the orderly aboral propagation of the bolus of food.



CONTRACTION

RELAXATION

D = Distension Receptor

I = Intermediate Neurone

- = Inhibition

+ = Excitation

It is becoming increasingly clear that a large number of different nerve types and neurotransmitters are present within the enteric nervous system. The number of nerve cells in the intestine parallels that found in the spinal cord (Furness and Costa, 1980) as does the complexity of the system. The initial rather simplistic concept of an excitatory cholinergic and an inhibitory adrenergic innervation is no longer tenable as a large number of other neurotransmitters are now implicated.

The main excitatory neurotransmitter in the gastrointestinal tract is acetylcholine (ACh). It is released from preganglionic parasympathetic fibres in response to vagal stimulation and acts upon ganglionic nicotinic receptors. Post ganglionic stimulation results in the release of acetylcholine from axonal varicosities with activation of membrane bound smooth muscle muscarinic receptors and resulting muscular contraction. (Paton, Vizi and Zar, 1971) The preganglionic activity is blocked by nicotinic antagonists such as hexamethonium and the postganglionic activity is blocked by muscarinic antagonists such as atropine.

(Kosterlitz and Lees, 1964)*

The classical inhibitory neurotransmitter is noradrenaline. All adrenergic fibres are extrinsic in origin as they disappear following denervation. Stimulation of these fibres which are congregated around the intramural ganglion results in prompt inhibition of excitatory cholinergic discharge (Norberg and Sjoquist, 1966). This inhibition is thought to be due to (Llewellyn-Smith et al., 1984)*

presynaptic action with inhibition of acetylcholine release rather than a direct action on intestinal smooth muscle.

In 1966 a non-adrenergic, non-cholinergic inhibitory pathway in the taenia of the guinea pig caecum was found (Burnstock, Campbell and Rand, 1966) and subsequently this has been shown to be present throughout the small intestine. The cell bodies of the pathway lie within the intestinal wall and receive input from both vagal efferents and locally originating afferent fibres. The descending inhibitory response elicited by Bayliss & Starling probably represents this pathway. It was initially proposed that adenosine triphosphate (ATP) was the neurotransmitter released by these nerves but more recently vasoactive intestinal peptide (VIP) (Goyal, Said and Rattan 1979) has been proposed for this role. Vagal stimulation activates both the cholinergic stimulatory pathway and the non-cholinergic non-adrenergic inhibitory pathway and experiments using tetrodotoxin (Wood, 1972) have shown that application results in circular muscle contraction and longitudinal muscle relaxation. This implies that at rest the predominant tone acting on the circular muscle layer is inhibitory, and that acting on the longitudinal muscle layer is excitatory.

It has been suggested that 5-hydroxytryptamine (5-HT) also acts as an excitatory neurotransmitter. Transneural electrical stimulation in the presence of atropinisation

results in muscular contraction implicating a non cholinergic excitatory pathway. (Collman, Grundy and Scratcherd, 1984) The transmitter is certainly not noradrenaline and the most likely candidate is 5HT.

The representation of the enteric nervous system described above is indeed a great oversimplification as the six neurotransmitters just mentioned have to be considered along with a great many other putative neurotransmitters. (Table 2.2) It has recently been proposed that some nerve endings may release 2 or even 3 neurotransmitters simultaneously. (Burnstock, 1981a) The more the enteric nervous system is studied, the more complicated it becomes.

Autonomic Nervous System

There are very close connections between the autonomic nervous system and the enteric nervous system through the sympathetic and parasympathetic outflow. A loss of these connections results only in minor modifications of enteric function outlining again the autonomy found in the enteric nervous system. Experiments in animals where the gut is divided from extrinsic neural controls (Ruckebusch and Bueno, 1977a) and in humans following vagotomy (Thompson, Ritchie and Wingate, 1982) show quite clearly that fasting intestinal motor function is maintained. The autonomic nervous system does however modulate the enteric nerves, provides a link between the

Table 2.2

List of Enteric Neurotransmitters (Proven and Putative)

Acetylcholine (ACh)

5 Hydroxytryptamine (5-HT)

Dopamine

Noradrenaline

Adenosine Triphosphate (ATP)

Gamma-aminobutyric acid (GABA)

Substance P

Vasoactive Intestinal Peptide (VIP)

Enkephalin

Somatostatin

Pancreatic Polypeptide (PP)

Angiotensin

Adrenocorticotrophic Hormone (ACTH)

Cholecystokinin (CCK)

Bombesin

Neurotensin

intestine and the central nervous system and allows the co-ordination of motor activity along the length of the gut through entero-enteral reflexes.

The parasympathetic link is through the vagal and sacral outflows and the sympathetic connection is through preganglionic fibre which arise from spinal segments T5-L3. (Grundy, 1985b)(Roman and Gonella, 1981a)*

Parasympathetic Nervous System

The vagus which provides the parasympathetic supply for the fore gut and mid gut carries both efferent and afferent fibres. In the cat the ratio of afferent to efferent is 10:1 (Agostoni et al, 1957) and as the efferent fibres also have a vasomotor and secretory function the number of fibres left to supply the enteric nervous system is relatively small. These fibres originate in the dorsal vagal nucleus and nucleus ambiguus in the brain stem and connect with enteric ganglion cells. This allows modulation of both cholinergic postganglionic excitatory fibres and non-cholinergic non-adrenergic inhibitory fibres.

The large number of afferent fibres have an important role in the reflex control of the gut and provides sensory information from chemo and mechanoreceptors in the mucosa and mechanoreceptors in the smooth muscle.

The Sympathetic Nervous System

Sympathetic discharges pass from T5-T12 of the spinal cord to the coeliac and superior mesenteric ganglia and from T12-L3 to the inferior mesenteric ganglion. From these prevertebral ganglia post ganglionic fibres pass to the enteric nervous system where they modulate cholinergic excitatory activity. As with the vagus, afferent fibres pass from enteric sensors along sympathetic fibres to the prevertebral ganglion and thence to the spinal cord.

Central Nervous System

Enteric motor function is modulated at a number of levels within the central nervous system. Vagal afferents converge on the tractus solitarius and are able to regulate efferent discharge from the nearby dorsal vagal nucleus. This innervation results in the activation of some fibres and the inhibition of others. With vagal efferents supplying both excitatory and inhibitory pathways this system allows the reciprocal activation of one agonist pathway with inactivation of antagonistic pathways. In this way the vago-vagal reflex is accentuated. (Davidson, 1983)

At the brain stem level centres exist for the integration of functions which require motor co-ordination between enteric smooth muscle and somatic

striated muscles such as swallowing, vomiting and defecation. (Roman and Gonella, 1981b)*

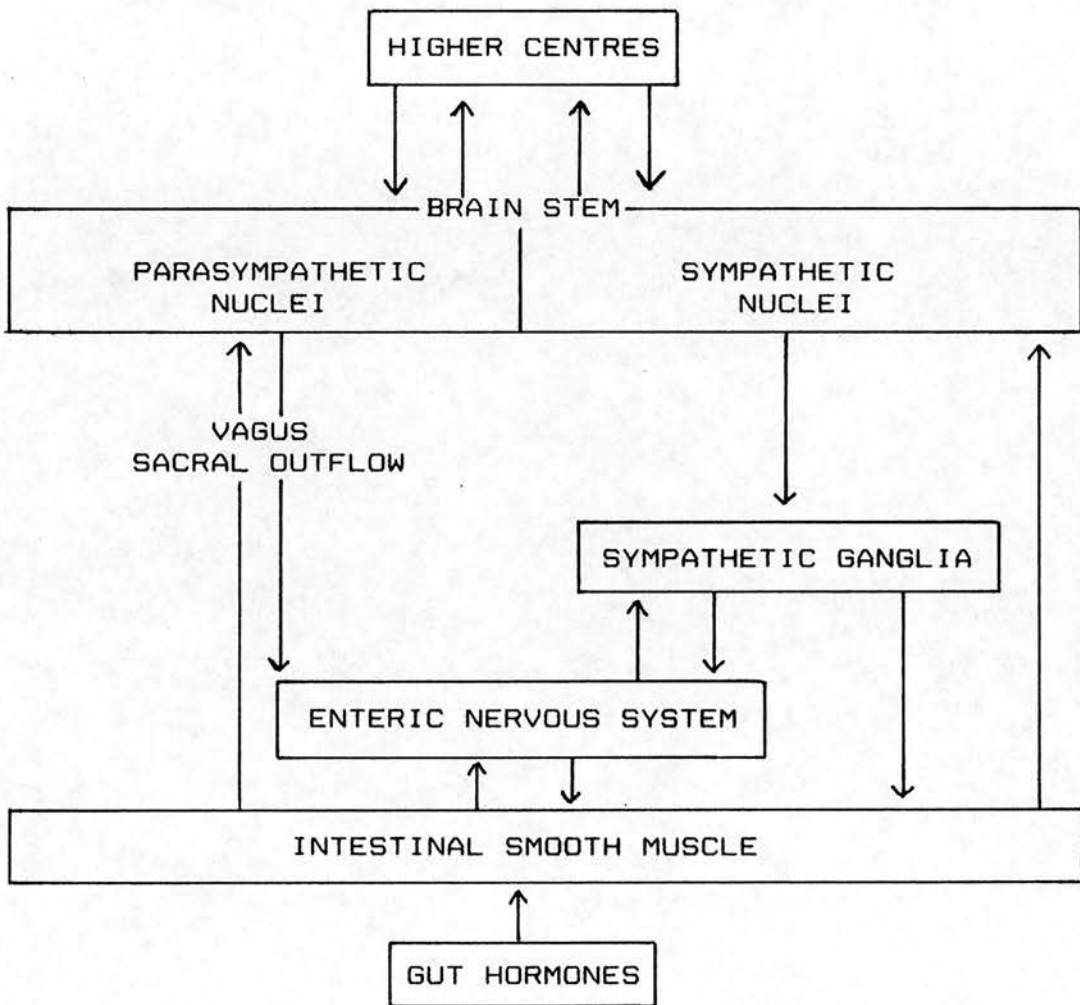
Afferent signals pass to higher levels through the hypothalamus which links with the limbic system, the cerebral cortex and other areas of the brain. Thus emotional disturbances, stress and the sight and smell of food may all alter intestinal motor function. Although intestinal pain is very poorly localised in humans, nociceptive fibres probably enter the spinal cord where they project to a visceral area on the neurosensory cortex.

Integration of Control

There is therefore a clear hierarchical control of enteric neural function. The vast majority of this control lies within the enteric nervous system, or "Gut Brain", with the higher levels modulating this activity. Reflex activity occurs at the level of the enteric nervous system, the prevertebral ganglion, the spinal cord, the brain stem and at the highest level with subconscious and conscious perception of intestinal activity. (Fig. 2.4) It is not surprising therefore that with such a complex set of controlling mechanisms that the number of possible interactions is very great.

Fig. 2.4

The control of enteric smooth muscle.



2.3.3 Humoral Controls of Motility

In addition to the neural controls of intestinal motility, a number of paracrine and endocrine substances provide an important modulatory role. While neural mechanisms rely on the release of neurotransmitters at their site of action, paracrine mediators rely on local diffusion of the substance and endocrine mediators rely on blood borne dispersion of the hormone. (Bloom and Polak, 1981)

These substances although very diverse in structure have a number of features in common. Most of the compounds as well as being found in the gut are also present within the central nervous system. Many have also been suggested as putative neurotransmitters and thus it is clear that there is a close relationships between neurocrine and endocrine function and between central nervous system and enteric nervous system controls. The main humoral modulators are a group of peptides referred to as the gut hormones. Many of the neurotransmitters which I have already discussed may also have a paracrine or endocrine role. It is however sometimes difficult to know from the published literature whether the action proposed for these peptides is purely pharmacological or whether in fact they have an important regulatory physiological role.

Gut Peptides

An increasing number of regulatory peptides have been defined and found to have important controlling influences on intestinal secretion, absorption, growth and motility. Some peptides with similar activities have differing chain lengths (ie Somatostatin 14 and 28) as a result of post translational modification of a common precursor peptide. Sequence homology is also found between peptides (ie Cholecystokinin and Gastrin) and probably results from the selective splicing of a common gene or the duplication and subsequent modification of an ancestral gene. As more than one form of any given peptide may be present there are great difficulties in measuring their activity and of knowing which form is the precursor, active substance or breakdown product. (Adrian, Polak and Bloom, 1982)

It is quite clear that the control of gut peptide activity is very complicated and is presently poorly understood. Some peptides stimulate the release of others, neurotensin stimulates pancreatic polypeptide release, while some, such as somatostatin actively inhibit peptide release.

Motilin

Motilin is a 22 amino acid peptide which is released from specific endocrine mucosal cells. It is present in

largest amounts in the duodenum and proximal jejunum but it is also present in the gastric antrum and distal jejunum.

On isolated strips of smooth muscle, motilin increases the level of electrical response activity and tonic contraction with a potency 50 times greater than acetylcholine. In the fasted animal the infusion of motilin initiates regular rhythmic motor activity in the stomach and proximal small bowel. (Vantrappen et al, 1979) Motilin is also released in response to intestinal distension. The role of motilin in the control of fasting motor activity will be discussed further in section 3.3.2.

Somatostatin

Somatostatin is a 14 amino acid peptide which has a range of largely inhibitory actions on other gut peptides. (Arnold and Lankisch, 1980) It is produced by gut endocrine cells and enteric nerves. It is more widely known for its anti-secretory activity which is thought to be modulated by a reduction in intracellular levels of cAMP and by an inhibition of vasoactive intestinal peptide (VIP). It does however inhibit the actions of motilin on the stomach and proximal intestine, described above, although it has a similar action to motilin on the more distal small intestine. (Poitras et al, 1979)

(Peeters, Janssens and Vantrappen, 1983)

Cholecystokinin

This peptide is found in a number of different forms but the activity resides in the C-terminal octapeptide which has sequence homology with gastrin. In isolated tissue it excites muscle activity by the release of acetylcholine from cholinergic nerve endings in a manner similar to gastrin. It is released from mucosal endocrine cells in the proximal small intestine in response to intraluminal nutrients and results in the prompt disruption of fasting motor activity with the initiation of post prandial activity. (Wingate et al, 1978)

Gastrin

This peptide is released from endocrine cells in the gastric antrum and is best known for its role in the control of gastric acid production. It does however promote antral motor activity and along with cholecystokinin is responsible for the maintenance of post prandial motor activity. (Wingate et al, 1978)

A number of other gut peptides influence intestinal motor activity in pharmacological doses but it is not clear whether these same actions occur at physiological levels. Substance P can cause smooth muscle contraction, while enteroglucagon can result in delayed small bowel transit.

Enkephalins and Endorphins

Although these compounds are also peptides, they are frequently grouped apart from the other gut hormones. They are produced by the enteric nerves and by endocrine cells within the gastric antrum and duodenum and act both as neurotransmitters and as gut hormones. They are derived from beta lipotrophin which is produced along with adrenocorticotrophic hormone (ACTH) and gamma melanocyte stimulating hormone (MSH) from a large molecular weight precursor protein. Cleavage of beta lipoprotein produces the endorphin and further cleavage down to a pentapeptide reveals Met-enkephalin and Leu-enkephalin with a carboxyl terminal methionine or leucine respectively. (Corder and Rees, 1981)

Opiate receptors are found on smooth muscle, on nerves throughout the gastrointestinal tract and within the central nervous system. The action of these varies depending on the opiate and on the part of the gut being investigated. Opiates generally slow the rate of luminal transit although they have also been shown to induce propagative activity. (Bueno et al, 1985a)

Blockage of opiate activity by the antagonist naloxone prevents CCK induced gall bladder contraction and blocks the inhibition of intestinal transit that is usually induced by ileal lipid indicating a likely role for opiates in both these pathways. (Kinsman and Read, 1984)*
(Crochelt, Shaw and Peikin, 1984)*

Central Action of Gut Hormones

As discussed above, most of the gut hormones which have been described have also been found in the central nervous system. Indeed, recently some central actions of these compounds have been described which do not occur when a similar dose is given peripherally.

Both calcitonin and PGE_2 when given into the lateral ventricles of rats restores a fasting pattern of motor activity which is blocked by pre-treatment with indomethacin (Bueno et al, 1985b) and similarly central administration of somatostatin and of cholecystokinin has been shown to modulate fasting cycle frequency. (Bueno and Ferre, 1982)

2.4 Conclusion

It is quite clear that the organisation and control of intestinal motility is highly complicated with its reliance on myogenic, neurogenic and endocrine mechanisms. Within each of these systems there are further hierarchies of control which allow for the finer tuning of intestinal motor function. The centre for these controls lies within the gastrointestinal tract, and particularly within the enteric nervous system which gives the gut "intelligence" and an ability to respond to a large range of differing events.

A failure of development of these mechanisms or a disruption of these intestinal motor controls results in loss of normal motor function and the development of gastrointestinal disease.

CHAPTER 3
SMALL INTESTINAL MOTILITY



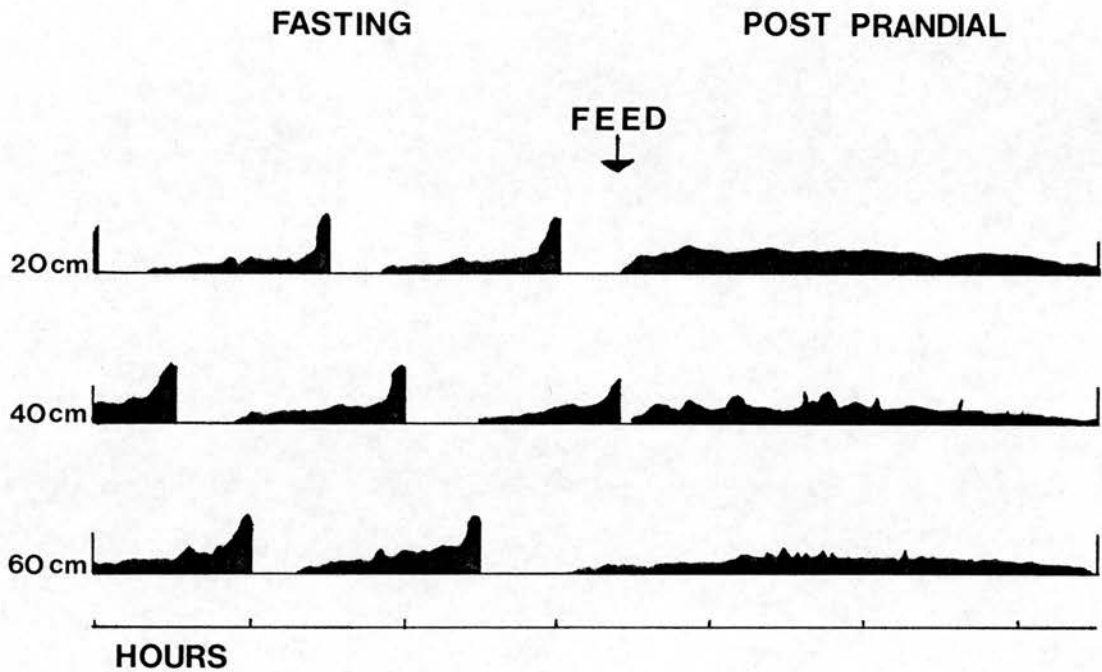
3 Small Intestinal Motility

Motor activity in the small intestine has to accommodate the passage of food from the stomach, promote its digestion and absorption by the small intestine and its movement at a controlled rate into the ileum and thence into the colon. A failure of these mechanisms results in either delayed gastrointestinal transit with abdominal distension and vomiting, or at the other extreme the rapid passage of food into the colon with resulting intestinal hurry.

The motor activity of the small intestine can be divided into two major types of activity. Between meals a cyclical fasting or interdigestive pattern of motor activity is seen. Following the ingestion of food this cyclical pattern is completely disrupted and replaced by continuous apparently random segmenting and mixing activity, the post prandial pattern. (Fig. 3.1)

Fig. 3.1

In this diagram of a small intestinal electromyographic recording the cyclical fasting pattern is completely disrupted by a feed and replaced with a continuous post prandial pattern. The electrode position is shown as the distance in centimetres from the pylorus.



3.1 Nomenclature of Fasting Motor Activity

Because our knowledge of small intestinal motor activity has expanded greatly, problems have arisen with the terminology that has been used. The problems relate to the fact that the same types of motor activity have been differently described by physiologists, radiologists, gastroenterologists and surgeons. The problem has been further compounded where different recording techniques have been used (electromyographic or manometric).

A number of cycles of fasting motor activity are shown in Fig. 3.2. The initial period of quiescence is frequently referred to as Phase I activity with the subsequent period of irregular activity known as Phase II activity. The highly organised propagated band of activity is Phase III activity with the short period of irregular activity following this called phase IV activity. (Code and Marlett, 1975)(Wingate, 1981)

An additional nomenclature is required for electromyographic recordings. The regular phasic slow wave activity is known as the electrical control activity (ECA) and when action potentials are superimposed upon this it is referred to as the electrical response activity (ERA). (Grundy, 1985a)

The random activity induced following the ingestion of food is referred to as post prandial activity.

The terminology outlined above will be used throughout this thesis. Table 3.1 lists many of the alternative terms which have appeared in the literature.

Fig. 3.2

The cyclical propagated nature of fasting motor activity is clearly seen in this diagrammatic representation of a small intestinal electromyogram. The electrode position is shown as the distance in centimetres from the pylorus.

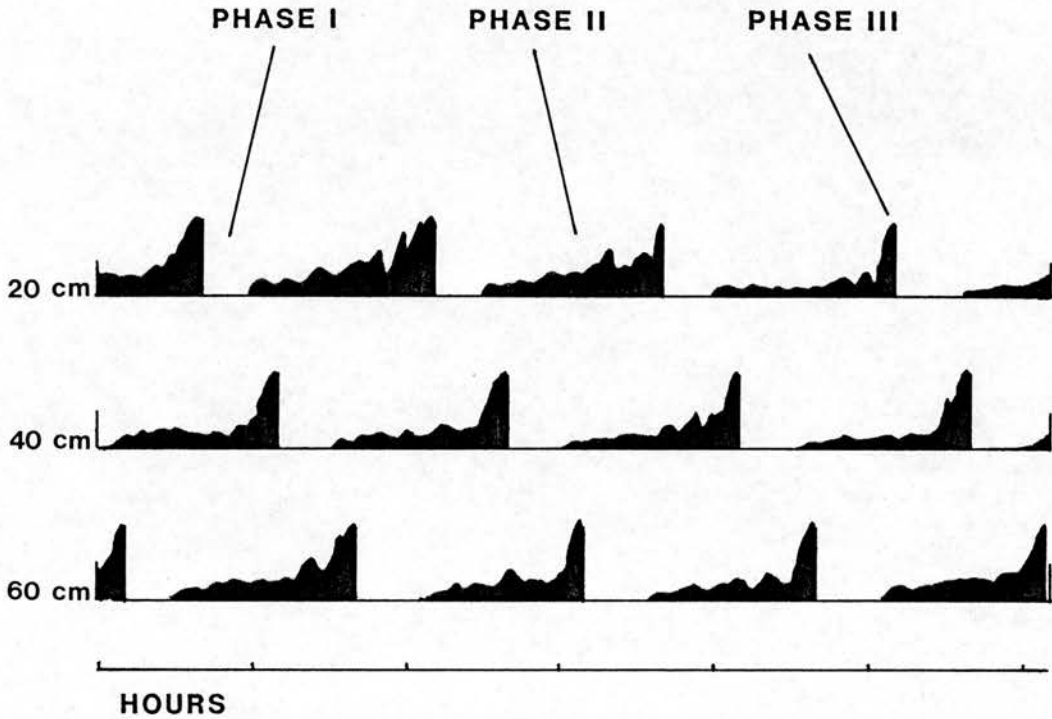


Table 3.1

NOMENCLATURE USED	SYNONYMS
Fasting	Interdigestive
Post prandial	Digestive
Phase I	Quiescence
Phase II	Irregular contractile activity
	Irregular spiking activity
Phase III	Migrating motor complex (MMC)
	Regular spiking activity
	Regular contractile activity
	Activity front
Electrical control activity (ECA)	Slow wave
	Pacemaker activity
	Basic electrical rhythm (BER)
Electrical response activity (ERA)	Spiking activity

3.2 A Historical Perspective

Although some of the first descriptions of small intestinal motor activity (Bayliss and Starling, 1899) are over 80 years old, it has only been in the last 20 years that accurate accounts of the cyclical nature of fasting small intestine motor activity have been obtained. (Szurszewski, 1969) The initial patterns of motor activity described were peristalsis, segmentation and mixing activity. The former type of activity is very efficient at moving the intraluminal content along the gut while segmenting and mixing activity is induced following a meal and is responsible for delaying luminal transit to allow adequate digestion and absorption of food. The major factors which hindered the full characterisation of small intestinal motor activity for many years were the relatively short period over which recordings were made and the poor techniques used.

In the dog a cyclical pattern of fasting gastric motor activity was noted in 1905 to be associated with the outpouring of pancreatic secretions. (Boldyreff, 1905) This activity had a regular period of 80 minutes and was disrupted by the ingestion of food. Unfortunately the nature of this periodic activity was not understood and Boldyreff results were largely forgotten. In 1949 a multiple balloon kymographic technique was used to record regular contractions of the small intestine (Chapman and Palazzo, 1949) which almost certainly represented the first true recording of Phase III

activity. Because of the relatively short recording time, the periodic nature of this activity was not recognised.

It was not until the development of improved myoelectric techniques and the ability to study long lengths of the small intestine for prolonged periods became available that "the complex came out of the closet", (Wingate, 1981) and the first comprehensive description of small intestinal motor activity became available. (Szurszewski, 1969)

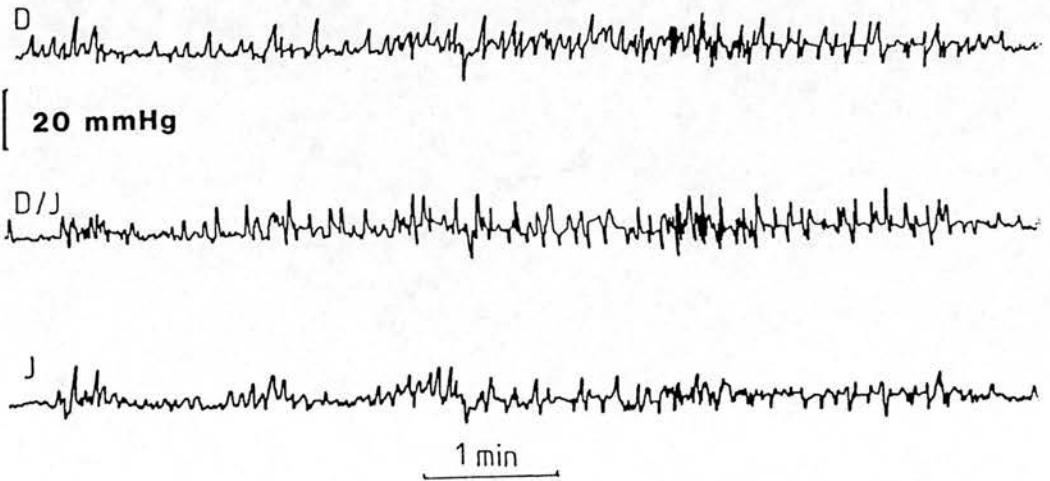
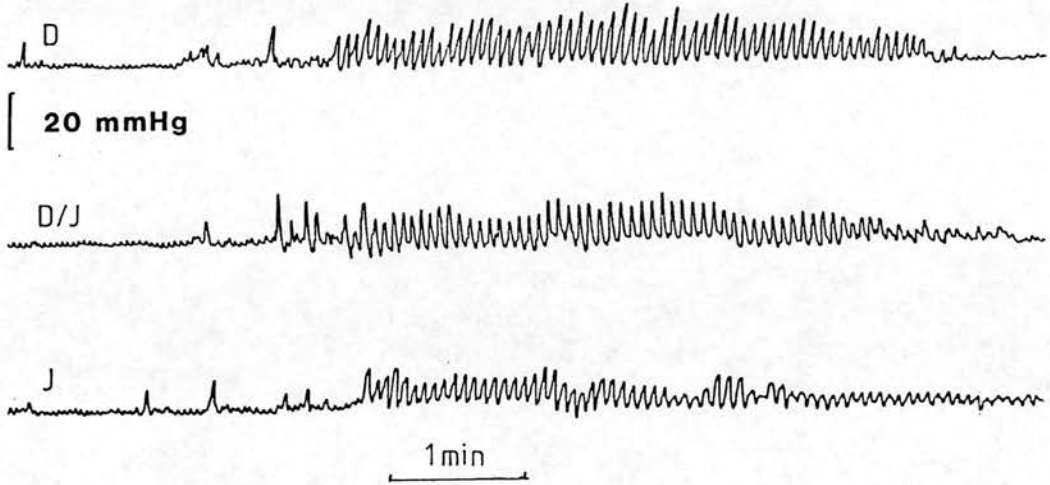
Using implanted uni and bipolar platinum electrodes placed along the small intestine from the duodenum to the ileum, the migration of intense spiking myoelectric activity in an aboral direction was seen in conscious mongrel dogs. This phasic activity had a period of between 120 to 180 minutes and was invariably preceded by diffuse random activity lasting from 15 to 40 minutes and followed by a period of quiescence of the myoelectric activity. This was the first time that the cyclical nature of fasting motor activity was clearly described. The extension of these animal techniques and the development of multilumen perfused catheter systems allowed the same changes to be recorded in humans. In normal humans it was clearly shown that similar patterns of fasting activity were seen. (Vantrappen et al, 1977)

3.3 Fasting Motor Activity

Fasting motor activity is characterised by a cyclical pattern of motor activity which continues until it is disrupted by the ingestion of food. Phase III is the most obvious feature of this activity and is characterised by a broad band of highly organised propagative activity which migrates slowly down the gut from the stomach to the ileum. (Fig. 3.3) Following the ingestion of a meal this activity is completely disrupted. (Fig 3.3)

Fig. 3.3

The organised Phase III motor activity in the fasting state (top) is contrasted with the apparently random post prandial activity (bottom).



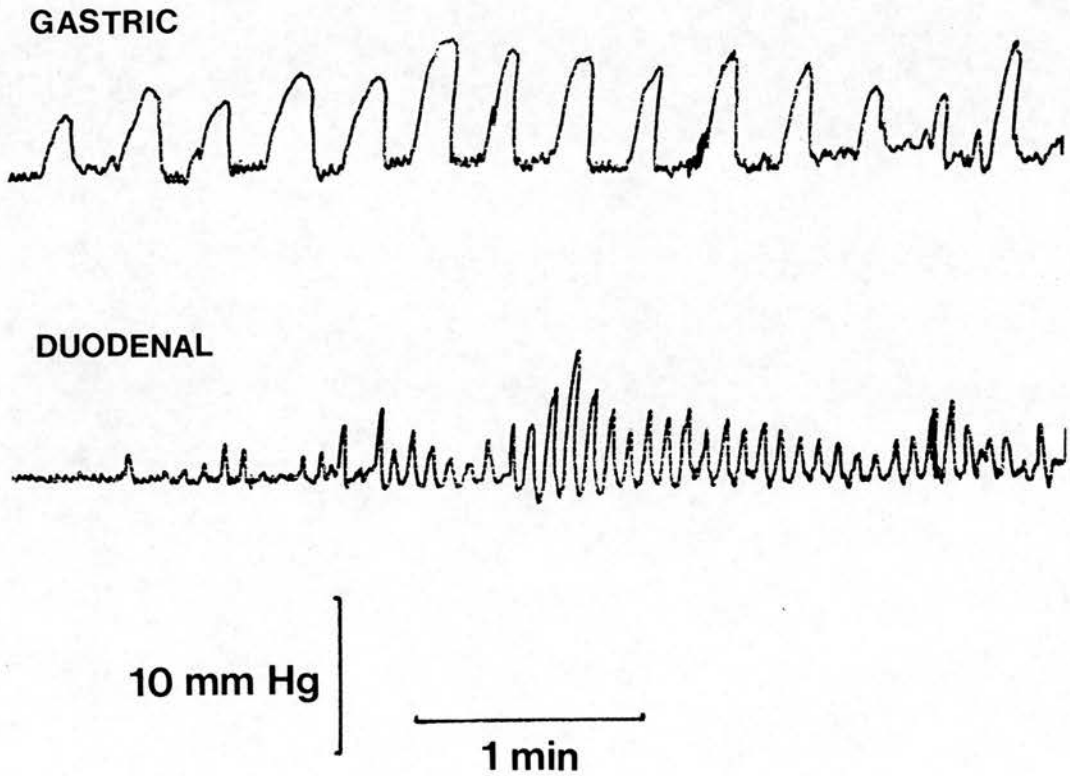
3.3.1 Phase III Activity

Phase III activity has been studied in detail in many animals including dog (Code and Marlett, 1975) and man. (Peeters, Janssens and Vantrappen, 1982) In the dog the cycle length ranged from 90 to 120 minutes with each period of Phase III taking 100 to 130 minutes to travel from it's start in the stomach to the ileum. The velocity of propagation slowed markedly from 6-12 cm/min in the proximal small intestine to 1-2 cm/min at the terminal ileum with the result that the length of gut simultaneously involved in Phase III activity is much shorter in the distal than the proximal gut. The origin of the Phase III activity was variable with 20% starting in the small intestine rather than the stomach and only 80% of the activity reached the terminal ileum. In the human the situation is similar with an interval of 82 ± 5 min (mean \pm SE n=38) between periods of Phase III activity although as few as 10% may actually reach the ileocaecal valve. (Quigley et al, 1984)

The frequency of motor activity during phase III is determined by the electrical control activity (ECA) of the enteric smooth muscle and as a result of this the contractile frequency in the human is 3/min in the stomach, 12/min in the duodenum and 9/min in the terminal ileum. The very large frequency gradient across the pylorus was used in the present study to help position the recording catheters. (Fig. 3.4) The small intestinal frequency gradient is also found in the

Fig. 3.4

In this trans-pyloric pressure recording the clear difference between gastric 3 cpm and duodenal 12 cpm motor activity can be seen.



experimental animal and has been investigated in some detail. (Diamant and Bortoff, 1969a & b) It was found that rather than there being a continuous gradient down the gut, it was in fact discontinuous. If however the gut was transected the ECA frequency in each segment showed a linear decline as one moved down the gut. This suggests that the smooth muscle is behaving like a series of linked oscillators (Wingate, 1983) with the more proximal higher frequency activity exerting control over the more distal smooth muscle, which is only relaxed when the gut is transected. This is analogous to the influence of the sino-atrial node on the heart and is responsible for the predominantly aboral propagation of motor activity from an area of high to low frequency.

When the enteric nervous system is divided by transection of the gut, Phase III activity fails to migrate along the gut when it is re-anastomosed. This however does not result in a functional obstruction as Phase III activity independently arises in the more distal segment of gut. (Sarna, Condon and Cowles, 1983) It is interesting to note that the Phase III cycle frequency is higher in a mid small intestine segment compared to that in the duodenum. The enteric nervous system is essential for the normal propagation of this activity as disorders of enteric neural function result in loss of the normal pattern of fasting motor activity. (Vantrappen et al, 1977)

3.3.2 The Control of Phase III Activity

Although Phase III activity can be initiated in the small intestine without external influences it is undoubtedly the case that extrinsic neural and humoral factors influence the appearance of this activity. It would also appear that the factors which cause one response in one part of the small intestine may well cause another elsewhere. There are differences in the response of the gastric antrum and of the jejunum to the effects of a number of gut hormones and to the effects of vagal cooling. (Wingate et al, 1978. Hall, El-Sharkawy and Diamant, 1982)

Hormonal

It has been known for some years that the passage of Phase III activity results in surges in the plasma levels of motilin (Itoh et al, 1978) and that infusion of motilin will induce gastric phase III activity. (Vantrappen et al, 1979) It was until recently thought that the motilin was inducing the phase III activity but it now seems more likely that the motilin is the response to, rather than the cause of this activity. (Hall et al, 1984)

Somatostatin is generally thought of as an inhibitory peptide and indeed it has been shown to inhibit the induction of Phase III activity which start in the stomach. (Peeters, Janssens and Vantrappen, 1983) It does however induce ectopic activity in the proximal

jejunum, a fact which exemplifies the differing control mechanisms for the foregut and midgut. (Hostein, 1984) (Table 3.2)

Extrinsic Neural Controls

The autonomic nervous system exerts control over the frequency of phase III activity through the sympathetic and parasympathetic outflows.

Human studies in patients who have undergone truncal vagotomy for peptic ulcer disease (Thompson, Ritchie and Wingate, 1982) have shown that although fasting motor activity remains unaltered, the length of post prandial activity following a meal was shortened and in some of these patients this resulted in rapid intestinal transit with diarrhoea. In animal studies carried out in the dog (Hall, El-Sharkawy and Diamont, 1982) rapid cooling of the exteriorised vagus resulted in a loss of spontaneous phase III activity from the stomach and duodenum with loss of phase II but not phase III activity more distally. The differences between the results of vagotomy in these two studies probably reflects the differences between the effects of chronic and acute denervation with reinnervation and adaptation occurring in the former.

Disruption of the sympathetic outflow by cord transection above T1 results in a reduction in Phase III activity originating in the stomach with a loss of gastro-duodenal motor co-ordination.

Table 3.2

Stimulating and Inhibiting Factors of Phase III activity.

	STIMULATE	INHIBIT
Foregut	Motilin Opioids	Gastrin Somatostatin CCK Food
Midgut	Opioids Somatostatin	Food

Fasting motor activity is also affected at the highest level by the central nervous system. Stress has been shown to reduce the expected frequency of phase III activity with an increase in phase II activity (McRae et al, 1982), intra-ventricular gut peptides have modulatory effects on fasting activity (Bueno and Ferre, 1982) (see 2.3.3) and it has been suggested that the fasting motor cycle and the sleep cycle are closely linked. (Finch et al, 1982)

The weight of evidence at present therefore suggests that the basic control mechanisms of fasting motor activity reside within the neural controls of the enteric nervous system and enteric smooth muscle but that these controls can be readily modulated by external neural and humoral influences.

3.4 POST PRANDIAL MOTOR ACTIVITY

Following the ingestion of a meal this fasting pattern of activity is completely disrupted and is replaced by a post prandial pattern of activity. This activity is characterised by largely segmenting and mixing activity with low grade peristaltic activity, (Ruckebusch and Fioramonti, 1975) (Fig. 3.1 and Fig. 3.3) which facilitates the orderly digestion and absorption of the intraluminal contents as they move slowly down the intestine. When disruption of fasting activity fails to occur and this highly propagative motor activity continues despite the administration of food, intestinal hurry will occur. This has been proposed as a possible mechanism for the irritable bowel syndrome in childhood. (Fenton, Harries and Milla, 1983)

The disruption of the fasting pattern of activity and the length of that disruption is determined by both the content of the feed and the frequency at which feeds are given. In herbivores such as the sheep where there is a steady oral intake of nutrients throughout the day the fasting pattern continues unaltered while in the carnivore such as the dog or an omnivore like the human where feeding is an intermittent process disruption of fasting activity occurs for many hours. It is possible to manipulate these events by controlling the rate of feeding. In experiments carried out in pigs (Ruckebusch and Bueno, 1976) animals fed ad libitum behaved like

herbivores while intermittent fed animals were more like carnivores. This suggests that the calorie density of nutrients in each meal is important in determining whether disruption will occur.

The character of a meal also determines whether fasting activity will be disrupted and how long that disruption will last. A solid meal is more disruptive than a liquid meal of the same size (Code and Marlett, 1975) and with similar meals the length of disruption is increased as the volume is increased. Thus as the caloric content of a meal increases so does its disrupting ability and with equi-caloric meals lipid is a more potent disrupter than protein or carbohydrate. (Weisbrodt, 1981)

The initiation of post prandial activity can be divided into an early phase with loss of Phase III activity and increased motor activity throughout the gut followed by a maintenance phase which is related to the arrival of food in that part of the intestine. The initial disruption relies on stimuli from the CNS, the stomach and from the intestine.

Visual, olfactory and gustatory stimuli which occur during sham feeding in both humans (DePhilippi and Valenzuela, 1981) and animals (Gregory, 1950) can initiate post prandial activity in the gut but this effect is short-lived and ceases when the sham feeding stops. Insulin induced hypoglycaemia also disrupts fasting activity through what is thought to be a vagal reflex.

Gastric distension due to the arrival of food in the stomach initiates post prandial activity through another vagally mediated reflex. In humans truncal vagotomy results in the premature reappearance of fasting activity following a meal (Thompson, Ritchie and Wingate, 1982) and in dogs (Diamant et al, 1980) vagal cooling during post prandial activity resulted in the abolition of gastric activity and the development of fasting activity in the small intestine.

The arrival of food in the small intestine consolidates and maintains the post prandial motor activity. The mechanism for this is not clear but it is known that enteral nutrients promote the release of cholecystikinin (CCK) and that intra-venous administration of this gut peptide results in the disruption of fasting activity with the production of post prandial activity in the absence of food. (Mukhopadhyay et al, 1977) The speed of nutrient transit is controlled by the "ileal brake" , an entero-ental reflex that responds to the presence of ileal lipid by a slowing of luminal transit. (Holgate and Read, 1985). This reflex is abolished by the administration of the opiate antagonist naloxone.

The factors which control the initiation and maintainance of post prandial activity remain to be fully elicited.

CHAPTER 4
THE ONTOGENY OF INTESTINAL MOTOR FUNCTION

4 THE ONTOGENY OF INTESTINAL MOTOR FUNCTION

Most of the information presented so far in this introduction has related to the mature animal or human. Clinical observation suggests that the gastrointestinal tract of the preterm infant is immature and is frequently unable to cope with the amount of enteral nutrition that would be required for optimal growth. An understanding of the developmental processes occurring within the gastrointestinal tract might allow us to understand better the complex nature of their controls and give some insight into the best way to care for preterm infants with immature gastrointestinal function.

4.1 DEVELOPMENT OF GASTROINTESTINAL STRUCTURE AND FUNCTION

The gastrointestinal tract first appears at about 4 weeks gestation as a hollow tube extending from the mouth to the cloaca. The most proximal part of this tube forms the oesophagus which is separated by the newly formed diaphragm from the developing abdominal cavity. The stomach is formed from a fusiform dilatation of the foregut at 5 weeks and by 7 weeks gestation it has attained its final position in the upper abdomen. Rapid growth of the distal foregut and midgut exceeds the capacity of the abdominal cavity resulting in the protrusion of this length of gut through the umbilicus. Before 10 weeks gestation this loop undergoes 270 degree counter-clockwise rotation and returns to the abdominal cavity. (Arey, 1974)

As early as 6 weeks gestation the cloaca becomes flattened from side to side and a septum forms dividing the rectum posteriorly from the anterior urogenital sinus. By 9 weeks hepatic and pancreatic tissue has appeared and by 12 weeks bile secretion has started. Thus by the end of the first trimester the layout of the gastrointestinal tract in the abdominal cavity is almost identical to that found in the newborn infant.

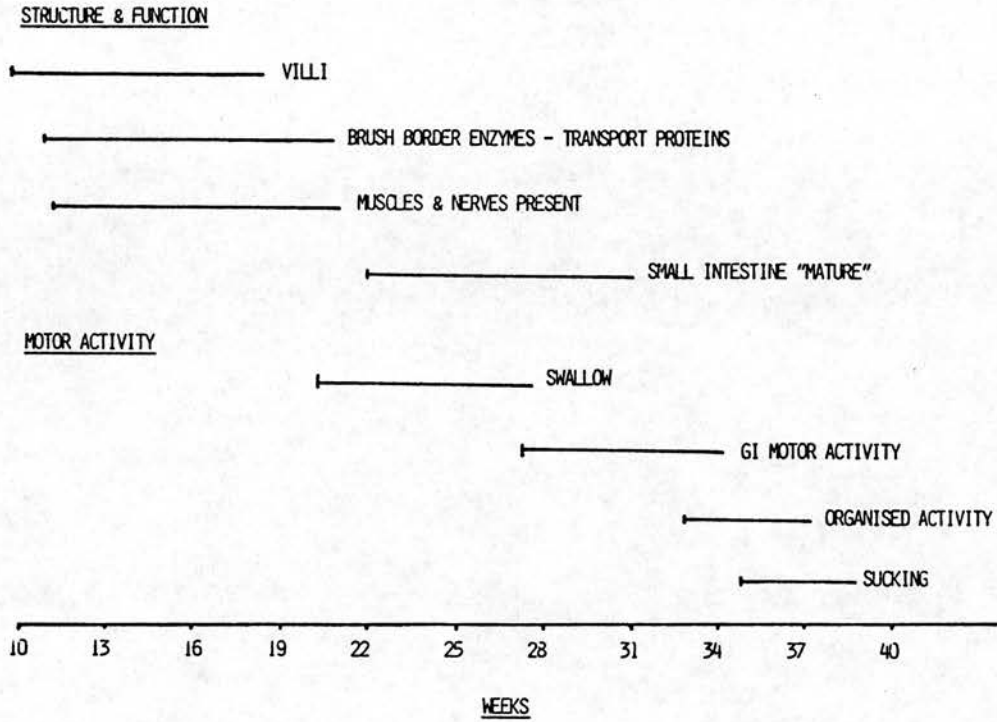
The appearance of rudimentary villi at 8 weeks gestation is followed by a period of intense proliferative activity which partially occludes the lumen. The recanalisation of the lumen is associated with

lengthening of the villi and the development of early crypts by 12 weeks gestation. (Moxey and Trier, 1978) The appearance of Auerbach's plexus in the small intestine at 9 weeks and Meissner's plexus by 13 weeks (Hart and Mir, 1971) coincides with the clear visualisation of smooth muscle throughout the intestine. The development of these structural features like so many other intestinal processes depends on an inherent species dependent pattern which invariably progresses in a cranio-caudal direction.

At the same time as these structural features are developing major maturational changes occur in intestinal digestive, absorptive and secretory function. In the human alpha-glucosidases such as maltase and sucrase appear by 12 weeks and by 32 weeks they have attained 70% of term newborn levels. (Grand, Watkins and Torti, 1976) Similar developmental changes are seen for most brush border enzymes. Studies of everted sacs of fetal intestine have shown evidence of electrogenic glucose uptake as early as 11 weeks gestation with a steady increase in glucose uptake and transmural potential difference with increasing gestational age. (Koldovsky et al, 1965) Levels of enterocyte Na^+/K^+ ATPase, an enzyme intimately involved in both absorptive and secretory function, increase during the second trimester as do enzymes of protein digestion. By 22 weeks gestation the fetal intestine is histologically mature with normal looking muscular and

Fig. 4.1

The ontogenic timetable of intestinal function.



neural elements. The intestinal mucosa contains a normal complement of endocrine and crypt cells with a clearly defined brush border on the surface enterocytes.

By 28 weeks gestation, although not yet at term levels, intestinal digestive, absorptive and secretory function is adequately advanced to handle enteral nutrition. Intestinal motor function however lags behind in developmental terms and is thus the major limiting factor in delaying the early introduction of enteral feeds. The relative development of these processes is summarised in Fig. 4.1.

The miniaturisation of recording techniques in children has shown quite clearly that the same patterns of motor activity as occurs in adults are present both in the fasting and postprandial state. (Barbero, Kim and Davies, 1958. Fenton, Harries and Milla, 1983) It is thus highly likely that between the end of the second trimester of pregnancy, when intestinal motor activity is almost completely absent, and the first few months of life, when motor activity is well developed, that there are very major maturational changes in intestinal control and function.

Studies carried out in children with pseudo-obstructive disorders have shown quite clearly that these complex motor controls are disrupted if either the enteric nervous system, the enteral smooth muscle or the neurohumoral environment of the gastrointestinal tract is disrupted. (Milla, 1986) In the preterm infant

therefore it seems highly likely that the integrated maturation of each of these systems determines the degree of motor organisation that is found in the small intestine.

4.1.1 SMOOTH MUSCLE

Very little is known about the maturation of smooth muscle in the fetus and preterm infant. (Burnstock, 1981b) As outlined above smooth muscle appears at about 12 weeks gestation. In the extremely preterm infant (< 26 weeks) small intestinal contractile activity is likely to be very poorly developed and it is unlikely that any useful activity will occur.

4.1.2 ENTERIC NERVOUS SYSTEM

Like smooth muscle neural elements appear in fetal intestine at a very early age but it is clear that it takes many months before a level of maturity is reached which will allow the enteric nervous system to exert control over smooth muscle function. The enteric neurones are generally believed to have migrated to the gut from the neural crest. Following colonisation of the gut there is a prolonged period of maturation during which time much change occurs in the neural microenvironment. There is an increasing body of evidence which suggests that the microenvironment in which the migrating neural crest cells ultimately find themselves may be critical in determining the final transmitter expressed by the cell. (Le Dourin, 1980, Patterson, 1978) Although many cells have transient catecholamine expression there is a sequential appearance of enteric neurones during ontogeny, with cholinergic and serotonergic neurones developing first, followed by adrenergic innervation and then peptidergic neurones. (Gershon, Payette and Rothman, 1983) Thus although neural precursor cells will tend to follow a given developmental path they remain "plastic" and open to environmental influences until a relatively late stage in their maturation. It is interesting to speculate therefore what effect the prolonged exposure of the fetus to sympathomimetics used in the treatment of premature labour, or to opiates in the children of

drug addicts, will have on the ultimate expression of these enteric neuronal cells.

Higher centres also influence motility as is all too clearly seen in neonates who have suffered from the effect of major cerebral insult. (Menkes, 1984)

It seems likely therefore that the combined maturation of the enteric nervous system, the autonomic nervous system and the central nervous system are to a large part responsible for the major developmental changes which occur in intestinal motor activity both before and after birth.

4.1.3 NEUROHUMORAL SYSTEM

Between 10-12 weeks gestation, as villi and crypts are beginning to form, endocrine cells are first seen in the human fetal small intestine. These transitional cells contain two types of secretory granules, one characteristic of very early precursor cells and the other more typical of adult-type endocrine cells. With increasing gestation the first type of secretory granules are lost leaving a population of mature adult-type endocrine cells. (Moxey and Trier, 1977)

The level of gut hormones produced by these cells during the preterm period and their response to enteral nutrition has been intensively studied. (Aynsley-Green, 1982) In preterm infants (<33 weeks) the first feed whether given as a bolus or an infusion fails to produce a significant change in glycolytic metabolites or in the levels of insulin, growth hormone or enteroglucagon when compared to the first feed in term infants. (Lucas, Bloom and Aynsley-Green, 1978) However if feeding was continued in these preterm infants a marked postprandial rise in motilin, enteroglucagon and neurotensin was noted over the subsequent 3 weeks. In those infants who did not receive enteral nutrition and who were fed parenterally basal plasma levels of these three hormones were significantly reduced. (Lucas et al, 1980a) It was concluded from these results that early enteral nutrition through the triggering of gut hormone release may play an important role both in the development of

intestinal motility and in the general physiological adaptation to extrauterine life. While this may indeed be correct it is important to note that the poor clinical condition of the parenterally fed infants is probably of importance as is the possibility that many of the changes seen between the preterm and term babies were due to inherent maturational processes.

4.2 SUCKING AND SWALLOWING

Swallowing has been observed in utero as early as 16-17 weeks gestation and using ^{51}Cr -tagged red blood cells administered into the amniotic fluid the volume of fluid swallowed has been shown to increase from 13-16mls/day at 20 weeks up to 450mls/day at term. (Pritchard, 1966) Fetal swallowing of amniotic fluid is probably an important mechanism in the maintenance of amniotic fluid volume in later pregnancy as oesophageal-atresia and small bowel atresia are frequently associated with polyhydramnios.

Unfortunately the preterm infant is unable to suck feeds effectively until about 34 weeks gestation as a result of an inability to coordinate the oral, pharyngeal and oesophageal phases of swallowing. Prior to this time most preterm infants are tube fed as attempts to initiate oral feeding prematurely results in reduced calorie intake with exhaustion of the infant and failure of pharyngeal clearance of the feed resulting in tracheal aspiration. Developmental studies of sucking and swallowing have shown that initially sucking is very feeble with mouthing of the teat and no nutritive sucking. Later the neonate develops short sucking bursts 4-7 sucks in length at a frequency of 1 per second. These periods are either preceded or followed by a swallow. Eventually the infant develops a mature sucking pattern with prolonged sucking bursts up to 30 sucks long at a frequency now of 2 per second associated with

a single swallow towards the end of the burst. (Crump, Gore and Horton, 1958) At the same time as these developmental changes occur with sucking, oesophageal motility shows a developmental progression from immature poorly propagated tertiary contractions to more highly organised peristaltic contractions initiated by swallowing. (Gryboski, 1965) Such immature contractions are frequently biphasic and are in many ways similar to the oesophageal contractions seen in children who clear acid poorly from the oesophagus in response to reflux. These changes in sucking and of oesophageal body motility are most probably due to the neurological maturation of cranial nerve function and control, and the coordination of this activity with the innervation and smooth muscle of the distal oesophagus. (Herbst, 1983)

As might be expected the onset of sucking is delayed in ill infants as are many other aspects of intestinal motility. The effect of non nutritive sucking has been studied in preterm infants and it has been shown that in addition to accelerating the maturation of the sucking reflex it improves enteral feeding tolerance, reduces intestinal transit time and results in increased infant weight gain when compared to matched infants who did not experience non nutritive sucking. (Bernbaum et al, 1983) It therefore appears that although sucking is a conditioned reflex it can be reinforced by learning experience. It is interesting to speculate whether the

improvement in more distal motor activity is related to the introduction of an oral and a cephalic phase to enteral feeding.

4.3 GASTRIC MOTILITY AND EMPTYING

In the very preterm infant (< 30 weeks) the delivery of feed directly into the stomach is frequently unsuccessful as marked delays in gastric emptying result in abdominal distension, respiratory embarrassment and increased gastro-oesophageal reflux with the resulting risk of aspiration. In preterm infants studied by dye dilution techniques it can be shown that the greater the caloric load the greater the delay in gastric emptying. (Siegel, 1983) It has been difficult to study developmental changes in gastric emptying as feed volumes vary greatly between infants of different ages but clinically it is clear that gastric feeding tolerance increases with increasing gestational age and where this maturation is interrupted by the clinical deterioration of the neonate, reduced tolerance results.

4.4 SMALL INTESTINE

With sucking, oesophageal motility, and gastric emptying the motor changes described above follow an inherent developmental timetable which results from the integrated maturation of enteric and central control systems. The development of human small intestinal motor function is under similar controls.

It has been known for a long time that the very preterm infant (< 30 weeks) is frequently intolerant of enteral nutrition and indeed the vomiting and abdominal distension which develops in response to feeding resembles the picture seen in acute intestinal obstruction. It has been clearly reported that this functional ileus occurs most commonly in very ill infants particularly those suffering from the respiratory distress syndrome (RDS) and that as the clinical condition of the child improves so the ileus resolves. (Dunn, 1963)

Studies of human small intestinal motor function in utero have been limited both by ethical constraints and lack of suitable non-invasive recording techniques but an amniographic study carried out in the USA in the 1960's (McLain, 1963) defined the movement of injected radiographic contrast along the fetal gastrointestinal tract. Before 30 weeks gestation there was little movement of contrast beyond the stomach but with increasing gestational age the contrast moved into the small intestine and by 34 weeks there was some movement

of contrast into the colon. Although these results could be criticised on the basis that the contrast was not followed for long enough it was quite clear that increasing gestational age resulted in increased intra-luminal transit.

Very elegant studies of small intestinal motor development have been carried out in fetal sheep and dogs using chronically implanted myographic electrodes. (Bueno and Ruckebusch, 1979) The fetuses were surgically delivered, electrodes were placed along the length of the intestine, and they were then returned to the uterus allowing gestation to continue. Thus both the magnitude and the degree of organisation of motor activity could be measured at intervals, both during pregnancy and after delivery.

In both of the above species there was a clear timetable of development with myoelectric activity and organisation increasing with gestation (Table 4.1, Fig. 4.2) until at term in the sheep and 16 days after term in the dog classical Phase III or MMC activity was seen. The later development in the dog may reflect the relative neurological immaturity of the dog at term compared to the sheep.

The first manometric studies in the human preterm infant to look directly at the ontogeny of motor activity used single lumen nasojejunal silastic feeding tubes to record luminal pressures. (Milla and Fenton, 1983b) Although similar patterns of activity to those in the

Table 4.1

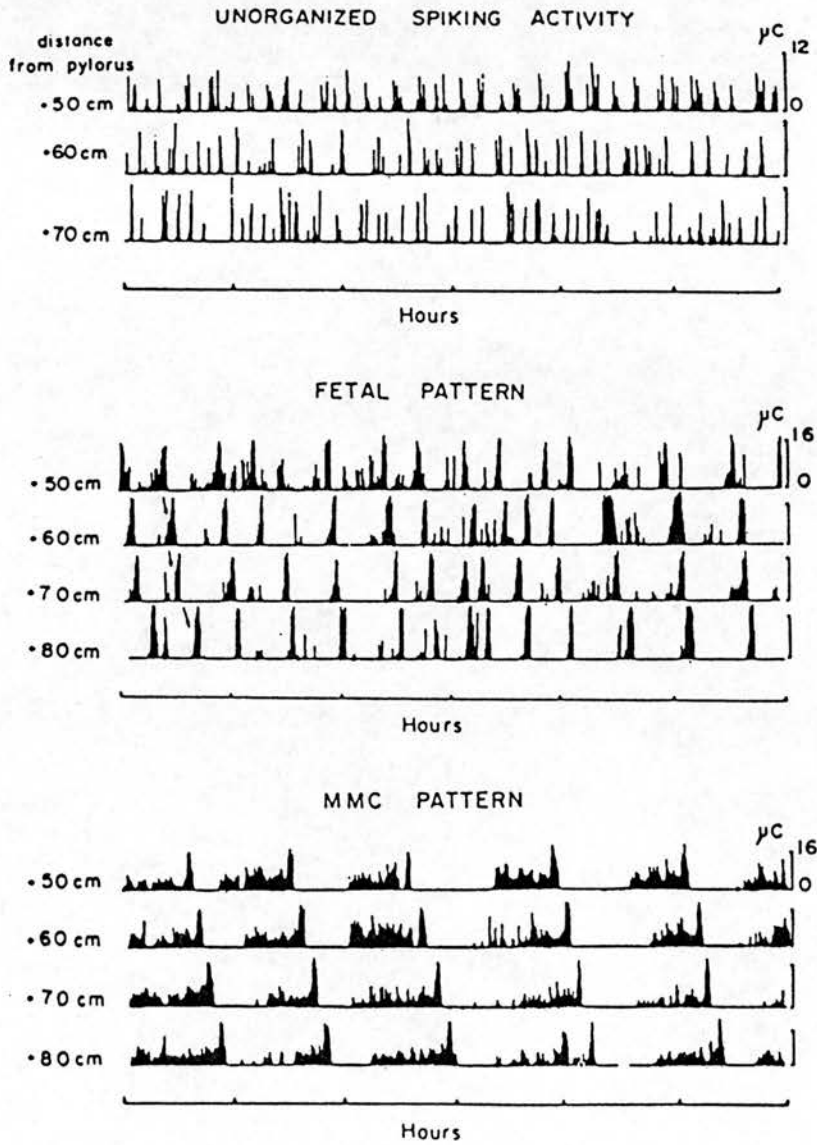
Timetable of motor development in the sheep and dog.
(from Bueno and Ruckebusch, 1979)

(expressed as a fraction of term)

	LAMB	DOG
UNORGANISED ACTIVITY	0.7	0.8
FETAL PATTERN	0.9	TERM
MMC PATTERN	TERM	16 DAYS POST TERM

Fig. 4.2

In utero electromyographic recording from the small intestine of the fetal lamb at 0.7 (top), 0.9 (middle) of term and at term (bottom). (from Bueno and Ruckebusch, 1979)



sheep and dog were seen the attenuated single channel
signal made the measurement of propagative activity
impossible.

4.5 THE EFFECT OF FEEDING ON INTESTINAL MOTOR FUNCTION

It is known that enteral nutrition facilitates the normal development of a number of intestinal functions in the preterm infant. In parenterally fed infants the levels of many gut hormones are depressed (Lucas et al, 1980a) compared to enterally fed controls. In parenterally fed rats the lack of luminal nutrients results in hypoplasia and hypofunction of the mucosa (Hughes and Dowling, 1980). These changes can be reversed by the re-introduction of enteral feeds. It is likely that similar changes occur in the human preterm neonate in response to milk feeds and it is interesting to speculate how enteral nutrition may modulate motor function. In the preterm infant and the young child one has to consider that not only is the frequency of feeds and the contents of these feeds altering as the child gets older but it is also likely that the underlying control mechanisms are themselves maturing.

However whether the early introduction of enteral feeds will promote the development of intestinal motor activity and thus further enhance enteral feed tolerance is not yet clear.

CHAPTER 5
PROPOSED STUDY

5 PROPOSED STUDY

Over the last 18 years investigation initially in the dog (Szurszewski, 1969) and more recently in the human (Vantrappen et al, 1977) has defined the basic patterns of fasting motor activity in the small intestine. Until recently however very little has been known about the development of small intestinal motility in the human infant and it is only in the last few years that any information has become available (Milla and Fenton, 1983b).

With the development of improved motility recording techniques it has become possible to extend these methods to study more adequately the developing gut of the preterm infant.

It was proposed to define the development of fasting small intestinal motor activity by the longitudinal study of a group of preterm infants and to assess the motor response of the gut to enteral nutrition. By the study of infants with a range of differing gestational ages, illnesses, clinical treatments and feeding regimes it was planned to assess the factors which control the development of, and modulate the expression of small intestinal motor function.

It is hoped that the information gathered will help in the understanding of neonatal gastrointestinal physiology and that the application of this knowledge will result in the rational development of improved

neonatal feeding regimes.

PART II
METHODS AND RESULTS

CHAPTER 6

METHODS

6 METHODS

There are at present two main methods for recording motor activity from the gastrointestinal tract. Either myoelectric activity generated by the intestinal smooth muscle or the pressure produced in the intestinal lumen by smooth muscle contraction can be recorded. The information obtained by each of these techniques differs slightly giving each method certain advantages and limitations.

6.1 MYOELECTRIC ACTIVITY

Myoelectric activity has been extensively recorded in the experimental animal as prolonged recordings are possible from surgically implanted electrodes. (Buono and Ruckebusch, 1979) However in the human the implantation of an array of electrodes along the length of the intestine is not generally possible. (Stoddard, Smallwood and Duthie, 1978) Myoelectric recordings in humans are however possible using catheter mounted electrode assemblies. Early examples of this technique relied upon fine needle electrodes but more recent developments have refined this technique with the construction of bipolar wire (Cu or Ag/AgCl) catheter mounted electrodes. While it is possible to obtain information about the patterns of motor activity and their electrical control from myoelectric recordings, there are a number of major limitations which preclude their use at present in the preterm infant. Catheter assemblies are at present too large and in the absence of pressure data one is unable to calibrate the motor response of the gut to the electrical activity recorded. It was felt that myoelectric methods would be technically very difficult in the preterm infant and that the information required could best be obtained by manometric methods.

6.2 MANOMETRIC METHODS

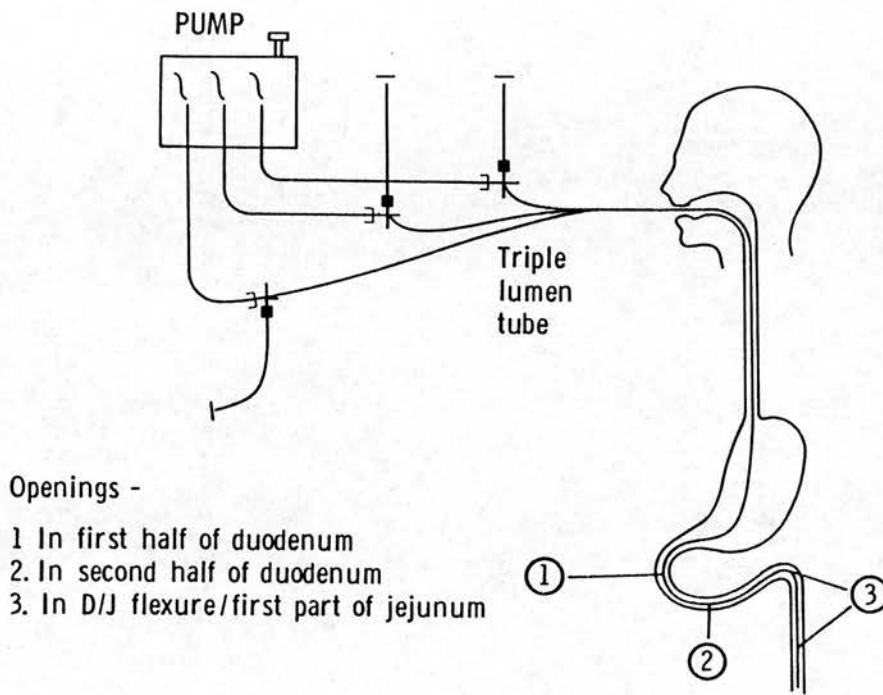
The earliest investigators of intestinal motility used manometric techniques to record intraluminal pressure data. Initially water filled balloons were used (Chapman and Palazzo, 1949) but this has been superseded by the use of low compliance continuous perfusion catheters to measure pressures within the oesophagus, gastric antrum, small intestine and colon. (Vantrappen et al, 1977) With a low compliance system long narrow catheters can be used without damping of the transmitted pressure signal. The measurement of pressures within large cavities such as the gastric body or fundus, or the rectum does however remain a problem. The great advantage of manometric against myoelectric techniques is the relative simplicity of the method and the ability to record pressure data. Manometric methods have been widely used in children in recent years (Fenton, Harries and Milla, 1983) and it was thus decided to use this technique in the preterm infants.

6.2.1 PRINCIPLES OF MANOMETRIC RECORDING

A manometric assembly contains three components 1) a perfusion system 2) a pressure sensor and display system 3) a catheter assembly. This is outlined diagrammatically in Fig. 6.1. The perfusion system delivers a steady continuous flow of fluid across the pressure sensor and through the catheter. An increase in the intraluminal pressure results in a rise in the pressure of the perfusion fluid which is transmitted along the catheter to the pressure sensors. The pressure rise in the perfusion fluid matches the intraluminal pressure and thus by calibration of the pressure sensor accurate measurements of intraluminal pressure can be obtained. The placement of multiple catheters in parallel, with their distal openings at different levels allows multiple pressures to be recorded simultaneously and thus facilitates the assessment of motor propagation.

Fig. 6.1

A diagrammatic representation of the multilumen perfused manometric assembly which was used in this study.



6.3 THE DEVELOPMENT OF A NEONATAL MANOMETRIC ASSEMBLY

While the manometric techniques required to measure small intestinal motor activity in the preterm infant are generally similar to those used in older children and adults there are a number of major limitations that are introduced by the small size of the patients being studied. Allowance must be made for this and at the same time the performance characteristics of the system must be maintained. (Table 6.1)

Most manometric systems use either water or saline as the perfusion fluid and perfuse at rates of between 1-5 mls/min. If the volume of fluid that is delivered into the gut over a 4-6 hour recording period is considered, then this can be very large and is totally unacceptable for the study of a baby who may weigh only 1 kilogram.

A further limitation is the need for a narrow perfusion catheter. Many adult assemblies use catheters with a total diameter of 6-10mm while paediatric catheters down to 2.5mm have previously been used. To be ethically acceptable the neonatal catheters have to be no larger than feeding tubes which are currently used in this age group (1.5mm ,5 F.G.) as blockage of the nasopharynx by large tubes can seriously embarrass respiration. The requirement for multiple lumens also compounds this problem.

Finally one would anticipate that intraluminal pressures will be of a relatively low magnitude in the preterm infant and thus a relatively more sensitive system will

TABLE 6.1

Specific requirements of a neonatal system.

LOW PERFUSION RATE

VERY NARROW CATHETER

INCREASED SENSITIVITY

be required.

In an efficient manometric system pressure changes within the gut will be transmitted through the column of fluid to the pressure transducers. The pressure transmission will be attenuated if the fluid column is incomplete (ie due to a bubble) or if the catheter is too long, too narrow or too compliant. When the catheter performance fails to meet the system requirements pressure signals are attenuated and there is a rise of the baseline as the signal fails to return to normal prior to the next contraction. The factors which affect system performance are listed in Table 6.2.

High performance recording systems are required to measure oesophageal motility as very large changes of pressure occur very quickly but in the small intestine of the preterm neonate the maximal frequency of contraction is that of the electrical control activity (12 cpm) and it is unlikely that pressures will reach more than 40 mm Hg. Thus a lower fidelity system will effectively record changes in neonatal motility allowing a low perfusion, narrow lumen system to be developed.

TABLE 6.2

Factors affecting performance of system

PERFUSION RATE

PERFUSION PUMP PERFORMANCE

CATHETER DIAMETER

CATHETER LENGTH

CATHETER COMPLIANCE

FREQUENCY RESPONSE OF RECORDING EQUIPMENT

6.3.1 NEONATAL CATHETER

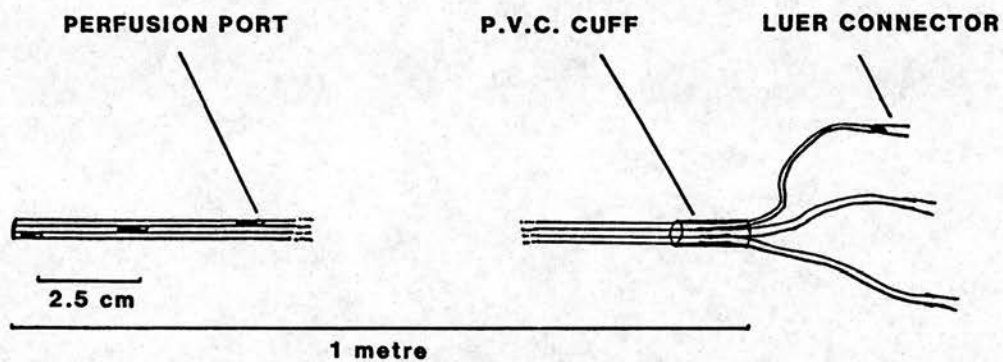
Initially attempts were made to develop a neonatal tube based on either a 5 F.G. or 6 F.G. silastic feeding tube. The main problem was the need for a multilumen system which would require the addition of extra lumens to the silastic tube. Attempts were made to insert an extra 0.5mm PVC catheter within the silastic tube, but this resulted in major problems with sealing off the channels and maintaining signal isolation. The technical difficulties were such that attempts to develop a silastic based catheter were abandoned at an early stage. An alternative system was developed based on soft PVC multilumen catheters which were obtained from Dural Plastics, Dural, N.S.W., Australia. One metre lengths of either double or triple lumen tubing were obtained which were expanded at one end to facilitate the attachment of connecting tubing. The tubing had an external diameter of 1.5mm with internal diameters of 0.7mm and 0.5mm in the double and triple lumen tubes respectively.

Outlet holes for the perfusion fluid were made for each channel with a separation of 2.5cm between ports. As these holes were very small (approx. 0.5mm diameter) an illuminated magnifying glass and a guide wire within each lumen was required to be certain of correct positioning. The lumen distal to these holes was blocked with silastic cement impregnated with barium sulphate. The proximal tube ends for each channel were connected

over a firm plastic splint to flexible tubing containing a female luer connector, and a rubber sleeve was passed over the connections to further secure them. A diagrammatic representation of this tube is shown in Fig. 6.2 with an illustration of the finished tube in Fig. 6.3 .

Fig. 6.2

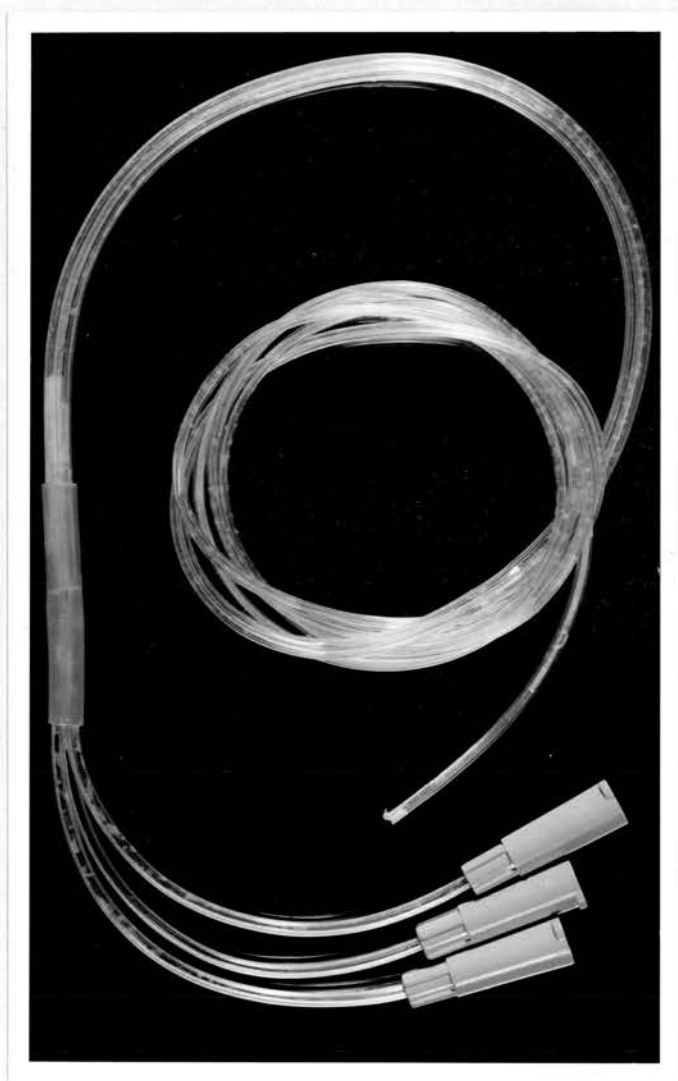
A diagram of a miniaturised triple lumen manometric catheter.



TRIPLE LUMEN P.V.C. CATHETER
(E.D. 1.5mm I.D. 0.5mm / channel)

Fig. 6.3

A triple lumen PVC catheter.



6.3.2 PERFUSION SYSTEM

It is essential that fluid is delivered at a controlled rate and that this delivery is continuous and smooth. A low continuous flow prevents the formation of bubbles within the tube and stops debris collecting over the distal ports. Any irregularity in the delivery of the fluid is transmitted to the pressure sensors and recorded as artefact. It is also essential that each recording channel is isolated and this can be obtained by the use of a parallel perfusion system (ie multiple syringe pumps) or a pneumo-hydraulic system with channel separation with capillary wires (ie Arndorfer system). A Harvard infusion pump (Boston, Mass., USA) with a three syringe assembly, a large range of flow rates and a smooth continuous action was chosen. A solution of degassed 0.9% saline was used as the perfusion fluid. This perfusion system delivered a steady controlled flow of saline with complete channel isolation. When tested with the complete manometric assembly (6.3.4) its performance was well within our required limits.

6.3.3 PRESSURE SENSOR

The pressure sensing system used is identical to that employed by Fenton over a number of years to measure motility in older children. (Fenton, Harries and Milla, 1983) Pressure transducers with a luer fitting (Gaeltec, Skye, Scotland) were connected through a 3-way tap to each perfusion channel and the signal produced was displayed on a multichannel oscillographic chart recorder (Washington MD4, UK ,LTD. The performance characteristics of the pressure sensing system were greatly in excess of requirements. The system is seen in use in Fig. 6.4 .

Fig. 6.4

The recording equipment in use: from a distance (top) and close-up (bottom).



i = infusion pump

c = catheter

t = transducer

p = polygraph

b = baby

bt = babytherm



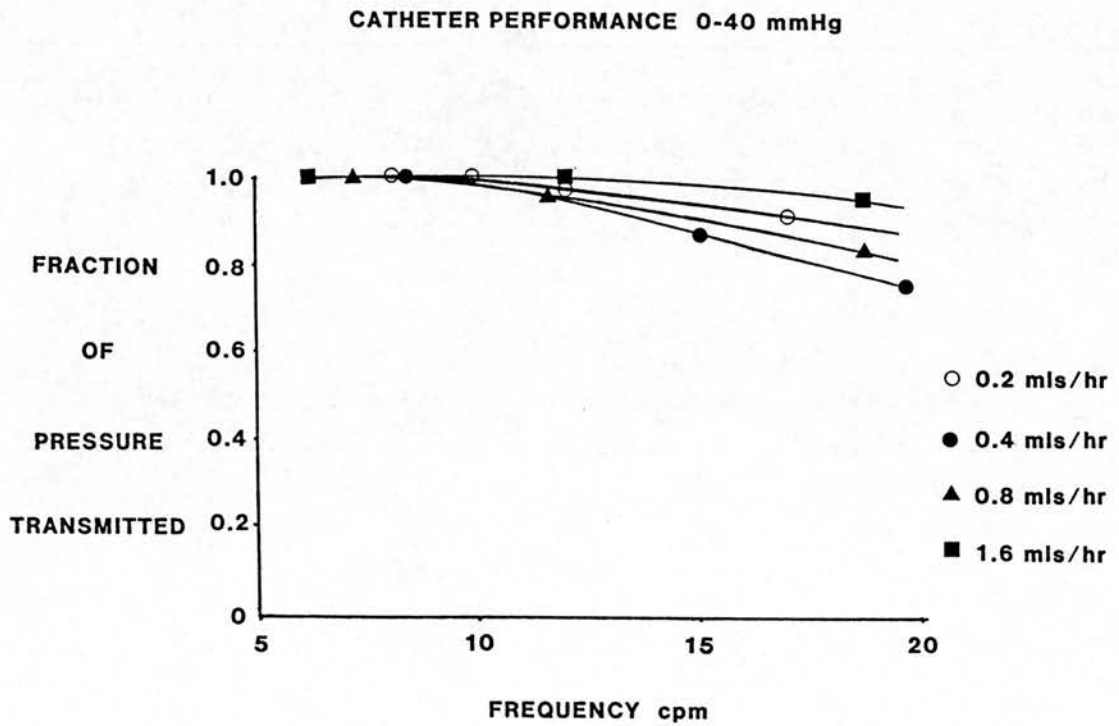
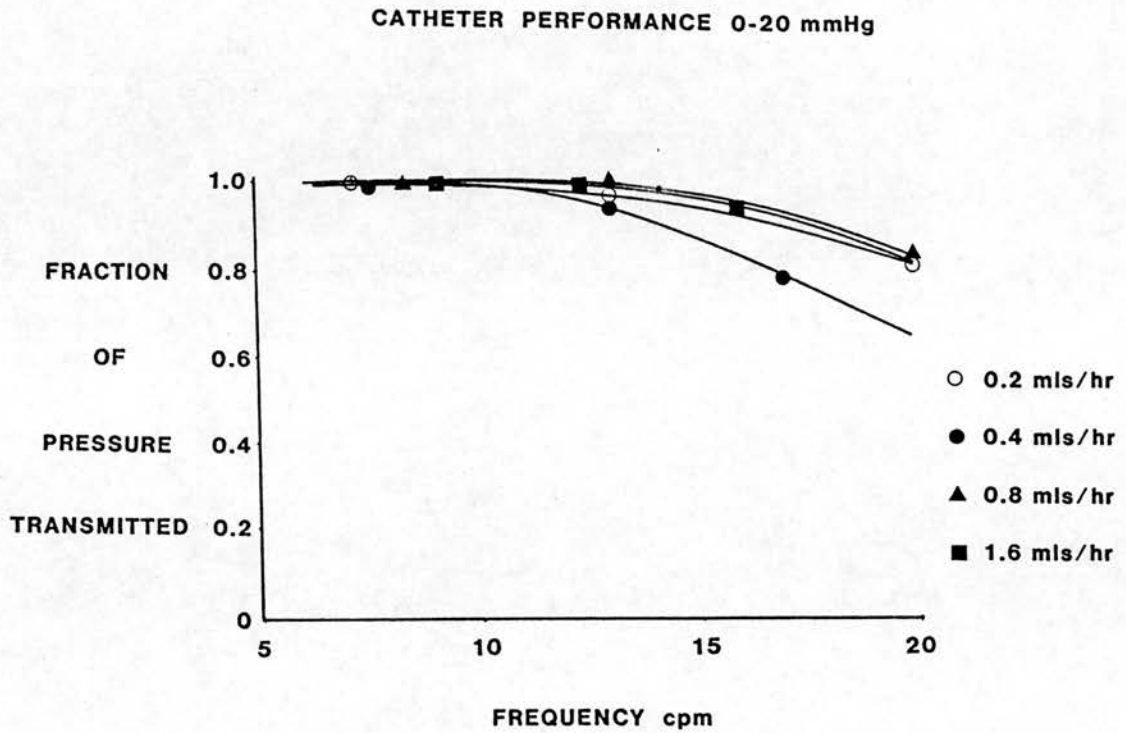
6.3.4 PERFORMANCE TESTING OF MANOMETRIC SYSTEM

Prior to use, the manometric system was bench tested to check that its performance characteristics were adequate to meet the requirements outlined above. The system was tested with a triple lumen PVC catheter (id 0.5mm) which was connected via 1 metre of tubing to the pressure transducers and perfusion system. The perfusion rate was varied between 0.2 and 1.6 mls/hr and the system was driven by pressure changes of 0-40 mm Hg at a frequency of 5-20 cycles per minute (cpm). These pressure changes were created either by raising and lowering the catheter tip above the transducers or by placing the catheter tip in an enclosed fluid filled length of Pauls tubing and inducing pressure changes by the rapid instillation and withdrawal of water by syringe. The former method was used for the more detailed performance studies. The effect of occlusion of the distal catheter tip was also assessed.

Experiments were carried out with pressure changes of 0-20 mm Hg and 0-40 mm Hg over the range of frequencies and perfusion rates already described with the results shown in Fig. 6.5. The efficiency of the system was measured by assessing the fraction of the true pressure signal which was transmitted to the transducer at different frequencies. As one might expect the pressures transmitted and thus the system performance began to fall at increasing frequencies. (Fig. 6.6) One would predict that pressures generated by the stomach will be

Fig. 6.5

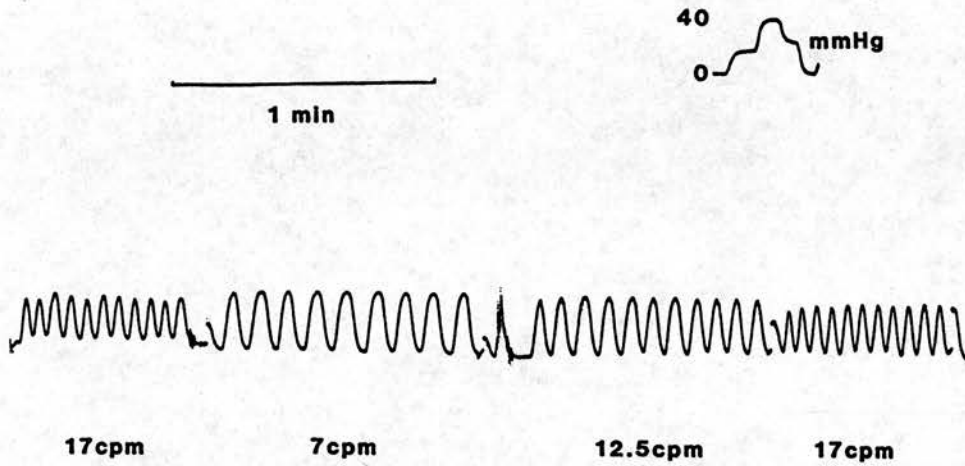
The performance of the manometric assembly was tested over the pressure ranges of 0-20 mmHg (top) and 0-40 mmHg (bottom).



PVC Catheter 0.5 mm I.D. 1 M Length

Fig. 6.6

A pressure recording showing the frequency response of the triple lumen catheter.



FREQUENCY RESPONSE OF MANOMETRIC ASSEMBLY

(flow 0.2 mls/hr)

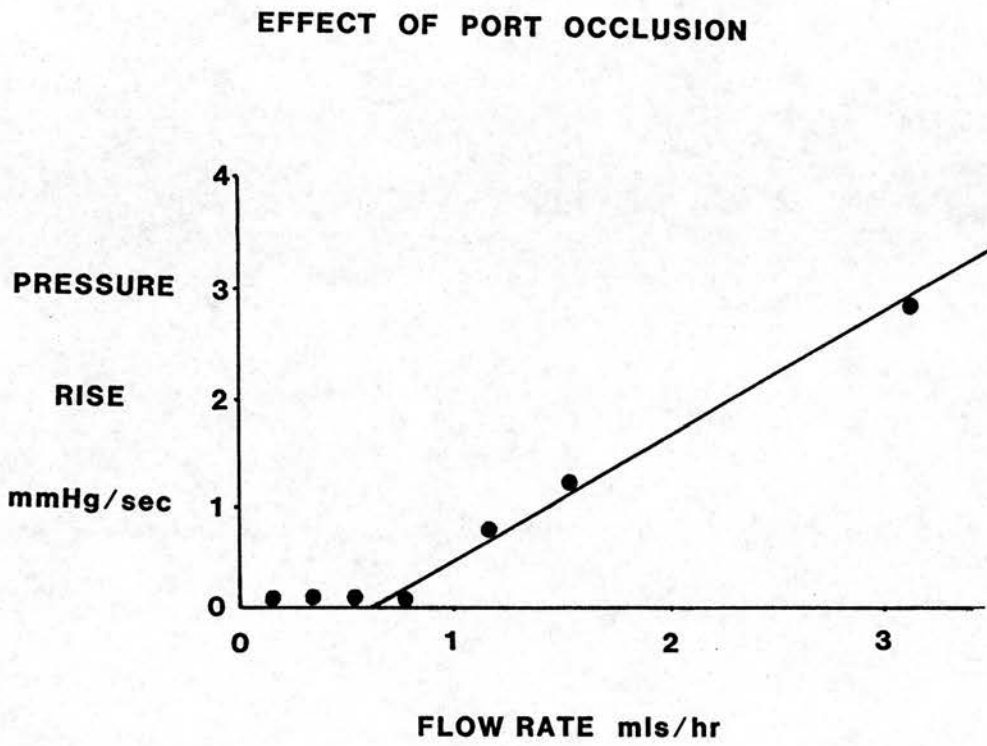
less than 40 mm Hg with a frequency of 3 cpm and duodenal activity will be less than 20 mm Hg at a frequency of 12 cpm. From the results shown in Fig. 6.5 this would suggest that the manometric assembly would perform very adequately with no significant signal attenuation (>95% signal transmission) under the anticipated recording conditions. Signal waveforms were accurately represented at all pressures and frequencies and at 12 cpm there was no rise of the baseline pressure. Alteration in perfusion flow rate did not appear to have a consistent effect on the tube performance.

The effect of catheter tip occlusion is shown in Fig 6.7. This shows quite clearly that below 0.8 mls/hr tip occlusion has no effect and that even above this flow rate the pressure rises seen were inadequate to account for the results seen in the previous experiment. This, along with the fact that flow rate has little effect on the catheter performance would suggest that at low flow rates catheter tip occlusion plays very little part in the generation of pressure signals and that pressure changes are most probably transmitted directly to the catheter fluid column through an air/fluid or fluid/fluid interface with the contents of the intestinal lumen.

A flow rate of 0.4 mls/hr/channel was used in the neonatal perfusion studies.

Fig. 6.7

At low flow rates catheter tip occlusion did not contribute to the transmission of pressure signals.



6.3.5 CATHETER STERILISATION

Preterm infants are particularly susceptible to infection and gastrointestinal superinfection such as occurs in necrotising enterocolitis can be a significant cause of morbidity and mortality. All multilumen catheters were therefore sterilised using ethylene oxide prior to use.

6.4 TUBE INSERTION

In order to record small intestinal pressures the manometric catheter was passed through the nose into the stomach and then through the pylorus into the small intestine. Tube insertion in older children and adults is usually carried out under x-ray control but in our study population this was not possible as most of the infants were confined to the special baby care unit and the use of x-ray was not ethically justifiable. It was therefore necessary to develop an alternative technique to ensure the correct placement of the tube in the small intestine. Initial attempts to use the pH or bile content of aspirated fluid as an indicator of tube position were not very successful.

In older children and adults gastric motor activity has a characteristic frequency of 3 cpm while duodenal motor activity is 4 times faster at 12 cpm. These differences of contraction rate reflect differences in the electrical control activity found in the smooth muscle of these two areas. Similar differences exist in animals of all ages and of all species. The tubes were therefore passed into the stomach, with the baby in the right lateral position, until it reached the pylorus. 10 mls of air was then injected into the stomach to induce motor activity. The recording equipment was running while the tube was being passed. While in the stomach 3 cpm activity was seen but as the tube was advanced slowly through the pylorus the characteristic 12 cpm

activity appeared. (Fig. 3.4) Even in the most preterm infants where pressures were very low this frequency change could be readily seen. Once through the pylorus the tube was then advanced for a further 5-10 cms. In 3 infants who required a x-ray for some other primary medical reason the correct positioning of the tube was confirmed.

There has in the past been some concern about the safety of PVC tubes in preterm infants as they have been reported to harden while in the gut with the resulting risk of perforation. (Boros and Reynolds, 1974) This risk appears only to be important when the tubes have been in situ for many days and where tube manipulation is attempted with hardened tubes. It was thus decided that all tubes would be removed within 48 hrs of insertion and that tube manipulation would be forbidden. The vast majority of tubes were in situ for less than 12 hours.

6.5 COMPUTERISED ANALYSIS

The measurement of the frequency of contractions during complexes of motor activity gives an accurate measure of the pacemaker frequency or electrical control activity (ECA) of intestinal smooth muscle. In an attempt to accurately define the ECA frequency a computerised signal analysis system was developed.

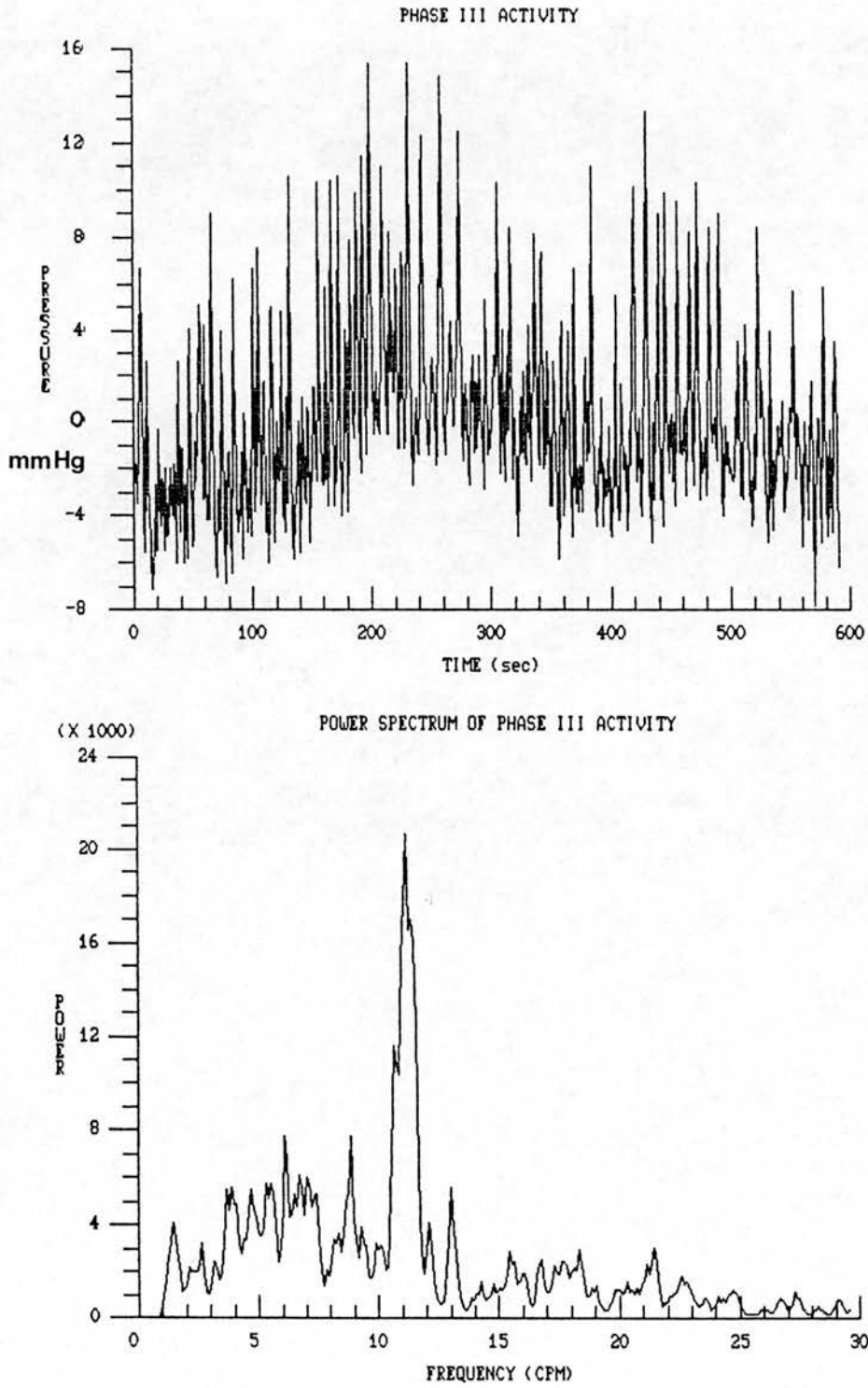
The monitor output (-5 to +5 Volts/channel) from the Washington MD4 recorder was digitalised by an 8 bit analogue to digital (A/D) convertors on an Acorn Electron microcomputer (Acorn Ltd, UK) and the data was stored on magnetic tape for later display and analysis. A fast Fourier transformation (FFT) algorithm obtained from Byte Magazine (Stanley and Peterson, 1978) was translated into BBC Basic and linked with Graphs and Charts (Acornsoft Ltd, UK) to create a frequency analysis and display system. (see Appendix 1 for a listing of the program) As the frequency of motor activity is relatively slow (10.5 cpm to 12.5 cpm) the analogue signal was digitalised at a rate of 1 Hz per channel and groups of 512 data points (8 min 32 sec/channel) were collected. This rather odd number of observations is required as the FFT algorithm requires 2^n data points and the total sampling time of $8 \frac{1}{2}$ mins should cover approximately 100 cycles of activity.

The programme worked very well but unfortunately the numerically intensive calculations took 7 minute on the Acorn Electron and 3 minutes on a BBC microcomputer for

each grouping of 512 data points. An example of a pressure recording with its digitalised representation and a plot of the power spectrum of the FFT of that data is shown in Fig 6.8 . The ECA frequency as estimated by visual planimetry and by FFT were very similar and it was decided that there was no great advantage in persisting with the computerised method given the very slow rate of analysis.

Fig. 6.8

A burst of duodenal Phase III activity (top) with its fast Fourier transform (bottom).



6.6 PATIENTS

The study was carried out in the Winicott Baby Unit, St. Mary's Hospital, Paddington, London W2., which caters largely for preterm infants born at St. Mary's Hospital and for a small number of babies born elsewhere. As almost all the infants remain in the unit until their discharge home, the population was ideal for a longitudinal study. The subjects for study were chosen by the unit medical staff with agreement from the nursing staff and informed consent was obtained from the parents prior to study. The study was approved by the standing ethical committee of St. Mary's Hospital. As an honorary member of the unit medical staff I had no role in the day to day care of the babies and in their choice for study.

In choosing infants for study preference was given to neonates of less than 34 weeks gestation who were born at St. Mary's Hospital. It was proposed to study each infant at 2 weekly intervals up to a total of 4 recordings but this was not always possible. Any infant that was deemed too ill by the medical or nursing staff was not considered for study at that time. As it was possible to pass the manometric catheters with very little disturbance to the babies a number of infants on respiratory support (ventilator, CPAP, headbox O₂) were studied. Prior to study the infants were fasted from between 4-24 hours but in some of the very preterm infants who were on continuous enteral feeds a fast of

only 2 hours was possible if hypoglycaemia was to be prevented. Other than this period of fasting the study was entirely non interventional and the treatment of the patient was not in any way altered or controlled for the purposes of the study. While it might have been helpful to manipulate the feeding or to control the drug therapy of the infants prior to study we felt that this was not ethically acceptable. Thus although the data presented is entirely uncontrolled the differences seen are so great as to overrule this potential objection.

Studies were attempted in 13 infants on a total of 33 separate occasions. The infants ranged in age from 28-42 weeks and in weight from 650-3260 grams. In 12 infants on 28 separate occasions the manometric catheter was successfully placed in the small intestine and on the remaining 5 occasions it was only possible to obtain pressure recordings from the stomach. Of the 28 successful small intestinal manometric recordings 25 were carried out with the multilumen PVC catheter already described and 3 with 5 French gauge (FG) silastic feeding tubes. It was an aim of this study to obtain mainly longitudinal rather than cross-sectional data as inter subject variation is a major source of error in cross-sectional studies. The number of studies was as follows:

3 subjects studied on 4 occasions
1 subject studied on 3 occasions
5 subjects studied on 2 occasions

3 subjects studied on 1 occasion.

Further details of the infants studied can be found in Appendix II.

6.7 STUDY METHODS

The infants were selected and prepared for study and the manometric catheters were passed as described above. The infants were studied for an average of 4 hours and during this period they received normal nursing care. 23 out of the 28 studies included a period when the infants also received milk during the recording, in a volume and at a frequency appropriate for the gestational age and clinical condition of the infant. It was thus possible to record both fasting and post prandial motor activity in the majority of infants studied.

At the time of each study, data relating to the past clinical history of the infant was collated along with information about the babies present nutritional, respiratory and pharmacological management, thus allowing the environmental and management factors which most influenced intestinal motor activity to be ascertained. In adult motility studies the relatively long cycle length (approx. 90-120 mins) and the prolonged periods of post prandial activity after a meal (2-4 hours) mean that many hours of recording are required. Fortunately in very small children and in preterm infants both the cycle length and the length of post prandial activity are reduced allowing 3 or 4 fasting cycles and a period of post prandial activity to be followed during a single recording of 3-4 hours.

6.8 DATA ANALYSIS

With the analysis of any physiological signal there is always a problem when it comes to adequately describing that signal and representing it in a form that can be readily understood. This problem is increased even further when the signals being recorded are not readily recognised by the general reader.

In the present study the analytical criteria have been heavily influenced by previous human (Peeters, Janssens and Vantrappen, 1982) and animal (Code and Marlett, 1975) work, by previous fetal animal work (Bueno and Ruckebusch, 1979) and by earlier human studies in preterm infants. (Milla and Fenton, 1983b) The analysis of intestinal motility recordings is rather subjective but fortunately the contrasts between results obtained at 28 wks and 40 wks gestation are suitably large to be readily recognised by most observers. These changes can be reinforced by a number of objective measurements which also show very significant changes in motility parameters with increasing gestational age.

FASTING ACTIVITY:

From the initial analysis of the recording results it was quite clear that a developmental progression of motility patterns existed. This could conveniently be divided into 4 characteristic patterns of activity which were scored 1-4 respectively.

PATTERN 1 (RANDOM)

Motor activity was generally random during this period.

The pressures generated by the small intestine were very low and there was little or no propagation of motor activity.

PATTERN 2 (CLUSTERED PHASIC ACTIVITY)

Short bursts of organised activity developed, which we have referred to as clustered phasic activity. There was evidence of propagation of the motor activity with some of these clusters.

PATTERN 3 (PROLONGED PHASIC ACTIVITY)

The motor activity became more prolonged with great variability of complex length and of complex interval. This activity was propagated.

PATTERN 4 (PHASE III or MIGRATING MOTOR COMPLEX)

Motor activity showed increasing organisation with well developed phase III activity. The previous variability in complex length and interval disappeared.

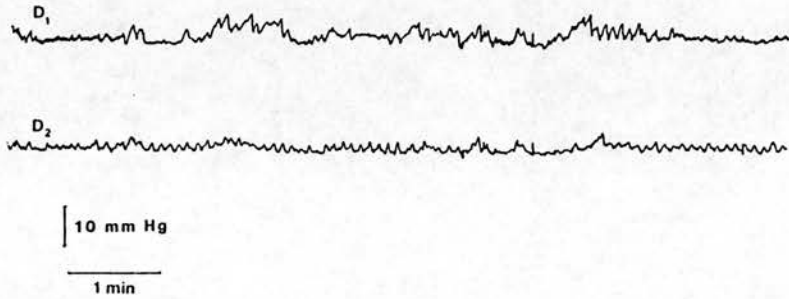
These major changes in small intestinal motor activity are clearly shown in Fig. 6.9.

In order to test that this assessment of the motility recordings was reproducible, all of the traces were scored (1-4) in a blind manner by my colleague Dr P J Milla who had no prior knowledge of the age or condition of any of the babies. There was a very good correlation ($r=0.84$) between the scoring of PJM and myself and of the 28 small intestinal traces which were scored there was complete agreement in 17 recordings and a difference of only one scoring unit in 11 recordings. On further analysis the same very obvious trends were

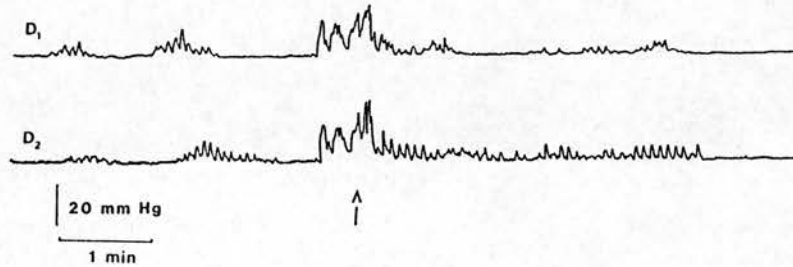
Fig. 6.9

Pressure traces were scored from 1-4 to reflect the major developmental changes in small intestinal motor activity which occur with increasing gestational age. (↑) Body arousal.

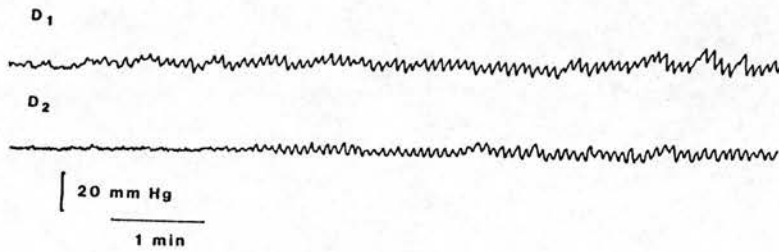
1) RANDOM



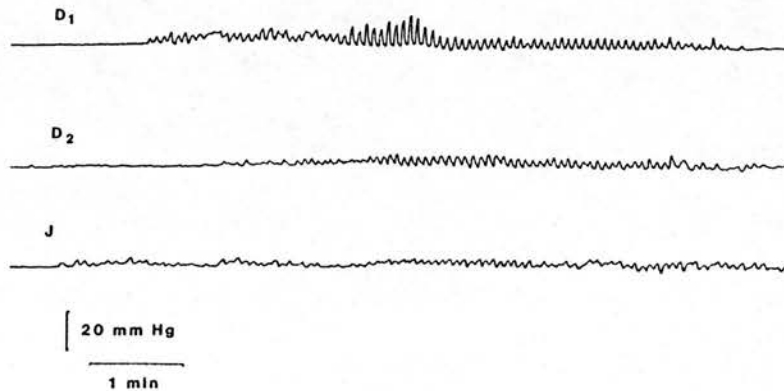
2) CLUSTERED PHASIC ACTIVITY



3) PROLONGED PHASIC ACTIVITY



4) PHASE III



present with both sets of data. This agreement results largely from the very obvious developmental changes which are seen in the recordings.

The parameters of fasting motor activity that were measured were:

MOTOR COMPLEX INTERVAL

The mean interval in minutes between clusters or complexes of motor activity.

MOTOR COMPLEX LENGTH

The mean length of clusters or complexes of motor activity in minutes.

DUODENAL MOTOR COMPLEX FREQUENCY: FASTING

The frequency of motor contractions during periods of maximal motor activity in cycles per minute. This frequency is the same as the electrical control activity (ECA) of the duodenal smooth muscle.

GASTRIC MOTOR FREQUENCY

The frequency of gastric (ECA) was characterised.

MAXIMAL GASTRIC PRESSURE

The maximal gastric pressure generated was documented (mm Hg) rather than the mean pressure as the total time spent recording gastric activity was relatively short. This data was obtained as the perfusion catheter was being passed through the stomach and in those patients where small intestinal recording was not possible.

MEAN DUODENAL PRESSURE

The mean duodenal pressure during periods of motor

activity was calculated. (mm Hg)

PROPAGATION INDEX

The propagation index was scored between 0-4 with 0 representing no propagative activity and 4 representing highly organised propagative activity.

PROPAGATION VELOCITY

This represents the average velocity of propagation of individual complexes of motor activity.

CLINICAL STATUS

The clinical wellbeing of the patients studied was assessed and the patients were classified into those who were ill and those who were well. The former group were largely infants receiving respiratory support in the form of ventilation, continuous positive airways pressure or head box oxygen.

POST PRANDIAL ACTIVITY:

As I have outlined, in adults it is usual for the ingestion of food to be followed by a prolonged period of post prandial motor activity in the small intestine with complete disruption of the fasting motor pattern. In the preterm infant where motor responses are less well developed there are 3 possible consequences from the ingestion of food.

- 1) No change to fasting pattern.
- 2) Induction of post prandial activity with continued fasting activity.
- 3) Induction of post prandial activity with complete disruption of fasting motor activity.

The parameters of post prandial motor activity which were measured were:

LENGTH OF POST PRANDIAL ACTIVITY

This was the length in time in minutes that post prandial activity was present. Post prandial activity was defined as the total period of continuous random motor activity following the ingestion of food. As described above it was possible for fasting and post prandial activity to co-exist in some patients.

DUODENAL POST PRANDIAL MOTOR FREQUENCY

The frequency of maximal post prandial motor activity. (cycles per minute)

SUCKING STRENGTH

The degree of nutritive sucking was assessed at the time of each study. A score of 0 represents no nutritive sucking while a score of 5 reflects a powerful nutritive suck.

STATISTICAL METHODS:

Parametric data is expressed as mean \pm 1 standard deviation (SD) and non-parametric data is expressed as the range and the median value. The relationship between variables is expressed by the correlation coefficient (r) and the significance of this relationship was derived from the F-score by linear regression analysis. Multiple regression analysis was used to define the significance of factors influencing the length of post prandial motor activity. The

significance of the difference between parametric variables was tested by the paired and unpaired student T-test and non-parametric variables was tested by the Mann-Whitney U test. Probability (p) values of 0.05 or less are taken to be significant.

The statistical analysis was carried out on the Control Data Corporation (CDC) mainframe at Imperial College London, using the MINITAB statistical analysis package and on a Zenith 248 microcomputer using the Statgraphics package (STSC).

CHAPTER 7

RESULTS

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SCRIPT

7 RESULTS

The results will be presented in three sections. The first relates to the results obtained in the fasting state, the second to the results obtained following the ingestion of milk and the last section relates to the development of sucking.

7.1 FASTING ACTIVITY

Despite the narrow perfusion catheter and the low perfusion rate good quality recordings were obtained for most patients without any attenuation of the pressure signal. Patient movement and body arousal did however produce artefactual signals which occasionally swamped the underlying physiological signal. It was possible however to reduce this to a minimum by keeping the babies dry and comfortable and when required by a combination of auditory and tactile stimulation. The babies were not sedated for this study.

It was noted that body arousals frequently occurred at the same time as the initiation of clusters or complexes of motor activity and it is interesting to speculate that an alteration in intestinal motility was resulting in changed CNS activity in much the same way as we are consciously aware of "hunger pains" during periods of Phase III activity.

The development of fasting motor activity in the small intestine of the preterm infant followed a clear developmental progression which could be divided into 4 phases of motor activity. (Fig. 6.9, Table 7.1.)

In the most preterm infants (28-32 weeks) and particularly those receiving respiratory support from a ventilator or from continuous positive airways pressure (CPAP), the motor activity was of a low magnitude with no evidence of propagation of that activity and very little organisation of the activity into groups of

Table 7.1

The age of infants in each motor development group.

PATTERN OF MOTOR ACTIVITY	NUMBER STUDIED	GESTATIONAL AGE (wks)
1) Disorganised random activity	5	28-32 (29.5)
2) Clustered phasic activity	11	28-35 (31)
3) Prolonged phasic activity	5	34-36 (35)
4) Phase III or Migrating motor complex	7	37-42 (39)

Values expressed as Range (Median)

contractions. (Fig 7.1) It was however possible to see very low pressure activity (<2 mm Hg) at the ECA frequency of 11 cpm which was invaluable in allowing us to accurately place our catheters in the small intestine. The poorly organised activity occurred at a time when the infants food tolerance was very poor and indeed some of the infants were on parenteral nutrition. With increasing maturation of the intestinal motility pattern short clusters of motor activity developed in infants between 28-35 weeks gestation. (Fig. 7.2) This clustered phasic activity lasted from 1-20 mins, median 4 mins, and occurred at intervals of 4-35 mins, median 12 mins. Initially only about 50% of these clusters were propagated aborally but this increased to over 80% in recordings where the clustered phasic activity was well developed. The median propagation velocity during this phase was 2.5 cm/min with a motor frequency of 11.0 cpm.

Subsequently, between 34-36 weeks, the motor complexes became very variable with the development of prolonged phasic activity. (Fig. 7.3) Inter-complex intervals were between 4-30 mins, median 10 mins, and complexes lasted for between 5-40 mins, median 12 mins. In some recordings there were regular phasic contractions at the rate of the electrical control activity (ECA) for a prolonged period with only a short interval before the next complex appeared. The median complex length of 12 mins was significantly longer ($p < 0.01$) than that found

Fig. 7.1

In the most preterm infants low magnitude random motor activity was frequently seen. D=duodenum

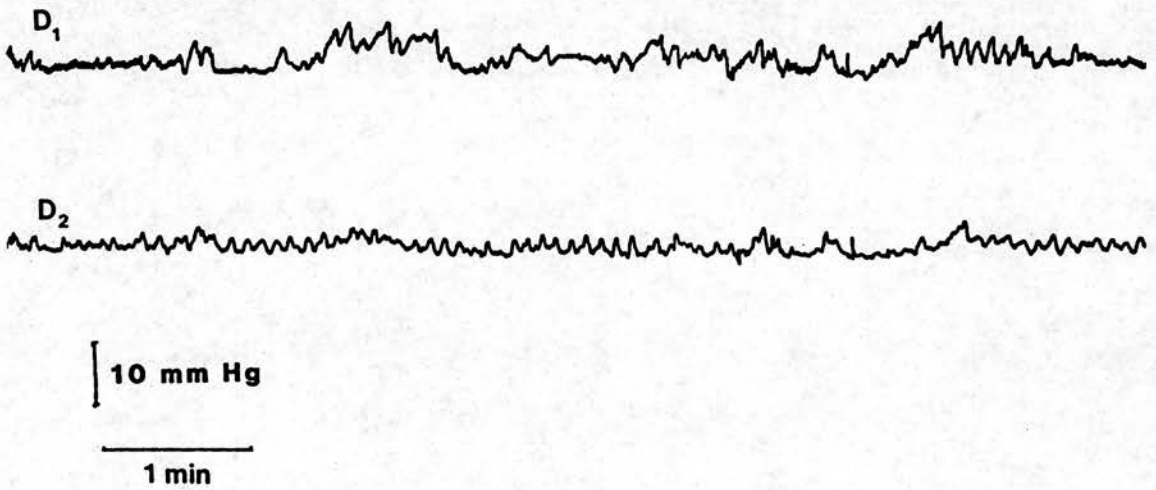
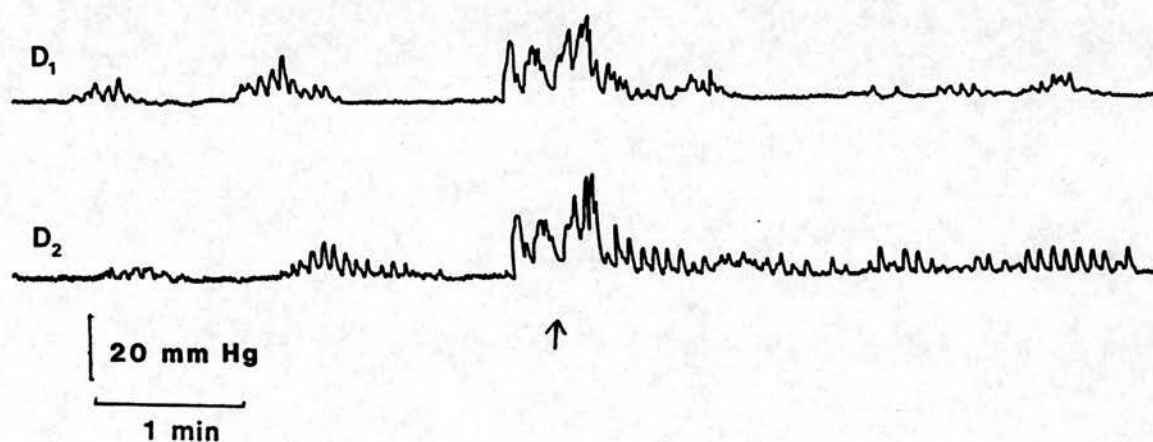


Fig. 7.2

Clearly propagated contractions are seen during clustered phasic activity. Body arousals frequently coincide with this activity. (↑) D=duodenum



during periods of clustered rhythmic activity and the frequency of the ECA at 11.7 cpm was also significantly increased ($p=0.02$). There was no significant difference in the propagation velocity of the phasic motor activity.

In the last few weeks prior to term (after 37 wks) increased enteric control results in the development of a well defined pattern of motor activity with readily discernable Phase I II III and IV activity. The previous variability of complex length and interval was now replaced by well organised aborally propagated Phase III activity. (Fig. 7.4) The complex length of 3-7 mins, median 4 mins, was significantly shorter ($p=0.03$) than during the previous developmental phase and the complex interval of 18-45 mins, median 25 mins, was significantly increased over the "clustered phasic activity" phase ($p=0.02$). The ECA frequency was marginally increased at 12.0 cpm with no change in the complex propagation velocity. The pattern seen at term in the fasting state is identical to that found in the older child (Milla, 1986) and adult (Vantrappen et al, 1977). However the motor complex interval at 25 mins although twice as long as that occurring at 32 weeks gestation is still between a third and a quarter of that found in the adult.

The results of the motor activity parameters which have been discussed are summarised in Table 7.2 .

A number of clear trends can be seen in these parameters

Fig. 7.3

In infants between 34-36 weeks gestation prolonged periods of phasic activity were seen.
D=Duodenum

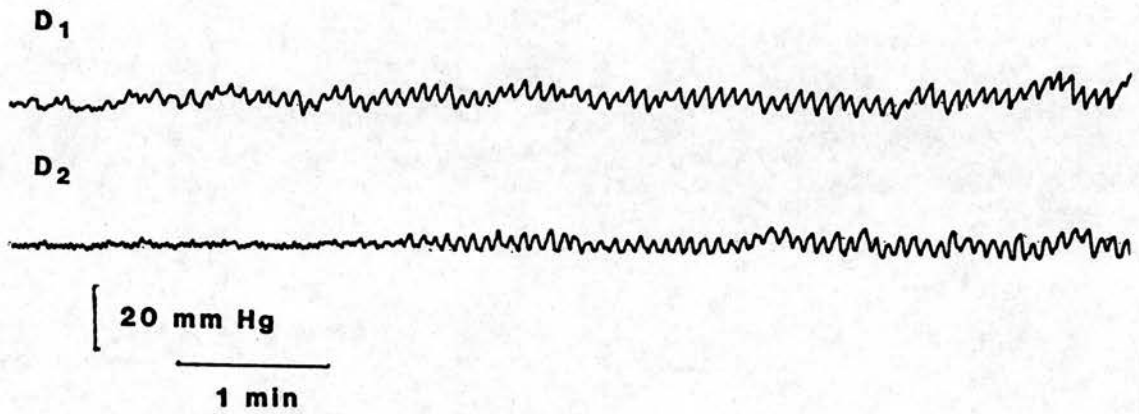


Fig. 7.4

By term well defined Phase III activity had developed.
D=Duodenum, J=Jejunum

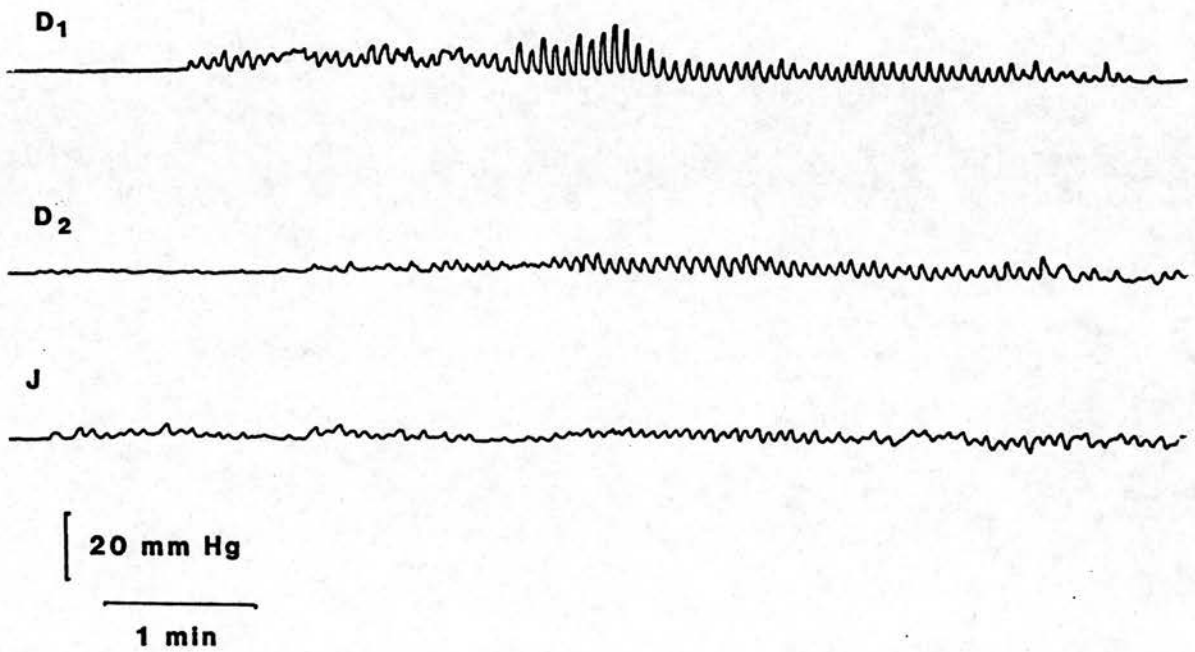


TABLE 7.2

Parameters of fasting motor activity.

MOTOR ORGANISATION	COMPLEX LENGTH (min)	COMPLEX INTERVAL (min)	MOTOR FREQUENCY (cpm)	PROPAGATION VELOCITY (cm/min)
1	0	0	10.5-11.5 (11.0)	0
2	1-20 (4)	4-35 (12)	10.5-12.0 (11.0)	0-5 (2.5)
3	5-40 (12)	4-30 * (12)	11.5-12.5 * (11.7)	1-5 (1.4)
4	3-7 (4)	18-45 (25)	11.0-12.5 (12.0)	0.7-7.5 (2.5)

Values expressed as range (median) * $p < 0.05$

as small intestinal motor activity matures. By term the variability in complex length has gone and the interval between complexes has become longer. With increasing gestational age the fasting motor frequency increases from 11 to 12 cycles per minute and the propagation velocity increases from 0 to over 2.5 cm/min.

The close gestational dependence of this motor activity can be seen more clearly in Fig 7.5 where the motor development score (1-4) is plotted against the gestational age of the child. The straight lines join results obtained in patients who were studied on more than one occasion. Although the relationship between gestational age and motor development is very clear from this figure there is a fair degree of inter individual variation. In Fig 7.6 the median and ranges of gestational age for each motor development score are shown in graphical form. Comparison between groups by non-parametric methods shows quite clearly that motor development is gestational age dependent.

As outlined in the introduction, the development of normal motor activity is dependent on the integrated action of enteric nerves, enteric muscle and on the correct neurohumoral environment for these tissues. While the description of the motor development score is in some ways rather subjective, objective indicators of each of these systems were chosen to assess their relative contribution to motor development.

The changes in myogenic activity were assessed by

Fig. 7.5

With increasing gestational age there was a clear rise in the motor development score. 1) Random 2) Clustered Phasic 3) Persistent Phasic 4) Phase III. Straight lines join those infants who were studied on more than one occasion.

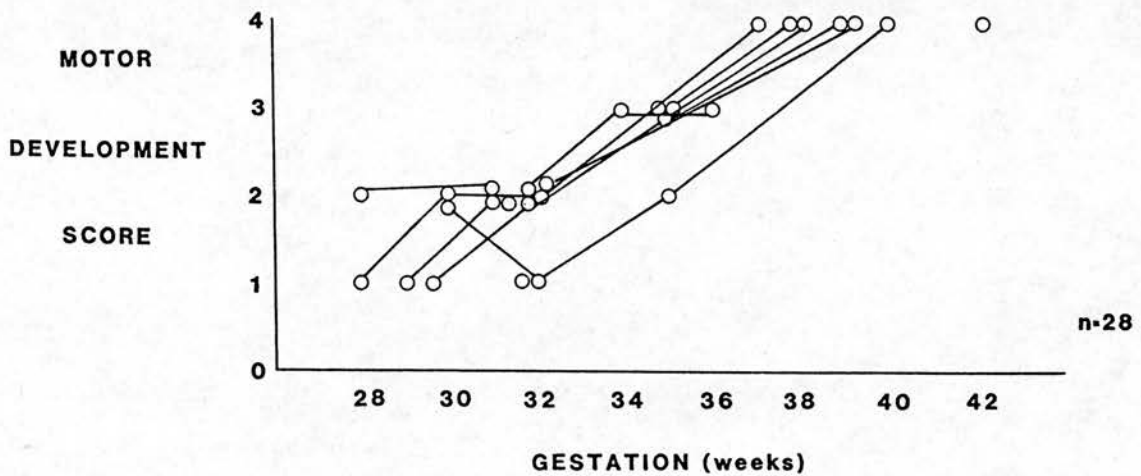
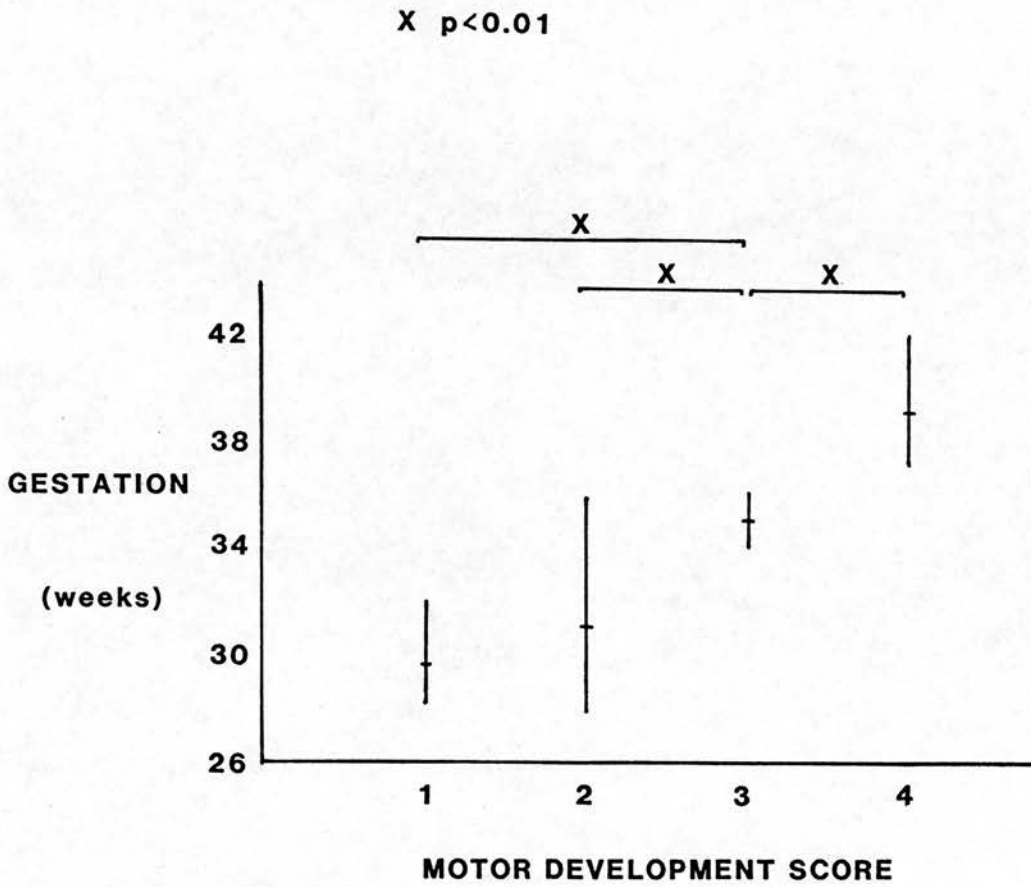


Fig. 7.6

The range and median gestational age for each motor development score is shown. There is a significant $p < 0.01$ rise in the gestational age with increasing motor development score. (Mann-Whitney U Test)



measuring the spontaneous pressures generated by the smooth muscle of the gastric antrum and of the duodenum. It can be clearly seen in Fig 7.7 and Fig 7.8 that there is a highly significant increase in intraluminal fasting pressures with increasing gestational age. ($p < 0.005$).

Increased motor activity on its own without neural organisation of that activity will result in delayed luminal transit. (Tanner, Smith and Lloyd, 1976) The degree of motor propagation was therefore assessed as an indirect measure of enteric neuronal maturation. The level of propagation for a given gestational age is shown in Fig 7.9 and again it can be clearly seen that there is a significant increase in the degree of propagation with increasing gestational age. ($p < 0.01$)

The frequency of the electrical control activity (ECA) of the duodenal smooth muscle is related to a combination of neural, humoral and also myogenic mechanisms. (see 2.3.1) In the infants we studied the ECA frequency increased with increasing gestational age (Fig 7.10) from approximately 11 cpm in the most premature infants to 12 cpm in the infants at term.

The frequency of the gastric ECA did not alter with changes in gestational age and remained at 3 cpm. The very clear difference between gastric and duodenal ECA is shown in Fig 7.11.

Clinically it is apparent that the ill preterm infant is less tolerant to enteral feeds than a well infant of the same gestational age. In this study the ill infants who

Fig. 7.7

With increasing gestational age there was an increase in the fasting pressures which were generated within the stomach.

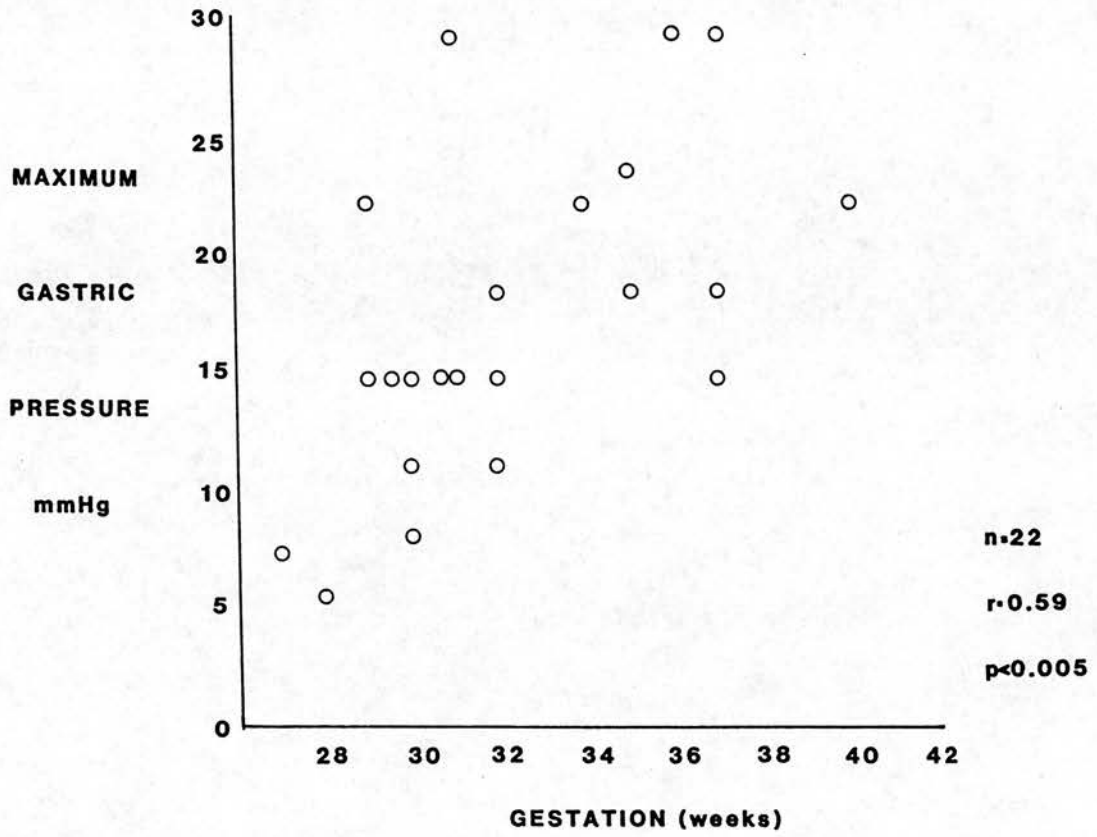


Fig. 7.8

With increasing gestational age there was a clear rise in fasting duodenal pressures.

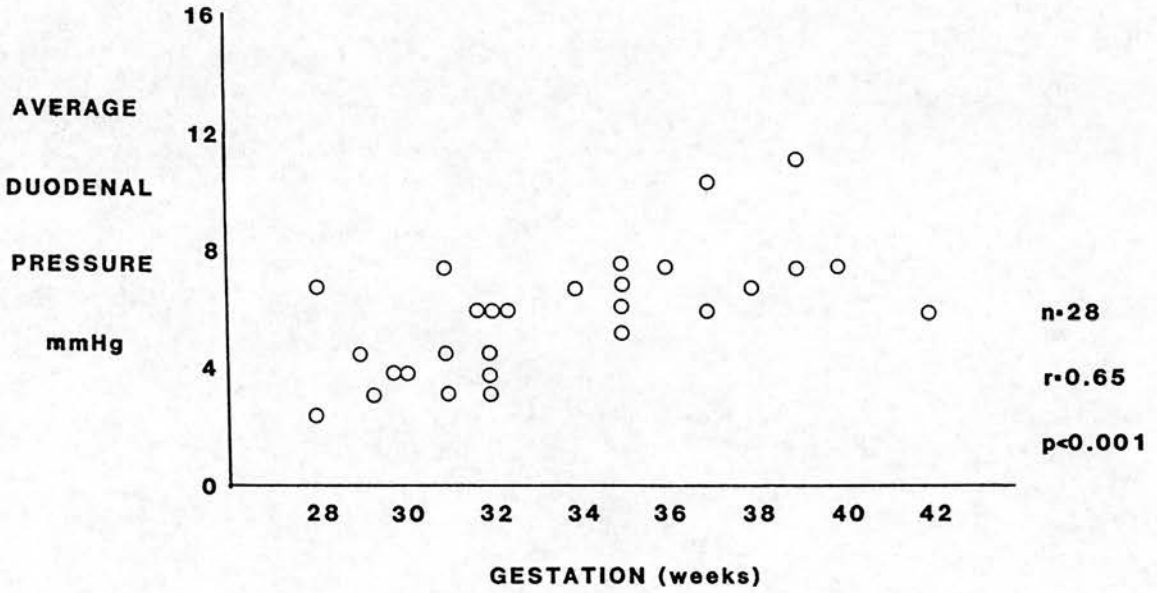


Fig. 7.9

The degree of propagation of fasting duodenal motor activity increased with increasing gestation. (The outlier in this figure was severely ill and on a ventilator.)

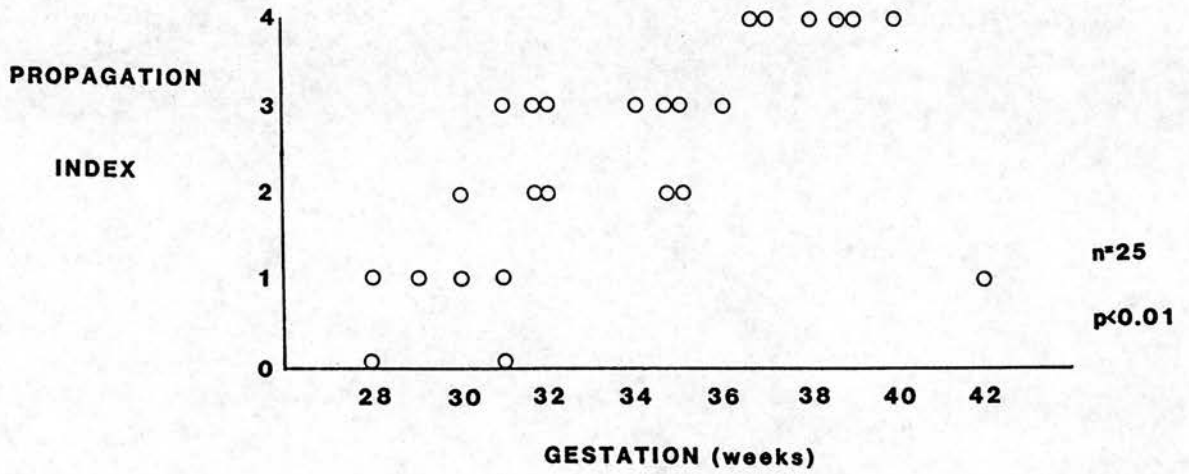


Fig. 7.10

The maximum frequency of fasting duodenal motor activity and thus the frequency of the electrical control activity increased with increasing gestational age. (The outlier in this figure was severely ill and on a ventilator.)

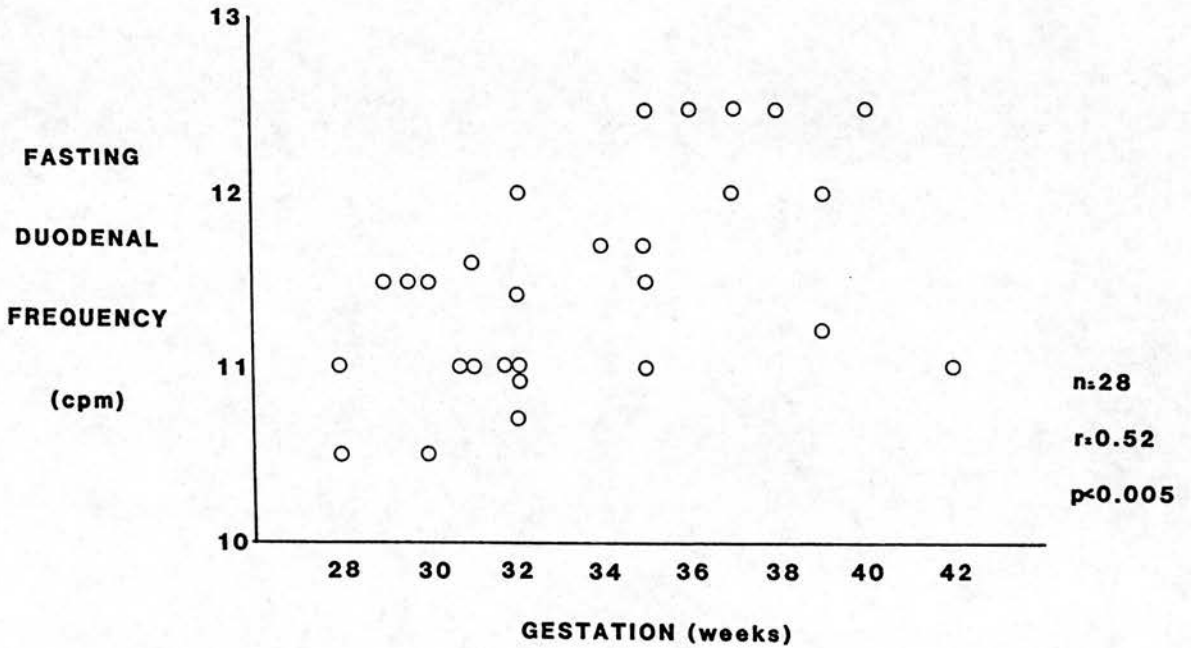
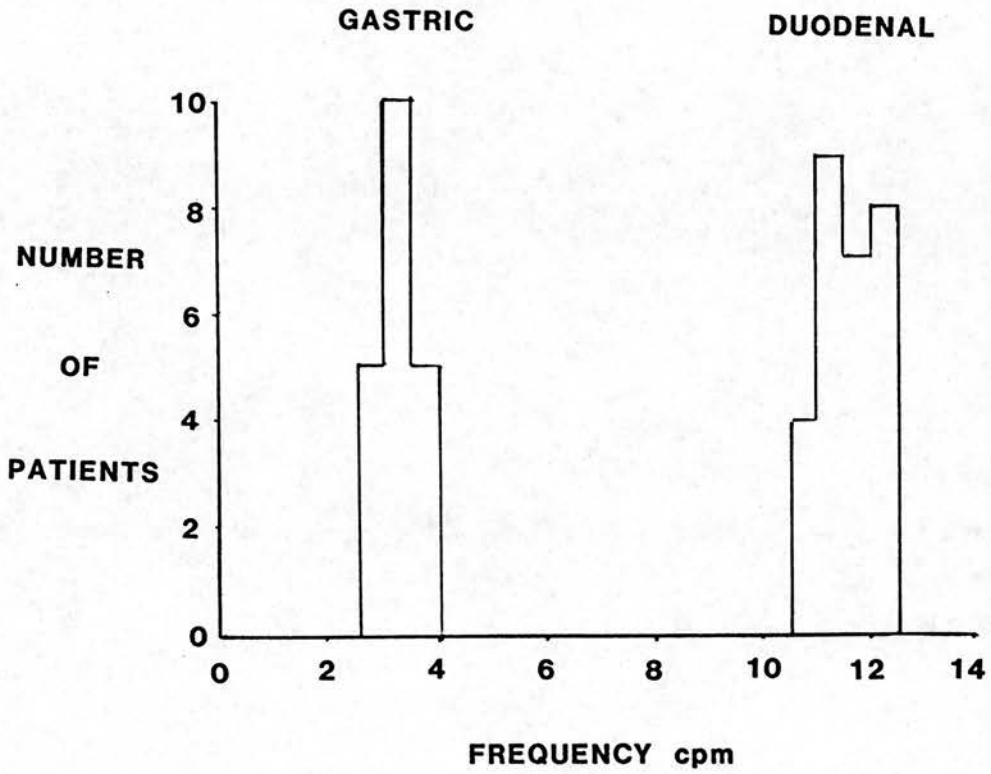


Fig. 7.11

The frequency of motor activity seen in the stomach (2.5-4.0 cpm) was clearly distinct from that found in the duodenum (10.5-12.5 cpm).



were examined were, with one exception, under 33 weeks gestation and as a result of this skewing of the data it was not possible to discern statistically significant differences between these two groups of infants. It is however interesting to note that the one ill older infant (42 wks) had a much reduced duodenal pressure, duodenal frequency and less well developed propagative activity although a clear cyclical pattern of activity could still be seen.

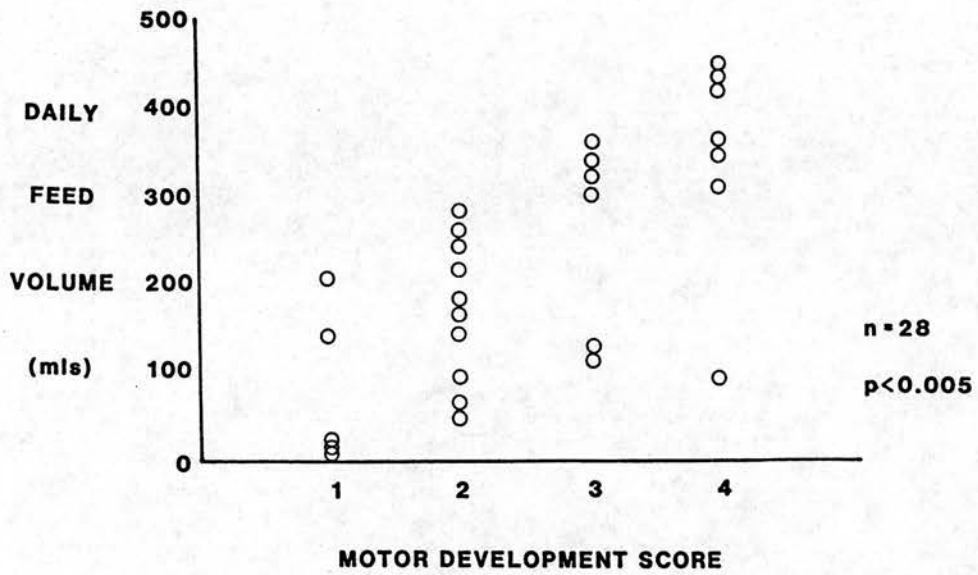
Analysis of the effect of theophylline on fasting motor activity was inconclusive as the infants receiving this drug were skewed towards the lower age group making meaningful analysis impossible.

There were no sex differences in the development of any of the motor parameters.

If the motor development score in the fasting neonate is a valid indicator of motor maturation it should correlate very well with other more objective indices such as the mode of feeding of an infant or the total volume of feed tolerated. This is indeed the case and in Fig 7.12 as can be seen quite clearly, as the level of motor maturation increases so the volume of enteral feed tolerated also increases.

Fig. 7.12

The daily feed volume of the infants studied increased as their level of fasting motor maturation increased. (The outlier in this figure was ill on a ventilator.)



7.2 POST PRANDIAL ACTIVITY

A total of 23 studies in 9 infants were carried out while small intestinal motility was being recorded. The amount given depended largely on the age and well-being of the infant. As a result the older infants received larger feed volumes. This is however more akin to the normal physiological situation than one would achieve if feed volumes were tightly controlled.

It was found that enteral feeding induced one of three responses. (Table 7.3) In the most preterm infants (<30 weeks) who were receiving low volumes of continuous enteral feed, post prandial activity was very poorly developed and if a fasting cyclical pattern was seen this was not disrupted by the enteral feed. (Fig 7.13) In the slightly more mature infants (30-35 weeks) the larger volumes of feed induced a degree of post prandial activity but frequently the underlying fasting pattern remained. (Fig 7.14) Finally in the older infants (>35 weeks) who were receiving large volumes of bolus feed there was complete disruption of the fasting activity with post prandial activity lasting up to 2 hrs. (Fig 7.15 .) However towards the end of this post prandial period fasting activity returned giving a pattern similar to that seen in Fig 7.14 .

In an uncontrolled study such as this there are many factors working together that may have an influence on the development of post prandial activity. It is therefore not always easy to separate one factor from

Table 7.3

Motor responses of the small intestine to enteral feeding in the preterm infant.

- 1) No disruption of cyclical fasting pattern with no post prandial activity
- 2) No disruption of cyclical fasting pattern with superimposed post prandial activity.
- 3) Complete disruption of cyclical fasting pattern with well organised post prandial activity.

Fig. 7.13

In the most preterm infants there was no post prandial response to feeds with preservation of the underlying fasting pattern. D=Duodenum

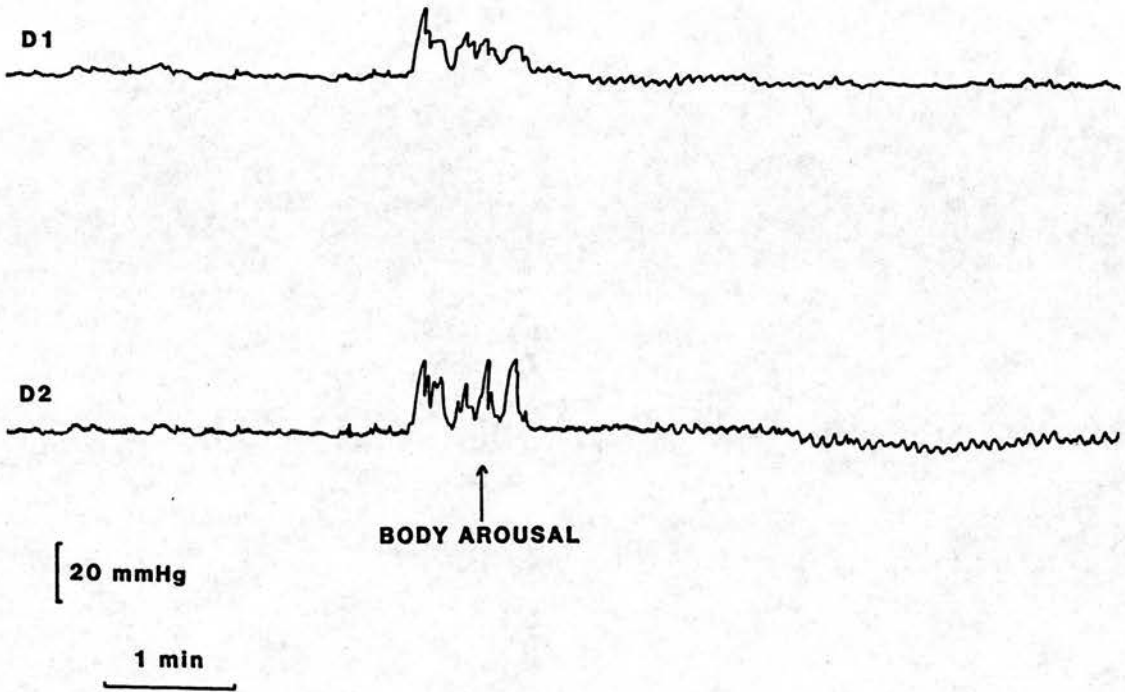


Fig. 7.14

In older infants there was incomplete disruption of the fasting pattern with post prandial and fasting activity occurring simultaneously. D=Duodenum, J=Jejunum
(↑) Fasting Activity

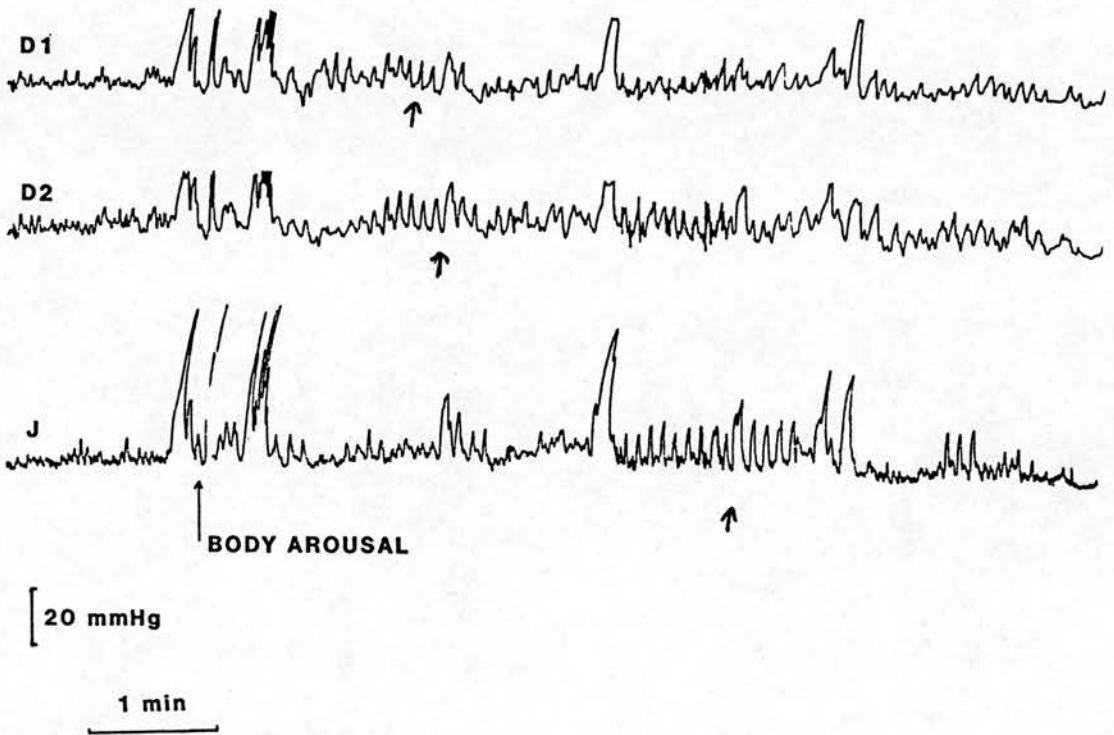
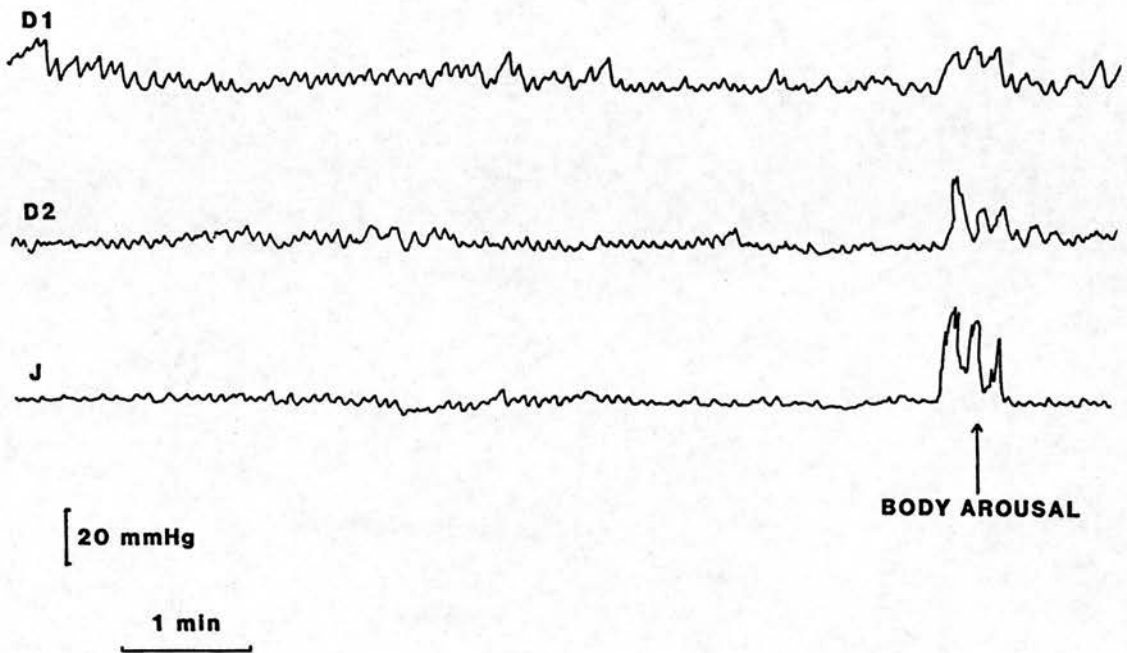


Fig. 7.15

When the infants were fed large volumes of feed there was complete disruption of fasting activity with replacement by post prandial activity.



another but by plotting out the raw data and by the construction of a multiple regression model, with the length of post prandial activity as the dependent variable and gestational age, bolus feed volume and time fed enterally as independent variables, it is possible to draw a number of conclusions regarding the likely controls of post prandial activity.

In Fig. 7.16 it can be seen that with increasing gestational age the length of post prandial activity following a feed increases ($r=0.6$). This increase however may reflect the fact that the more mature infants were receiving larger volumes of feed and indeed using the multiple regression model described above with gestational age and feed volume as the independent variables it can be clearly seen that the former ($p=0.37$) contributes little to the model while the latter ($p=0.005$) appears to be the major determinant of the correlation. This is reflected in Fig. 7.17 where the length of post prandial activity plotted against feed volume shows an improvement in the correlation with the length of activity from 0.6 to 0.78.

In both Fig. 7.16 and 7.17 those infants born before 29 weeks (o) are differentiated from those born after 29 weeks. (●) In Fig. 7.16 where the length of post prandial activity is plotted against the gestational age, the difference between the two groups of babies does not reach statistical significance. ($p=0.07$) However for a given feed volume (Fig. 7.17) those born

Fig. 7.16

The length of post prandial activity increased as the infants became older.

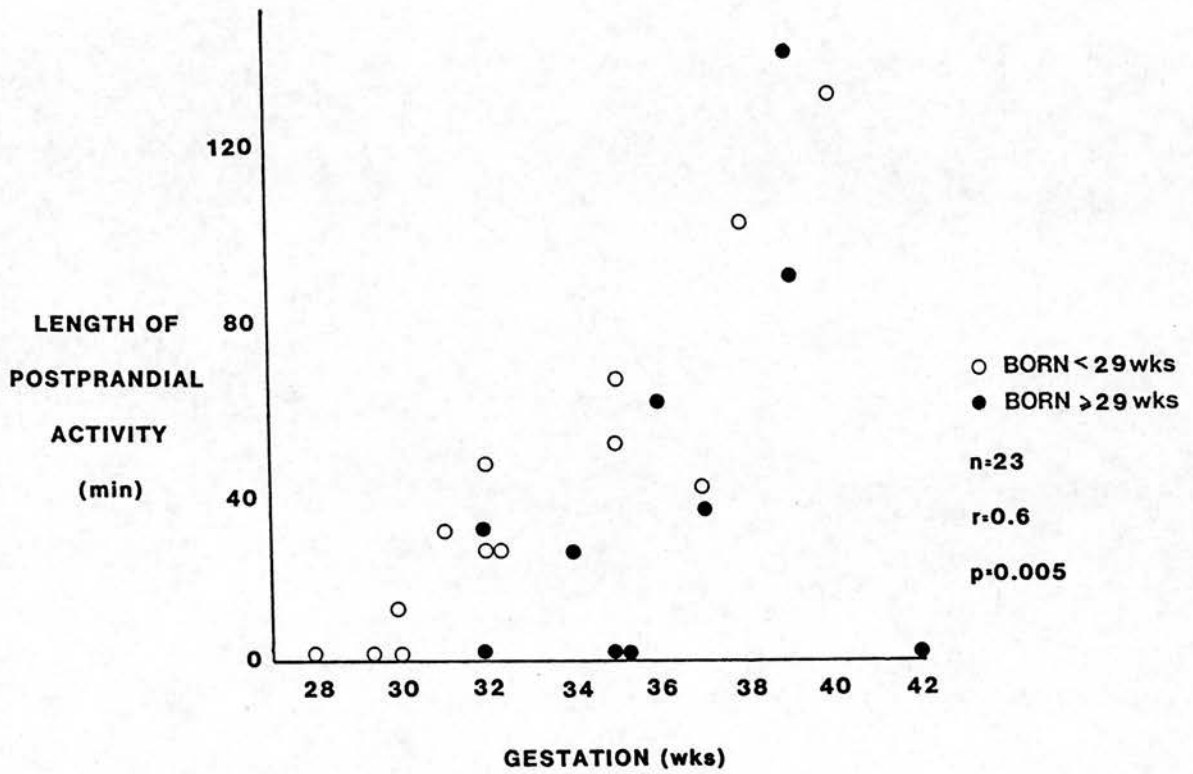
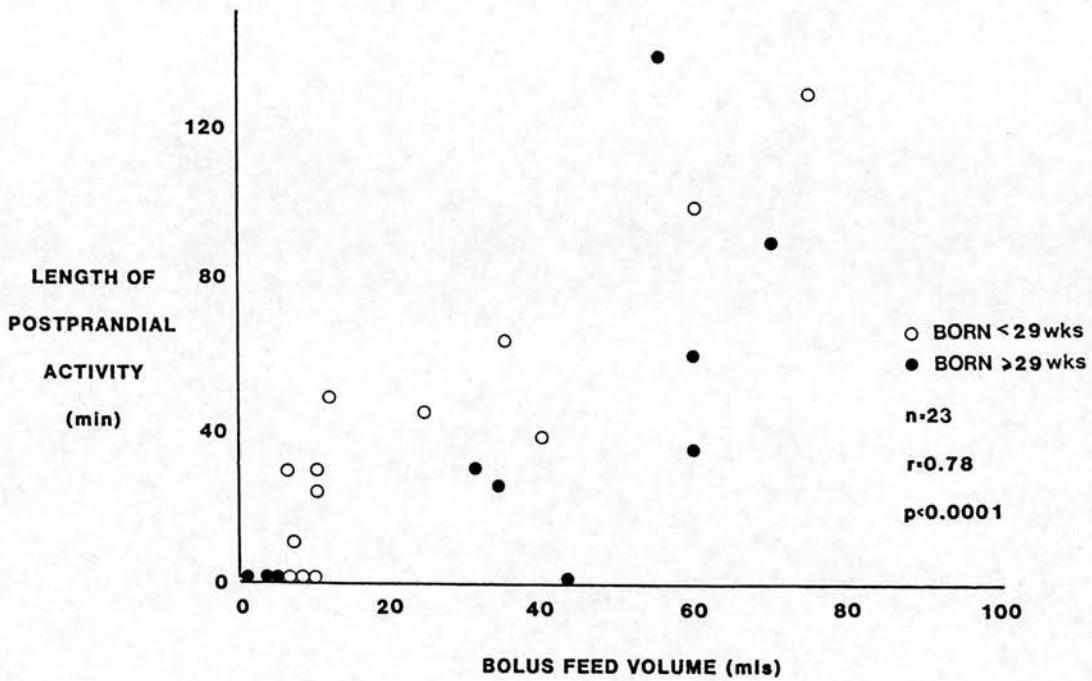


Fig. 7.17

The length of post prandial activity increased as the infants feed volume was increased. Those infants born before 29 weeks gestation had significantly longer ($p < 0.05$) post prandial activity for a given bolus feed volume when compared to those born after 29 weeks gestation.



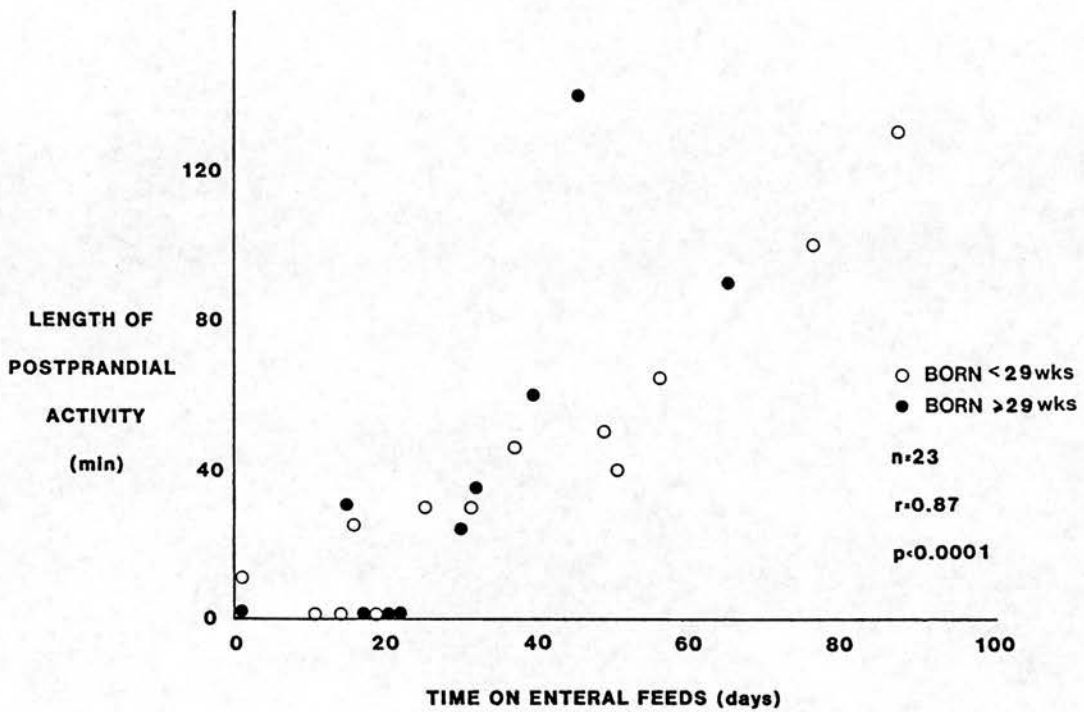
more premature have a significantly longer ($p=0.03$) post prandial response. As the infants born more prematurely will be older for a given post-conceptual age and will have been enterally fed longer the differences described above may reflect adaptive changes resulting from enteral feeding rather than a gestationally dependant maturational process. In Fig. 7.18 the length of time that each infant had been on enteral feeds is plotted against the length of post prandial activity. The very good correlation between these variables ($r=0.89$, $p<0.0001$) strongly supports this hypothesis. In addition the previous differences between the two groups of preterm infants (those born before and after 29 weeks gestation) have now disappeared. Using the multiple regression model previously described it can be clearly shown that the length of time that the infant has been on enteral feeds and to a lesser extent the feed volume are major determinants of the post prandial motor response while the gestational age of the infant appears to be of relatively little importance.

The length of post prandial activity increased progressively from the continuously fed infants to those receiving 4 hourly bolus feeds ($r=0.66$, $p=0.001$). It is very difficult to draw any direct conclusions from this information as the bolus fed infants had been on enteral feeds longer and were receiving larger feed volumes.

As described in the previous section (Fig 7.12) there is a good correlation between the level of fasting

Fig. 7.18

The length of post prandial motor activity correlates particularly well with the length of time the infants had been on enteral feeds. The previous difference between those infants born before and after 29 weeks gestation is no longer present.



motor development and the volumes of feed tolerated. It is not surprising therefore that there is also a positive correlation between the pattern of fasting motor activity and the degree of post prandial motor activity.

The factors which correlate with post prandial activity are summarised in Table 7.4.

It would have been of interest to look at the differing effects of formula and of breast milk feeds on post prandial activity but the large number of other variables along with the relatively small number of infants precluded this.

The frequency of the ECA in the duodenum during the post prandial phase of activity was not significantly different from that found in the fasting state.

TABLE 7.4

Correlation of the following variables with the length of post prandial activity. ($p < 0.005$ in all cases)

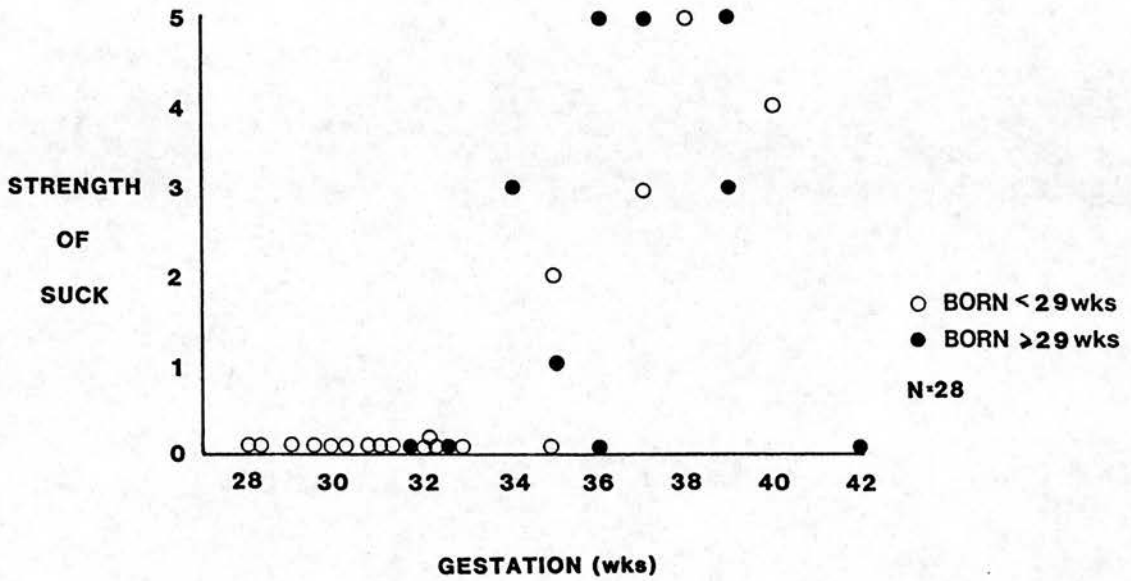
Variable	Correlation
Fasting Motor Activity Score	0.56
Gestational Age	0.60
Reduced Feed Frequency	0.66
Chronological Age	0.78
Bolus Feed Volume	0.78
Daily Feed Volume	0.8
Time Fed Enterally	0.87

7.3 SUCKING

The development of nutritive sucking is a major milestone in the maturation of the gastrointestinal tract in the preterm infant as prior to this time all infants require to be fed either by nasogastric or nasoduodenal tube or intravenously. In those infants studied it can quite clearly be seen from Fig 7.19 that the development of nutritive sucking is gestationally dependant with useful nutritive activity occurring only after 33 weeks gestation.

Fig. 7.19

The ability to suck nutritively is gestationally dependant and increases dramatically after 33 weeks gestation.



PART III
DISCUSSION

CHAPTER 8

DISCUSSION

B.1 FASTING MOTOR ACTIVITY

The ontogeny of fasting small intestinal motor activity in the human shows evidence of a species specific programme of development with a clear pattern of maturation with increasing gestational age. The pattern is characterised by an increase in the strength and frequency of contraction of intestinal smooth muscle associated with an increase in the degree of propagative activity and the eventual development of a cyclical pattern which characterises fasting intestinal motility in older children and adults. (Vantrappen et al, 1977)

The results of this study extend those obtained previously using single lumen silastic feeding catheters (Milla and Fenton, 1983b) and parallel those found in the fetal sheep and dog (Bueno and Ruckebusch, 1979). These experimental animal studies were carried out in utero and in the fasting state shortly after birth and show a very similar developmental profile of motor activity to that seen in the human. In the dog, fasting cycle time is shorter than in the human reflecting a species specific difference in control mechanisms, and in the sheep the presence of fasting activity during feeding probably reflects the low calorie density of feeds. These differences however do not detract from the fact that in the fasting state these animal studies provide a very useful model for our understanding of how similar developmental processes occur in the human.

In the very preterm infants (28-32 weeks gestation) motor activity was characterised by low magnitude, poorly organised non-propagative activity. This is equivalent to the random activity seen between 0.6-0.8 of term in the sheep and between 0.8-0.9 of term in the dog. (Bueno and Ruckebusch, 1979) At the equivalent time amniographic studies in the human fetus (McLain, 1963) showed very little aboral transit of contrast. Those infants with random activity were intolerant to enteral feeds when studied. As normal propagative motor activity relies on the integrated action of the enteric smooth muscle and nerves it is therefore likely that immaturity of these motor elements is responsible for this paucity of motor activity.

With increasing maturation (28-35 weeks gestation) short clusters of motor activity occurred. These bursts of motor activity lasted for approximately 4 minutes and were, as maturation progressed, increasingly aborally propagated. This phase of fasting motor development is analogous to that seen in the sheep and dog between 0.8 of term - term and 0.9 of term - 16 days post term respectively. The clustered phasic activity may be similar to the migrating action potential complex which is seen in older humans. (Summers, Anuras and Green, 1983) This phase of activity was associated with the increasing tolerance of enteral feed and towards the end of this period, with the first signs of effective nutritive sucking. Previous studies (Lucas et al,

1980a) have shown an increase in the levels of a number of gut hormones including motilin at this time. Surges in motilin have been associated with the initiation of Phase III activity (Itoh et al, 1978). It is tempting to speculate that the increased levels of motilin in the preterm infant are driving the major changes in motor activity but in the light of recent evidence regarding the aetiology of motilin surges (Hall et al, 1984) it is more likely that these increased levels result from the changes in motor activity rather than cause them. It would appear therefore that central and enteral neural influences along with hormonal factors are active during this gestational period.

Between 34-36 weeks gestation this clustered phasic activity became increasingly longer with great variability of complex length and interval. In the central nervous system it is common for excitatory pathways to develop in advance of the reciprocal inhibitory pathway and it seems likely that this may also occur in the enteric nervous system and account for the variability observed.

Beyond 37 weeks gestation well defined Phase III activity is seen with very little variability of complex length and a cycle length which has increased twofold to 25 minutes. These complexes are all clearly propagated aborally and are identical to the Phase III activity seen in older children and adults. This pattern

is seen in the fetal sheep at term and does not occur in the dog until 16 days post-partum (Bueno and Ruckebusch, 1979). Similarly there is an increase in cycle length in both experimental animals with increasing maturation. It is likely that the development of inhibitory processes are responsible for this consistent increase in cycle length. Two possible mechanisms have been proposed one residing within the autonomic nervous system and the other within the enteric nervous system. It is known that in the adult sheep combined vagotomy and splanchnicectomy results in a decrease in the fasting motor cycle time from 110 minutes to 60 minutes. (Ruckebusch and Bardon, 1984) The increase in fasting motor cycle time with increasing gestation may therefore reflect an increase in vagal inhibitory influence.

There is also some evidence that serotonergic nerves within the enteric nervous system may have an important role in this control. It is likely that the duodenal bulb acts as a control area for the initiation and the control of cyclical fasting motor activity. (Ruckebusch and Bardon, 1984) This area of the gut has a high serotonin concentration which falls as one moves in a caudal direction down the gut. In the calf duodenal serotonin concentration has reached mature levels by 6-8 weeks before birth. (Branchek Kates and Gershon, 1984) Given that the gestational period of the calf is about 9 months and that the fasting motor development of the

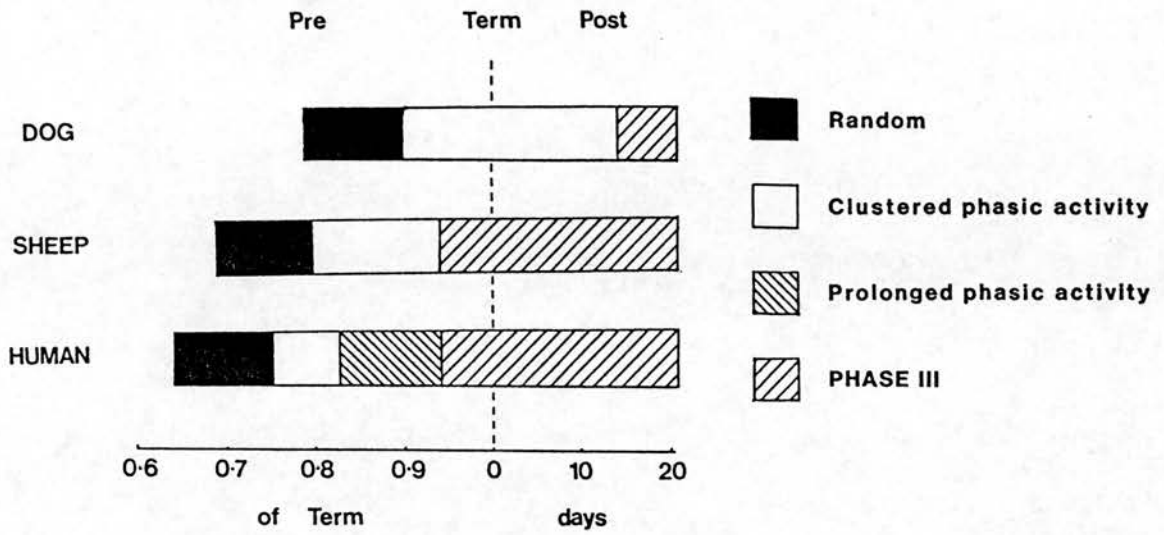
calf and the human are very similar this equates with a time when increasing organisation is seen in the human small intestine. It has also been shown in sheep that the intravenous or intra-duodenal administration of the serotonin antagonist methylsergide results in a halving of fasting cycle length (Ruckebusch and Bardon, 1984) which suggests that serotonin may be an important regulator of fasting cycle length. The progressive increase in cycle length is therefore likely to be due to the combined action of these two processes. The functional significance of this lengthened cycle time remains unclear.

Although the preterm infant is exposed to many environmental influences after birth, the underlying developmental patterns are no different from those seen in the experimental animal which remains protected in utero. These similarities are shown very clearly in Fig. 8.1 where allowance is made for the differing gestational lengths by expressing the ages as a decimal fraction of term. Thus there is a clear developmental pattern of fasting motor activity which only differs in timing between species.

It is also clear that with increasing gestational age the pressures generated by the smooth muscle of the stomach and of the duodenum are significantly increased. This is likely to result from a combination of both increased smooth muscle bulk and increased excitation by humoral and neural stimuli.

Fig. 8.1

The developmental profile of fasting small intestinal motor activity in the human, sheep and dog is very similar. (adapted from Bueno and Ruckebusch, 1979)



The frequency of the duodenal electrical control activity (ECA) also increased significantly from a median level of 11 cycles per minute (cpm) associated with random activity to 12 cpm during periods of Phase III activity. This change may reflect an alteration in the excitatory characteristics of the smooth muscle membrane, through changes in energy dependant ion pumps, or membrane permeability or an alteration in the neurohumoral environment acting upon that membrane may be responsible. The ECA frequency is known to be increased by increasing plasma levels of catecholamine (Bulbring, Ohashi and Tomita, 1981) and by increased sympathetic tone within the enteric nervous system. One can only speculate as to which of these factors is responsible for this change.

Although smooth muscle acts as a syncitium, motor activity can only be propagated over very short distances without the presence of an intact organised enteric nervous system. With advancing motor development the increased degree of propagation and the velocity of that propagation reflects the increased organisation of enteric neural connections.

8.1.1 ENVIRONMENTAL INFLUENCES ON FASTING MOTOR ACTIVITY

Although the general trends of motor development are essentially similar from one patient to the next it is important to know what effect the environment has on this activity. There are undoubtedly many factors which may adversely affect intestinal motor function ranging from the effect of drugs to hypoxia, hypoglycaemia, acidosis and sepsis.

As discussed already in section 4.1.2 the developing enteric nervous system remain very "plastic" until a late stage in development. The fetus may be exposed to a wide range of drugs while in utero and there is evidence certainly in animals that these may alter neurotransmitter expression. Sympathomimetic agents can induce the persistence of the early transient catecholamine expression of developing neural cells (Jonakait et al, 1979) a fact which is of great clinical relevance when one remembers that many infants who go into premature labour are exposed to the beta adrenergic agonist ritodrine (Duphar) sometimes for many weeks. Maternal glucocorticoids may also be of importance to the fetal gut as they have been shown to influence neurotransmitter expression. (Black et al, 1981)

It is interesting to speculate whether the way we feed and care for the preterm infant may influence the ultimate programming of the enteric nervous system and

thus the development of patterns of intestinal motor activity.

With the relatively small group of patients in this study it was impossible to differentiate the effect of the various noxious factors, as most of the "ill" infants were grouped at the lower gestational ages. There was however one exception in a 42 week gestation infant who was ill with septicaemia and on a ventilator. In this infant the underlying fasting pattern of activity was preserved with evidence of Phase III activity although the level of duodenal contractility, motor co-ordination and ECA frequency were all much less than expected. This suggests that the underlying gestationally dependant patterns of motor activity are fairly resistant to noxious insult but environmental factors may modulate the expression of each particular pattern. Clinical experience tells us that the ill preterm infant is less likely to tolerate a given feed volume than a well infant of similar gestational age and this may be explained on the basis of the differences which have been suggested above.

Stress also can have an adverse effect on intestinal motility. (McCrae et al, 1982) Labyrinthine stimuli have been shown to inhibit gastric antral activity and induce gastric tachyarhythmias. (Stern, 1987) and abnormal intestinal motility has similarly been described following both cold and auditory stress. The preterm infant is very vulnerable to a wide range of

such stresses and it must be remembered that the noise within an incubator or the pain of a tissing drip may adversely affect feeding tolerance.

An ability to promote the development of fasting intestinal motor activity is likely to result in improved feed tolerance, better growth and improved survival. The data from this study shows that in the fasting state the basic patterns of motor development are gestationally dependant and although a good general medical condition or the early introduction of enteral feeds may advance this development slightly it is not possible for fasting activity to depart much from its species dependent time-table of development. One can draw an analogy with the young child who is learning to walk. While active stimulation and training may bring forward the time of walking from 11 months to 10 months, it would be quite impossible to think of this occurring at 4 months as the necessary controlling and co-ordinating mechanisms will have not developed by this time. One should think of the developing enteric nervous system in much the same way.

8.2 POST PRANDIAL MOTOR ACTIVITY

Unlike fasting motor activity which probably represents developmental changes in neural control, post prandial activity represents the motor response of the gut to a given stimulus. One might therefore predict that the response will depend on the nature of the stimulus (ie the feed) and on the ability of the gut to respond to that stimulus which in turn is likely to depend on the gestational age of the infant. Studies in dogs (Code and Marlett, 1975) and more recently in older preterm infants (Amarnath et al, 1986) has shown that the degree of post prandial activity increases with the volume and with the caloric density of the feed. It would have been of interest to look at the difference in response between a breast milk feed and a formula feed but unfortunately this was not possible as the study was non interventional. It seems likely therefore that as the volume of enteral feed increases with increasing gestation age so the degree of post prandial activity will also increase. This is indeed the case and from the analysis of the data it would appear that the increased time on feeds and the increased feed volume are the major determinant of this change and not the gestational age.

In the most preterm infants (<30 weeks) who were receiving low volumes of continuously delivered feed the basal random or clustered phasic pattern was not disrupted, while in the term infants receiving 4 hourly

bolus feeds there was complete disruption of fasting activity for over an hour with well developed post prandial activity. It is generally accepted that the stimuli required to induce post prandial activity reside both within the gut itself and within the autonomic and central nervous system. The presence of food within the lumen of the gut stimulates the release of a number of gut hormones. Among these, cholecystokinin (CCK) is able to induce post prandial activity and thus the larger the stimuli the longer the CCK level will remain above the threshold needed to induce this activity. There is certainly some evidence to suggest that the humoral response to enteral feed is attenuated in the preterm infant (Lucas, Bloom and Aynsley-Green, 1978) and this may partly explain the poor response in the most preterm infants.

It was interesting to note that in those infants where there was incomplete disruption of fasting activity and in the term infants towards the end of a period of post prandial activity, Phase III or prolonged phasic activity appeared superimposed on a background of post prandial activity. With time the post prandial activity faded and the fasting activity became stronger, giving the impression that fasting motor control mechanisms were slowly overcoming the waning post prandial stimuli. The former reside within the enteric and central nervous systems and are active continuously while the latter are likely to be primarily humorally

mediated and are only present transiently after feeds. As well as the humoral mechanisms described above the vagus also influences the post prandial motor response to enteral feeds. In post-vagotomy patients (Thompson, Ritchie and Wingate, 1982) there is a reduced period of post prandial activity after a standard feed with a premature return of fasting activity and in animal studies, acute cooling of the exteriorised vagus results in the complete disruption of post prandial activity with an immediate reversion to fasting activity. (Diamant et al, 1980) The reduced post prandial response which is seen in the preterm infant may be due in part to the incomplete development of autonomic tone particularly that of the vagus nerve.

It is quite clear that those infant who were less preterm at birth (>29 weeks) had shorter post prandial activity for a given corrected post-conceptual age and also for a given feed volume than the very preterm infants (<29 weeks) who had received a longer period of enteral feeding. Thus the length of time that an infant had been exposed to enteral nutrition seems to be important and indeed the parameter which had the best correlation with post prandial activity was the length of time on enteral feeds. This suggests that the hormonal stimuli which are responsible for the initiation of post prandial activity are enhanced by the exposure of the gut to enteral nutrition. Support for this hypothesis is provided by previous human studies

(Lucas et al, 1980a & b) which showed that the hormonal response to an enteral feed was increased as the time on enteral feeds increased.

8.2.1 FEEDING THE PRETERM INFANT

A great debate continues on the best way to feed the preterm infant.

When should feeding be started ?

How should feeds be delivered ?

How frequently should they be given ?

The data from this study suggests that as enteral feeding enhances the post prandial humoral response it should be started as early as possible. It is possible that even very small nutritionally insignificant volumes of feed will be of benefit to infants where full volume feeds are not tolerated. This feed is beneficial not only in enhancing the humoral responses of the gut but also in promoting villous absorptive (McNeish et al, 1979) and digestive function. (Hughes and Dowling, 1980) It is quite clear that the feeds should be given enterally if at all possible as parenteral feeding reverses the beneficial effects of enteral feeds described above. If feeding by the nasogastric route is not possible transpyloric feeding should be tried.

The question of bolus versus continuous feeds is frequently raised. In this study there was a significant correlation between the increased length of post prandial motor activity and the introduction of bolus feeds ($r=0.66$, $p=0.001$), but one must remember that many other factors may also be contributing to this

change and it is unclear how much of this was due specifically to the alteration in the frequency of feed delivery. There are however two other pieces of information which support the hypothesis that the frequency of food delivery affects the post prandial motor response.

Firstly it has been clearly shown that in bolus fed infants major surges of metabolites and gut hormones occur when compared to continuously fed infants. (Aynsley-Green, 1982) If a threshold level of a gut hormone is required to disrupt the fasting pattern and induce post prandial motor activity this requirement is most likely to be met in the bolus fed infant. In this present study the continuously fed preterm infants had no post prandial activity while in the bolus fed term infants this was well developed.

Secondly, studies of the motor response to feeding in pigs (Ruckebusch and Bueno, 1976) have shown quite clearly that in animals fed ad libitum, the basic fasting pattern of motor activity is not disrupted while in animals fed every 12 or 24 hours a period of post prandial activity lasting for 3 and 6 hours respectively is seen. This again suggests that a certain volume and calorie density of feed is required to produce a humoral response large enough to induce post prandial activity and that in the pig this threshold is not reached by continuous feeding.

These facts suggest that the method of feed delivery is

of great importance in determining the post prandial response and that bolus feeding is likely to induce the greatest response.

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8.3 ENTERIC AND CENTRAL NEURAL MATURATION (A COMPARISON)

The clear developmental profile which has been described for the motor activity of the small intestine parallels in many ways similar developmental changes which are occurring at the same time in the central nervous system. The function of both systems is highly dependent on the maturation of a variety of different neural cell types and complex neural connections. It is thus not unreasonable to compare the development of the enteric and the central nervous system.

The functional maturation of the central nervous system has been well defined in terms of the tone, posture and reflex response of the preterm infant and indeed the Dubovitz score (Dubovitz, Dubovitz and Goldberg, 1970) is routinely used to determine the gestational age of preterm infants when reliable dates have not been determined by either the last menstrual period or by maternal ultrasound scan. In a similar but perhaps in a less precise manner, it is possible from a knowledge of the gestational age of an infant to determine the level of maturation of the enteric nervous system and thus the likely level of small intestinal motor function.

This close relationship can be defined more clearly if the development of intestinal motor activity is correlated with the development of the central nervous system (CNS) in the human and then compared with data that is available for the sheep and the dog. (Ruckebusch, 1986) The development of the CNS in the

human and the experimental animal has been defined on the basis of the maturational patterns of the EEG (Ruckebusch, Gaujoux and Eghbali, 1977b, Roffwarg, Muzio and Dement, 1966) and by the development of sensory evoked cortical responses. (Bernard, Kaiser and Kolmodin, 1959, Schulte et al, 1977)

From the ontogenic profile of fasting small intestinal motor activity discussed in section 8.1 and shown in Fig. 8.1 it can quite clearly be seen that this is delayed in the dog with clear Phase III activity not occurring until after term. When CNS maturation is defined as described above it can be clearly shown that in the human, calf and sheep the pattern of development is very similar with the development of alpha rhythms and an awake / asleep cycle prior to term. In the dog however these patterns of cerebral electrical activity only develop after birth and like intestinal motor activity show evidence of a marked delay.

Further evidence for a link between the development of the enteric and central nervous systems can be found if one looks at the timing of cyclical events within these two systems. In the newborn human infant the period of the sleep cycle is 25-50 minutes while in the adult this rises to 90 minutes. (Oswald et al, 1963) It is interesting to note that in this study the cycle time of fasting motor activity at term was 18-45 minutes and that in the adult this increases to approximately 82 mins. (Peeters, Janssens and Vantrappen, 1982) A similar

increase in both sleep and fasting intestinal cycle time is seen in the sheep after birth. (Ruckebusch, 1984) It is unclear whether one common central mechanism is controlling both these processes as has been suggested (Finch et al, 1982) or whether they are under independent control.

8.4 SUMMARY

In this study the ontogeny of human small intestinal motor activity in the fasting and in the post prandial state has been defined.

Fasting motor activity shows a gestationally dependant species specific timetable of development which relies largely on the integrated maturation of enteric and central neural elements. The timetable in the human follows a general pattern previously shown for the sheep and dog. As with other developmental processes which rely on the maturation of neural connections, such as nutritive sucking, environmental influences may cause small alterations to the ontogenic profile but are unlikely to change it dramatically.

In contrast the post prandial motor response, although influenced by the volume of feed given, appears to be particularly dependent on the length of time that the infant has received enteral feeds. As it is likely that the post prandial motor response is largely mediated by humoral factors this would strongly suggest that the enteric humoral response is enhanced by the exposure of the gut to food.

It is hoped that our increased understanding of the development of intestinal motor function resulting from this study will lead to the development of more rational feeding practices in the preterm infant.

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LIST OF PUBLICATIONS

No papers relating to the work in this thesis have yet been published but the following paper is in press.

Bisset W. M., Watt J., Rivers R. P. A., Milla P. J. (1988). The ontogeny of fasting small intestinal motor activity in the human infant. Gut (in press)

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APPENDIX I

The BASIC programs in this appendix were used to capture motility data (Program Monitor), to redisplay that data (Program Retr) and to carry out a 512 point fast Fourier transformation (FFT8).

PROGRAM "MONITOR"

```

10*FX16,2
20DIM Q%(640)
30DIM Z%(640)
40DIM A%(640)
60MODE 0
65SEC=1
70 PRINT TAB(20,1) "PRESS SPACE BAR TO RECORD SCREEN"
80PRINT TAB(66,17);"<----->";TAB(68,18);"1 min"
90MOVE 2,800:DRAW 2,880:PRINT TAB(0,2)"10cm water"
100MOVE 2, 350:DRAW 2,430 : PRINT TAB(0,17)"10cm
    water"
105TIME=0
107FFF=0
110FOR A=1TO638
117REPEAT UNTIL TIME>=FFF+(SEC*99) :FFF=TIME
120Q%(A)=INT(ADVAL(1)/140)+500
130A%(A)=TIME
140Z%(A)=INT(ADVAL(2)/140)
150IF A=1 MOVE 2,Q%(1) ELSE PLOT 5,(A)*2,Q%(A)
160IF A=637 THEN GOTO 240
170MOVE (A*2)+2,Q%(A+1)
180PLOT 7,(A*2)+4,Q%(A+2)
190IF A=1 THEN MOVE 2,Z%(1) ELSE MOVE (A-1)*2,Z%(A-1)
200PLOT 5,A*2,Z%(A)
210MOVE (A*2)+2,Z%(A+1)
220PLOT 7,(A*2)+4,Z%(A+2)
230MOVE (A*2),Q%(A)
240 PRINT TAB(65,2);INT TIME/100 DIV 60;" min ";INT
    TIME/100 MOD 60;" sec "
270IF INKEY$10=""THEN GOTO 290
280IF INKEY$10=CHR$32 THEN GOTO 320
290NEXT
300MOVE 0,750
310GOTO110
320W=OPENOUT "DATA"
330FOR G=A TO 637+A
340IF G>638 THEN X=G-638 ELSE X=G
350PRINT# W,A%(X)
360PRINT# W,Q%(X)
370PRINT# W,Z%(X)
380NEXT
390CLOSE# W
395PRINTTAB(0,3)" " :A=1
400GOTO210

```

PROGRAM "RETR"

```
5INPUT "NAME OF FILE",X$
6MODE128
10A=OPENIN X$
20DIM A%(640)
39DIM B%(640)
40DIM C%(640)
50FOR G=1 TO 638
60INPUTE A,A%(G)
70INPUTE A,B%(G)
80INPUTE A,C%(G)
90NEXT
100MODE128
101PRINT TAB(2,1);A%(2) DIV 6000;" ";(A%(2) MOD
6000)DIV 100 ;TAB(70);A%(638) DIV 6000;"
";(A%(638) MOD 6000)DIV 100
103MOVE 5,400 :DRAW 5,480:PRINT TAB(2,17);"10cmWater"
110MOVE 2,B%(1)
120FOR H=1 TO 638
130DRAW H*2,B%(H)
140NEXT
150MOVE 2,C%(1)
160FOR K=1 TO 638
170DRAW K*2,C%(K)
180NEXT
190CLOSEE A
```

PROGRAM "FFT8"

```
5@%=&0040A
6INPUT"NAME", NM$
7INPUT"NUMBER", NUM$
8INPUT"DATE", DATE$
9PRINT NM$:PRINT NUM$:PRINT DATE$
10DIM X1(512),X2(512),B%(512),C%(512)
11DIM X3(512)
15INPUT "CHANNEL",CH
20N=512: L=9
30PROC_INPUT
40PROC_REDUCE(CH)
45MODE 128
50PROC_FFT
55PROC_PLOT
56VDU23,1,0;0;0;0; :VDU30 : PRINTTAB(0,0)"
":PRINTTAB(0,1)" "
57END
200END
490DEF PROC_FFT
540 B=X1(0)
550FOR Z=0 TO N-1
560IF ABS(X1(Z))>B THEN B=ABS(X1(Z))
580NEXT Z
640FOR Z=0 TO N-1
650X1(Z)=X1(Z)/N
```

```

655X2(Z)=0
660NEXT Z
680I1=N/2:I2=1:V=2*PI/N
682TT=(FINNISH-START)/100
684PERM=TT/(N*60)
686FREQ=1/(2*PERM)
690FOR I=1 TO L
700I3=0:I4=I1
710FOR K=1 TO I2
720X=INT(I3/I1)
730GOSUB 1300
740I5=Y
750Z1=COS(V*I5)
760Z2=-SIN(V*I5)
770FOR M=I3 TO I4-1
780A1=X1(M):A2=X2(M)
790B1=Z1*X1(M+I1)-Z2*X2(M+I1)
800B2=Z2*X1(M+I1)+Z1*X2(M+I1)
810X1(M)=A1+B1 :X2(M)=A2+B2
820X1(M+I1)=A1-B1 :X2(M+I1)=A2-B2
830NEXT M
840I3=I3+2*I1 :I4=I4+2*I1
850NEXT K
860I1=I1/2 :I2=2*I2
870NEXT I
970B=0
980FOR Z=0 TO N/2
985X=Z
990GOSUB 1390
1000IF X3>B ANDZ>8 THEN B=X3
1010NEXT Z
1020 FOR Z=0 TO N/2
1025X=Z
1030GOSUB 1390
1060X3(Z)=X3
1100NEXT Z
1280GOTO1420
1300Y=0 :N1=N
1310 FOR W=1 TO L
1320N1=N1/2
1330 IF X<N1 THEN GOTO 1360
1340Y=Y+2^(W-1)
1350X=X-N1
1360NEXT W
1370RETURN
1390GOSUB 1300
1400X3=SQR(X1(Y)^2+X2(Y)^2)
1410RETURN
1420ENDPROC
2000DEF PROC_REDUCE(CH)
2010QQ=0
2020IF CH=1 THEN GOTO 2050
2030IF CH=2 THEN GOTO 2070
2050FOR X=0 TO N-1
2052QQ=QQ+B%(X)
2054NEXT X

```

```

2056AVER=QQ/N
2058FOR X=0 TO N-1
2060X1(X)=(B%(X)-AVER)/250
2064NEXT X
2068GOTO 2140
2070FOR X=0 TO N-1
2080QQ=QQ+C%(X)
2090NEXT X
2100AVER=QQ/N
2110FOR X=0 TO N-1
2120X1(X)=(C%(X)-AVER)/250
2130NEXT X
2140ENDPROC
3000DEF PROC_INPUT
3005INPUT "NAME OF FILE",X$
3010A=OPENIN X$
3020INPUT£ A, TM%
3030INPUT£ A, B%
3040INPUT£ A, C%
3050FOR X=0 TO N-1
3060INPUT£ A, TM%
3070INPUT£ A, B%(X)
3080INPUT£ A, C%(X)
3090IF X=0 THEN START=TM%
3100IF X=N-1 THEN FINNISH=TM%
3110NEXT X
3120PRINT "START"; (START DIV 100) DIV 60; "min"; (START DIV
100) MOD 60; "sec"
3130PRINT "FINNISH"; (FINNISH DIV 100) DIV 60; "min"; (FINNISH DIV
100) MOD 60; "sec"
3135CLOSE£ A
3140ENDPROC
4000DEF PROC_PLOT
4005PROC_SMOOTH
4010PROC`INIT(0)
4020`XL=0: `YL=0: `XH=30: `YH=B
4030PROC`AXES(0)
4035PROC`MOVE (12/256*FREQ, X3(12))
4040FOR X=12 TO N/2
4045J=X*FREQ/(N/2)
4050PROC`DRAW (J, X3(X))
4060NEXT X
4065VDU5
4066PROC`MOVE((FREQ*K/(N/2)), C)
4067PRINT " "; (FREQ*K/(N/2)); " cycles/min"
4068VDU4 :VDU30
4070ENDPROC
5000DEF PROC_SMOOTH
5005C=0
5010X3(0)=0: X3(1)=0
5015P=X3(2)
5020FOR X=12 TO 254
5030M=X3(X)
5040X3(X)=(0.25*P)+(0.5*X3(X))+(0.25*X3(X+1))
5050P=M
5055IF X3(X)>C THEN K=X

```

```

5057IF X3(X)>C THEN C=X3(X)
5060NEXT X
5070ENDPROC
6065PRINTTAB(5,79);(K/(N/2))*FREQ ;"cycles/min"
10000:REM Graphs and Charts
10010:REM Copyright (C) Acornsoft 1982
10020:REM L1-2D
10060DEF PROC`INIT(M%): `M%=M%
10070`XL=-10:`XH=10:`YL=-10:`YH=10:`ZL=-10:`ZH=10
10080`XD=0:`YD=0:`ZD=0:`XI%=7:`YI%=7:`ZI%=7
10090`XN%=1:`YN%=1:`SN%=1
10100IF M%=2 OR M%=5 THEN `CH%=64 ELSE `CH%=32
10110`YB%=0:`YS%=1023:`XB%=3*`CH%:`XS%=1279-`XB%
10120`VM%=64064:`HM%=2*(1000*`CH%+`CH%):`CH%=1000*`CH%+3
2
10130`XP%=484040225:`YP%=504040225:`ZP%=540040225
10140IF M%=1 OR M%=2 OR M%=5 THEN `XC%=1010203 ELSE
`XC%=0
10150`YC%=0:`ZC%=0
10160`TH=1.3:`PH=-1.3
10170ENDPROC
10200DEF FN`I(N%,LO,HI):LOCAL A,B,C
10210IF0>=N%THENPROC`er("Bad no. of intervals")
10220C=(HI-LO)/N%:IF0>=C THENPROC`er("Bad axis range")
10230C=FNmax(C,FNmax(ABS(LO),ABS(HI))/1E6)
10250A=10^INT(LOG(C)):B=C/A
10270IFB>7.1THENB=10ELSEIFB>3.2THENB=5ELSEIFB>1.4THENB=2
ELSEB=1
10280=A*B
10310DEF PROC`ax(O,LO,HI,I)
10350IF LO-I/2>=0 OR O>=HI THEN O=INT(LO/I-.1)*I:LO=O
10370LO=O+I*INT((LO-O)/I+.1)
10380HI=O-I*INT((O-HI)/I+.1)
10400`O=O:`1=LO:`2=HI:ENDPROC
10430DEF PROC`se:LOCAL S%
10440S%=(`SN%-1)MOD(`XN%*`YN%)
10450`SXS%=`XS% DIV `XN%:`SYS%=`YS% DIV `YN%
10460`SXB%=`XB%+S%MOD`XN%*`SXS%
10470`SYB%=`YB%+S%DIV`XN%*`SYS%:ENDPROC
10490DEF
FN`fa(S%,M%,HI,LO):`O=HI-LO:=(S%-(M%MOD1000)-(M%
DIV1000) )/`O
10510DEF FN`pp(L,M%)
10520`O=FN`pr(M%,0)*L/100
10530ON 1+(FN`pr(M%,2) MOD 3) GOTO 10540,10550,10560
10540=0.
10550=-`O
10560=-`O/2
10590DEF PROC`co(C%,N%):IF FN`pr(C%,6)>0 THEN GCOL
O, FN`pr(C%,N%)
10600ENDPROC
10630DEF FN`su(lo,hi,I,f%):LOCAL i%,j%,c%,d%,s%,p%
10640i%=INT(LOG(I)+.01):j%=INT(LOG(FNmax(ABS(lo),ABS(hi)
))+.01)
10660IF j%>0 THEN c%=j%+1: ELSE c%=1
10670IF NOT i%<0 THEN d%=0:p%=0: ELSE d%=-i%:p%=1

```



```

10690IF lo<0 OR hi<0 THEN s%=1 ELSEs%=0
10710IF NOT(f%<p%+s%+c%+d%) THEN '0=0 ELSE
    d%=0:p%=0:'0=FNmin(-i%,f%-j%-s%-1)
10730 IF d%=0 THEN i%=&10000+f% ELSE i%=&10200+d%
10740=f%+&100*i%
10760DEF FNmax(a,b):IFb>a THEN=b ELSE=a
10770DEF FNmin(a,b):IFb<a THEN=b ELSE=a
10780DEF FN`pr(n%,d%)=(n%DIV(10^d%))MOD100
10790DEF PROC`er(a$):PRINT "Graphics package error"
10800PRINT a$:STOP:ENDPROC
12010DEF PROC`MOVE(X,Y):PLOT 4, FN`x(X), FN`y(Y):ENDPROC
12020DEF PROC`DRAW(X,Y):PLOT 5, FN`x(X), FN`y(Y):ENDPROC
12030DEF PROC`PLOT(K%,X,Y):LOCAL x,y
12040IF K%MOD8<4 THEN
    x=`XFA*X:y=`YFA*Y:`XSC%=`XSC%+x:`YSC%=`YSC%+y:ELSE
    x=FN`x(X):y=FN`y(Y)
12050PLOT K%,x,y:ENDPROC
12060DEF FN`POINT(X,Y)=POINT FN`x(X),FN`y(Y)
12070DEF FN`x(X):`XSC%=`XCR%+`XFA*(X-`SX0):=`XSC%
12080DEF FN`y(Y):`YSC%=`YCR%+`YFA*(Y-`SY0):=`YSC%
12100DEF PROC`AXES(M%):LOCAL A,B,f%,d%,a%,l%,w%,L$,y%
12110IF M%=1 THEN GOSUB 12140 ELSE IF M%=2 THEN GOSUB
12300 ELSE IF M%=3 THEN GOSUB 12400 ELSE GOSUB
12140:GOSUB 12300:GOSUB 12400
12120ENDPROC
12140`SXI=FN`I(`XI%,`XL,`XH):`SYI=FN`I(`YI%,`YL,`YH)
12150PROC`ax(`X0,`XL,`XH,`SXI):`SX0=`0:`SXL=`1:`SXH=`2
12160 PROC`ax(`Y0,`YL,`YH,`SYI):`SY0=`0:`SYL=`1:`SYH=`2
12180PROC`se
12200`XFA=FN`fa(`SXS%,`HM%,`SXH,`SXL):A=`0*`XFA
12210`YFA=FN`fa(`SYS%,`VM%,`SYH,`SYL):B=`0*`YFA
12230`0=ABS((`XFA-`YFA)/(`XFA+`YFA))
12240IF ABS((`XFA-`YFA)/(`XFA+`YFA))<.15 THEN
    `XFA=FNmin(`XFA,`YFA):`YFA=`XFA
12260`XCR%=`SXB%+(`HM% DIV
    1000)+`XFA*(`SX0-`SXL)+(A-`XFA*(`SXH-`SXL))/2
12270`YCR%=`SYB%+(`VM%DIV1000)+`YFA*(`SY0-`SYL)+(B-`YFA*
    (`SYH-`SYL))/2
12280RETURN
12300PROC`co(`XC%,4):PROC`MOVE(`SXL,`SY0):PROC`DRAW(`SXH
,`SY0)
12310PROC`co(`YC%,4):PROC`MOVE(`SX0,`SYL):PROC`DRAW(`SX0
,`SYH)
12320B=FN`pp(`SYI,`XP%):PROC`co(`XC%,2)
12330FOR A=`SXL TO `SXH+`SXI/2 STEP `SXI
12340PROC`MOVE(A,`SY0+B):PROC`DRAW(A,`SY0+B+`0):NEXT
12350A=FN`pp(`SXI,`YP%):PROC`co(`YC%,2)
12360FOR B=`SYL TO `SYH+`SYI/2 STEP `SYI
12370PROC`MOVE(`SX0+A,B):PROC`PLOT(1,`0,0):NEXT
12380RETURN
12400f%=FN`pr(`XP%,4):w%=`CH%DIV1E3
12420a%=@%:@%=FN`su(`SXL,`SXH,`SXI,f%)
12440IF`XFA*`SXI>(1+f%)*w%ANDNOT(`M%=2OR`M%=5)THEN1%=TRU
E ELSE1%=FALSE
12460VDU 5:PROC`co(`XC%,0):A=`SXH
12470IF`0<>0THENL$="E"+STR$(-`0)ELSEL$=""

```

```

12480d%=`SXB%+`SXS%:y%=FN`y(`SYD)+( `XP%DIV1E6)-500
12490REPEATIFABS(A)<`SXI/2THENA=0
12500L$=STR$(A*10^`0)+L$:B=LEN(L$)*w%
12510d%=FNmin(FN`x(A)-B/2,d%-B-w%DIV2)
12520PLOT4,d%,y%:PRINTL$:L$=""
12530IF1%THENA=A-`SXI ELSEA=`SXL:1%=TRUE
12540UNTILA<`SXL-`SXI/2
12560f%=FN`pr(`YP%,4):y%=`CH%MOD1E3:d%=y%+`YP%DIV1E6-500
12570@%=FN`su(`SYL,`SYH,`SYI,f%)
12580IF`YFA*`SYI>2*y%ANDNOT(`M%=2OR`M%=5)THEN1%=1ELSE1%=
0
12590PROC`co(`YC%,0):B=`SYL
12600REPEAT PROC`MOVE(`SX0,B)
12610IF ABS(B)<`SYI/2 THEN B=0
12630PLOT0,-w%DIV2,d%:FORA=1TOf%:VDU8:NEXT:PRINTB*10^`0;
12640IF1%=1THENB=B+`SYI ELSE B=`SYH:1%=1
12650UNTILB>`SYH+`SYI/2
12660IF `0<>0 THEN PRINT"E";-`0
12670VDU 4:@%=a%:RETURN

```


APPENDIX II

List of patients studied and their clinical condition and management.

Respiratory Status: V=Ventilated, CPAP=Continuous Positive Airways Pressure, O=Added Oxygen, A=Air

Feeding: P=Patenteral, NJ=Nasojejunal, NG=Nasogastric, S=Sucked

G = Only gastric motor activity recorded

* = Studies which included post prandial data.

S A This girl was born at 26 weeks gestation weighing 830 grams. She developed severe RDS, a Staph. epidermidis septicaemia, a urinary candida infection and mild retinopathy of prematurity. She was discharged home well with no neurological deficit.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1	28	15	650	CPAP	P	-
2 *	30	27	830	V	NG	1
3 *	32	42	1020	V	NJ	16
4 *	37	78	1720	A	NG	52

P A This boy was born at 31 weeks gestation weighing 1470 grams. He had moderately severe RDS and subsequently developed necrotising enterocolitis, pulmonary haemorrhage and died on day 24 following a colonic perforation.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1	32	7	1300	CPAP	NJ	3

A C This boy was born at 26 weeks gestation weighing 1200 grams. His clinical course was complicated by a bacteroides septicaemia, recurrent apnoeic spells and by a small right sided intraventricular haemorrhage. At discharge he seemed very well.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 G	27	7	1040	V	P	-
2	29	21	1250	CPAP	P	-
3	31	36	1530	A	NG	14

A F This girl was born at 30 weeks gestation weighing 1920 grams. She had very mild RDS with an otherwise uneventful clinical course prior to discharge home.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 G	31	11	1750	A	NG	3

L G This boy was born at 39 week gestation weighing 3260 grams. He developed a listeria pneumonia shortly after birth which was complicated by brochopulmonary dyspasia and right heart failure. He died shortly after discharge home.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 *	42	21	3260	V	NG	1

C H This boy was born at 30 weeks gestation weighing 1200 grams. He had moderate RDS but otherwise had an uneventful clinical course.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1	31	5	1150	V	NONE	-

K M This girl was born at 31 weeks gestation weighing 1925 grams. She suffered from mild RDS and a mild pseudo obstructive episode which may have been related to chronic maternal pethidine administration. She subsequently did very well.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 *	35	28	1850	A	P+NG	20
2 *	39	58	2520	A	S+NG	50

S O This girl was born at 30 weeks gestation weighing 1360 grams. She had prolonged jaundice but otherwise had an uneventful neonatal course prior to discharge home.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 *	32	16	1400	A	NG	15
2 *	34	30	1800	A	S+NG	29
3 *	36	40	2040	A	S	39

R O This boy was born at 27 weeks gestation weighing 1130 grams. He suffered from apnoea of prematurity but otherwise had an unremarkable clinical course.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 *	28	13	1020	A	NG	11
2 *	31	26	1300	A	NG	25

H P This girl was born at 29 weeks gestation weighing 1280 grams. She suffered from mild RDS and from persistent hyponatraemia. She was discharged home well.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 G	30	6	1080	O	NJ	2
2 *	32	21	1430	A	NG	17
3 G	37	56	2280	A	S	52
4 *	39	69	2620	A	S	65

C Q This boy was born at 24 weeks gestation weighing 690 grams. His clinical course was complicated by severe RDS, recurrent apnoea, a staph. epidermidis septicaemia and a right upper lobe pneumonia. He subsequently did well.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 *	30	42	990	V	NJ	14
2 *	32	59	1120	V	NJ	31
3 *	35	76	1490	O	NG	48
4 *	40	115	2520	A	S	87

R S This boy was born at 33 weeks gestation weighing 1460 grams. He had an uneventful clinical course and was discharged home well.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 *	35	17	1750	A	S+NG	17
2 *	37	31	2160	A	S	31

(cont.)

G W This boy was born at 26 weeks gestation weighing 1040 grams. His clinical course was complicated by moderate RDS, severe neonatal jaundice, right upper lobe consolidation and small bilateral intraventricular haemorrhages. Despite these problems he subsequently did very well.

Study	Gest. (wks)	Age (days)	Weight (g)	Resp. Status	Feed Method	Days on Milk Feed
1 G	28	19	1100	O	NJ	13
2 *	29	25	1170	O	NJ	19
3 *	32	42	1480	A	NG	36
4 *	35	62	1940	A	NG	56
5 *	38	82	2200	A	S	76