Maturation of the Gastrointestinal Tract: When is Baby Ready to Feed?

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Mead Johnson Nutritionals

Overview

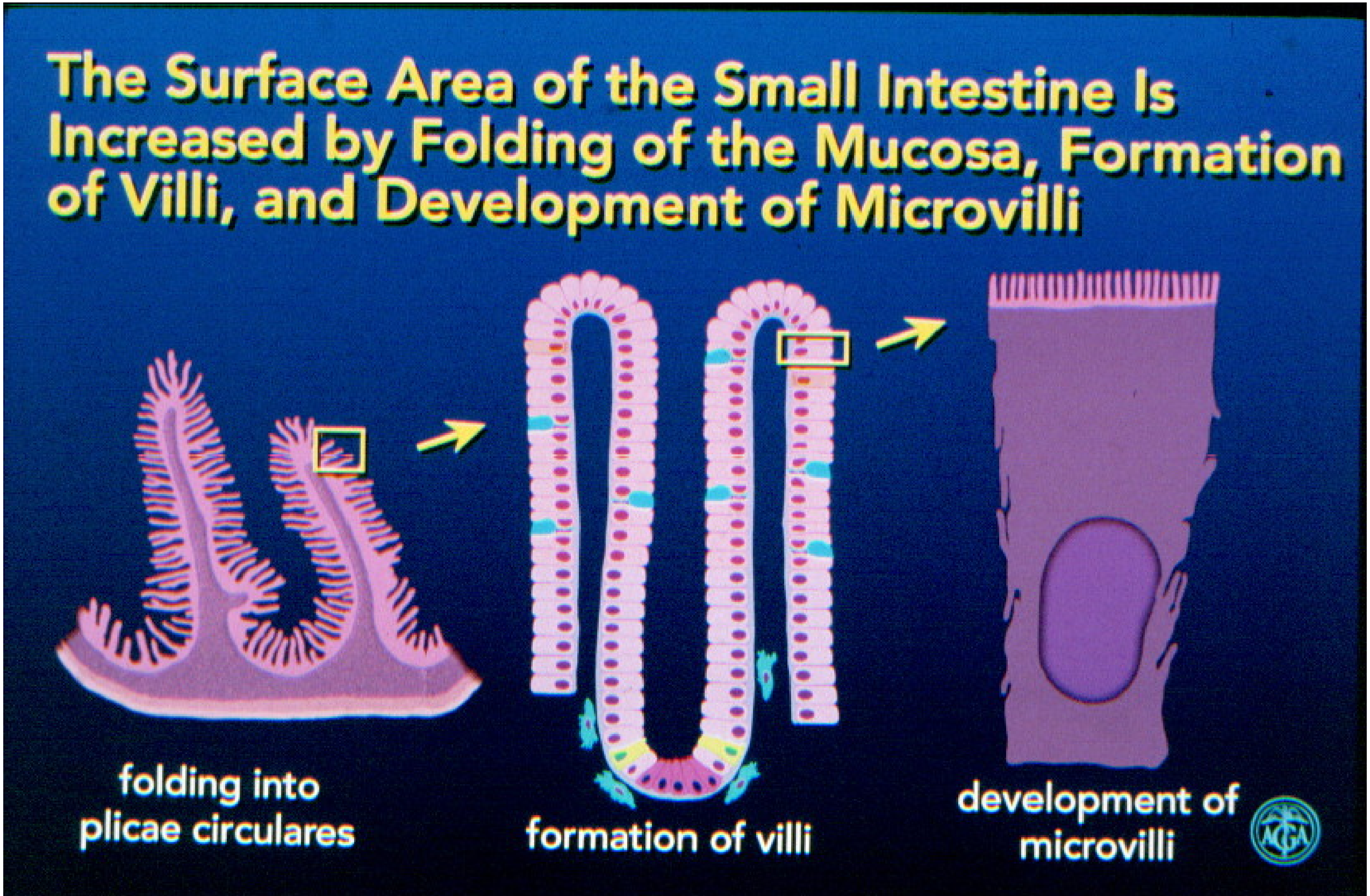
- Basic development of GI tract
- Immaturity of intestinal absorption
- Basic physiology of motor function
- Immaturity of gastrointestinal motor function in the preterm infant

Development of the Gastrointestinal Tract Occurs in 3 Successive Phases

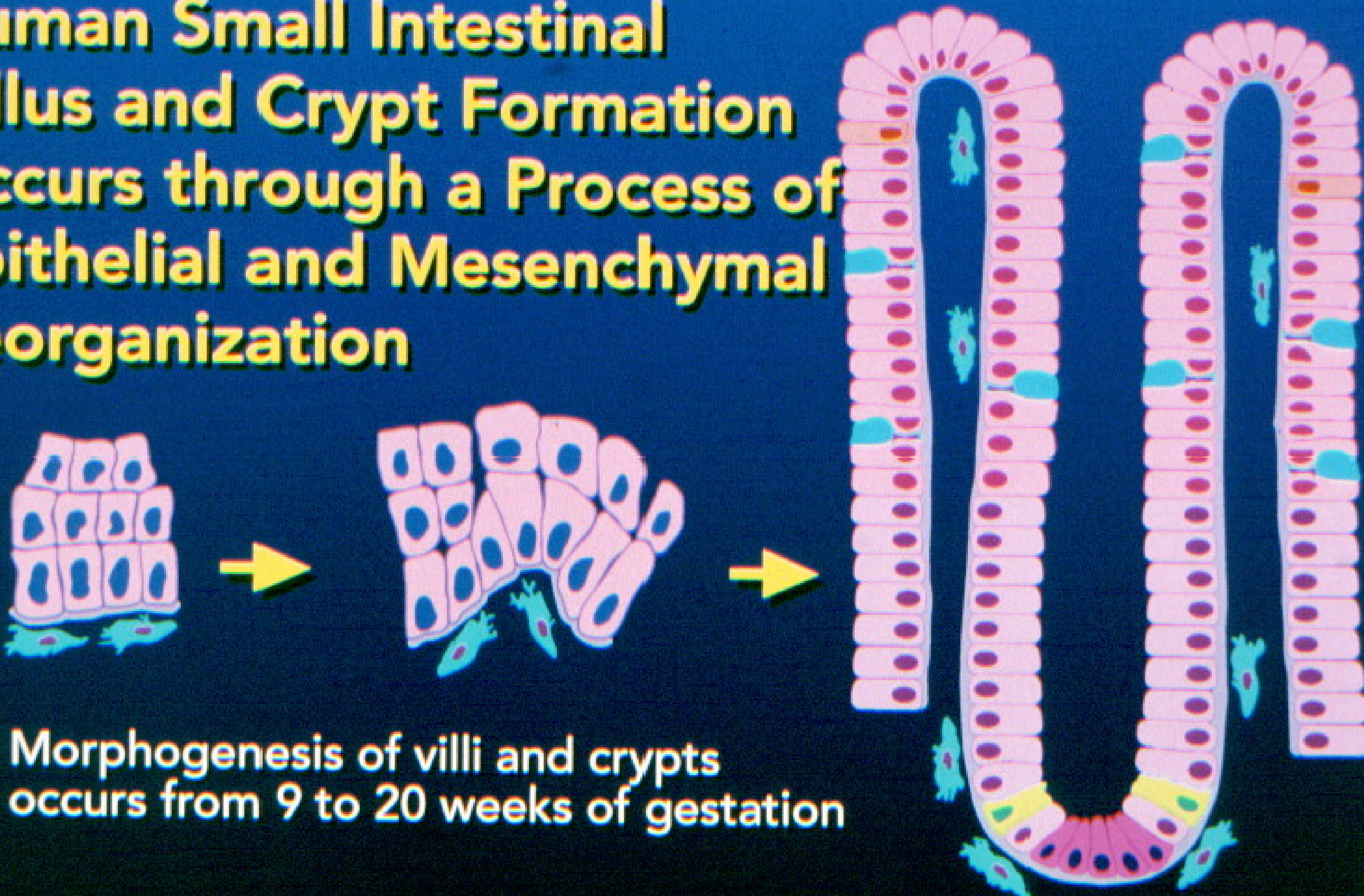
Formation of the primitive gut
- Cell proliferation
- Growth
- Morphogenesis

Cellular differentiation
- All cell types appear
- Functional capacity develops

Functional enhancement
- Growth
- Functional capacity increases


The Surface Area of the Small Intestine Is Increased by Folding of the Mucosa, Formation of Villi, and Development of Microvilli
folding into plicae circulares
formation of villi
development of microvilli

Human Small Intestinal Villus and Crypt Formation Occurs through a Process of Epithelial and Mesenchymal Reorganization

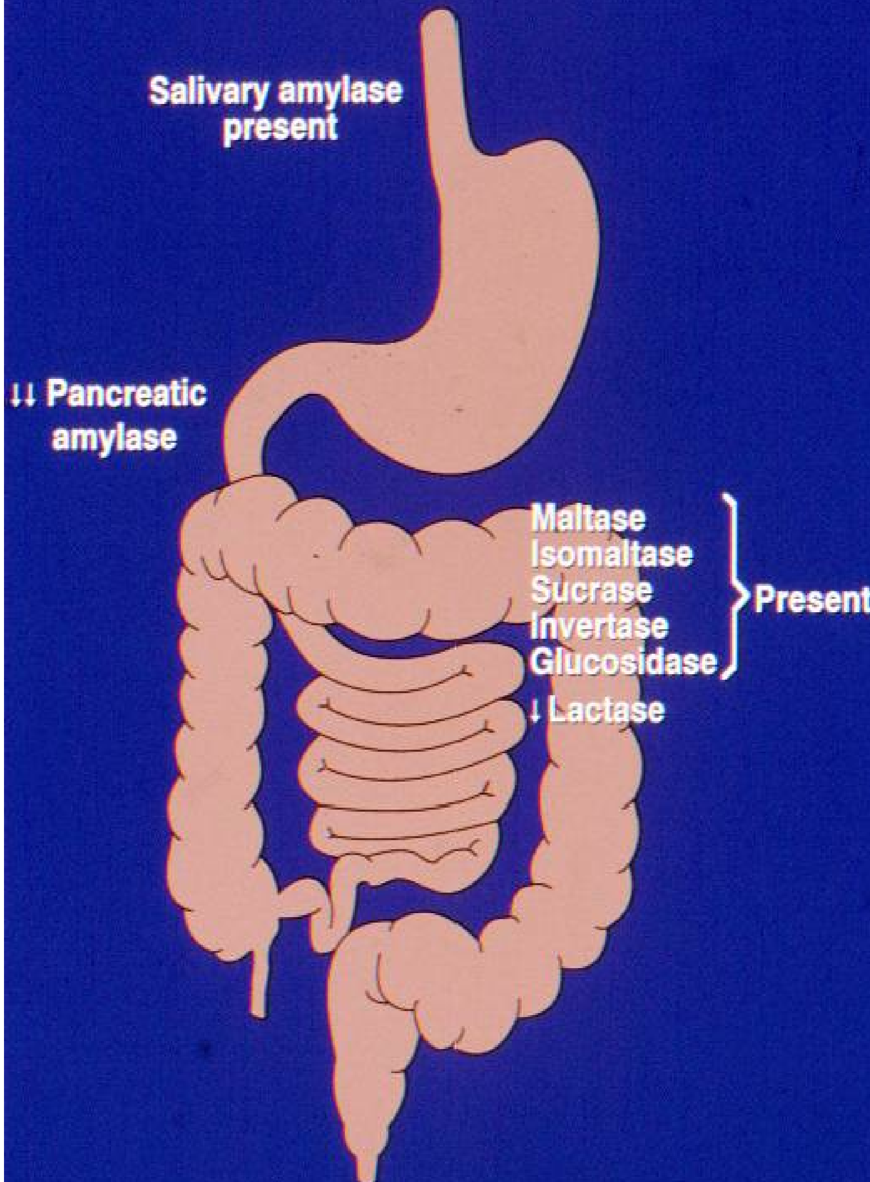


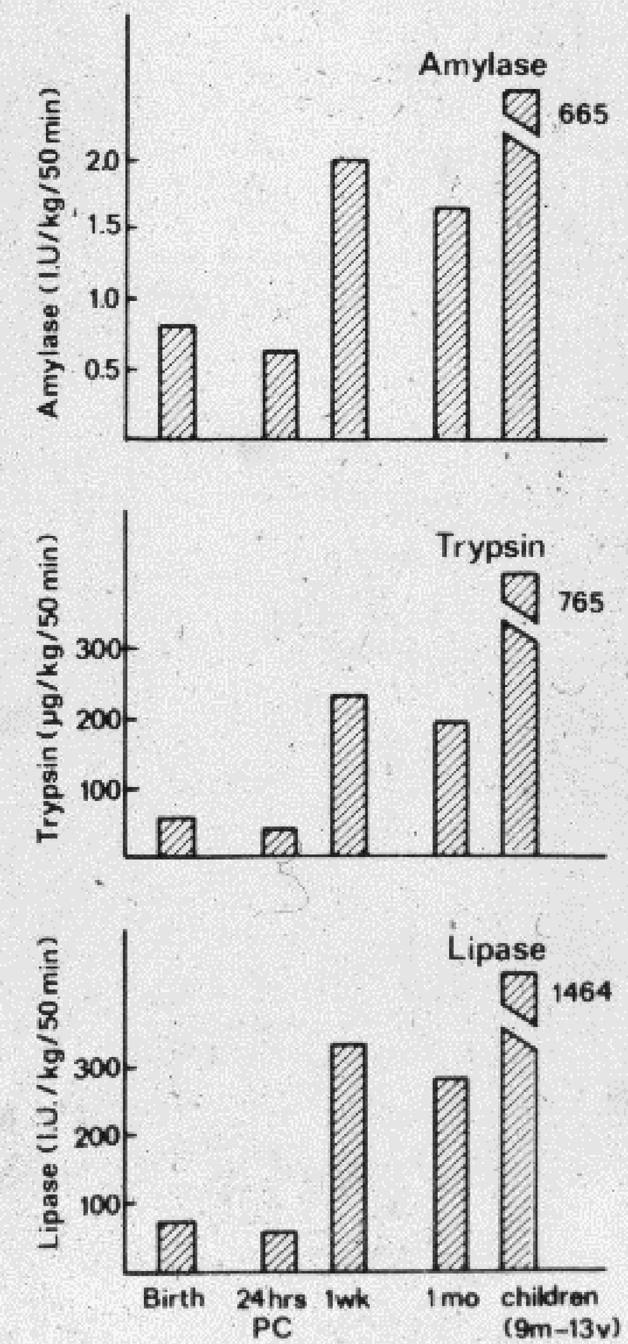
- Morphogenesis of villi and crypts occurs from 9 to 20 weeks of gestation

Growth in Length

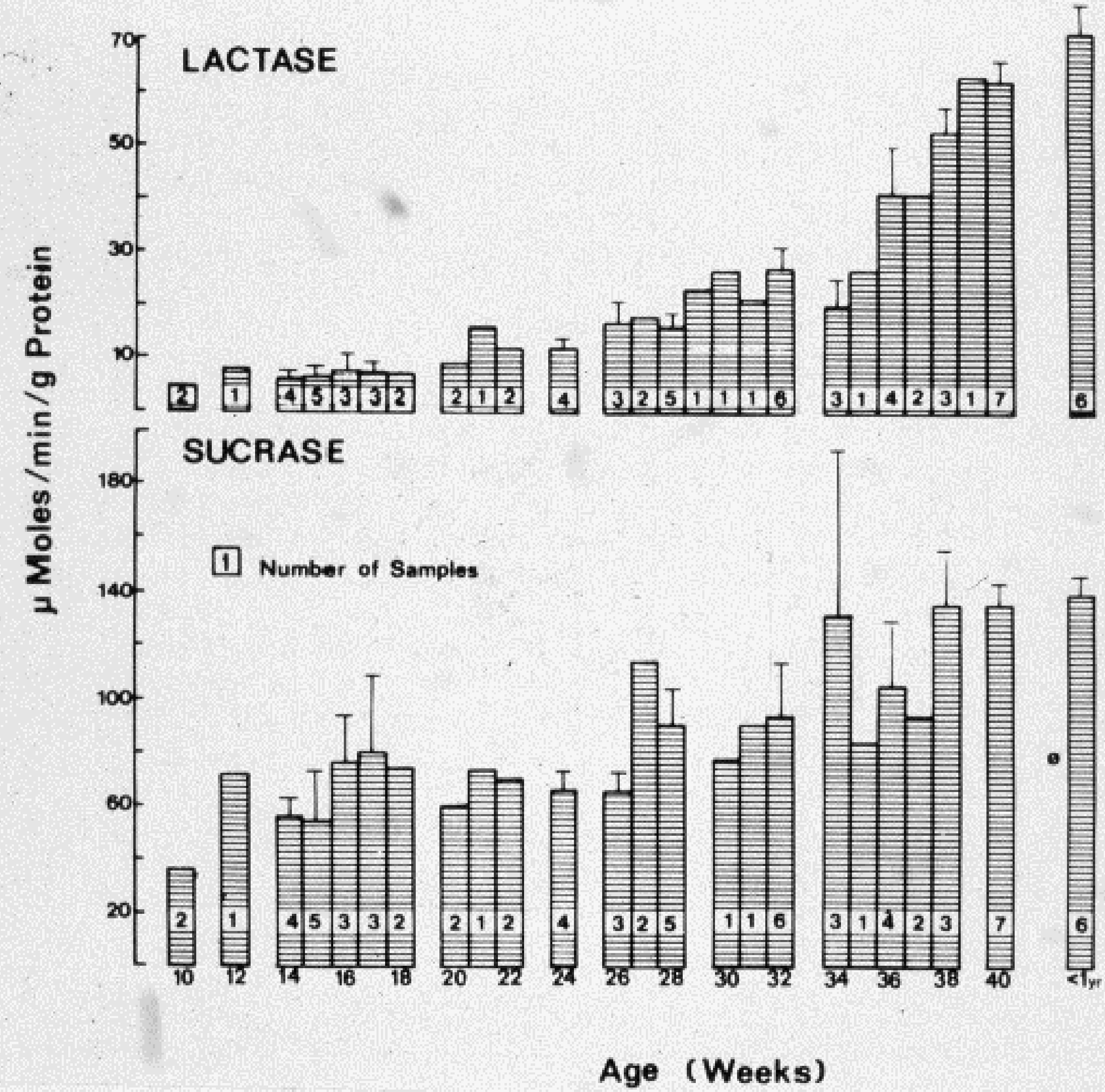
- Human fetal intestine elongates 1000 fold from 5-40 weeks.
- Length doubles in last 15 weeks of gestation.
- Mean length at birth term is 275 cm.

Digestion and Absorption of Carbohydrate



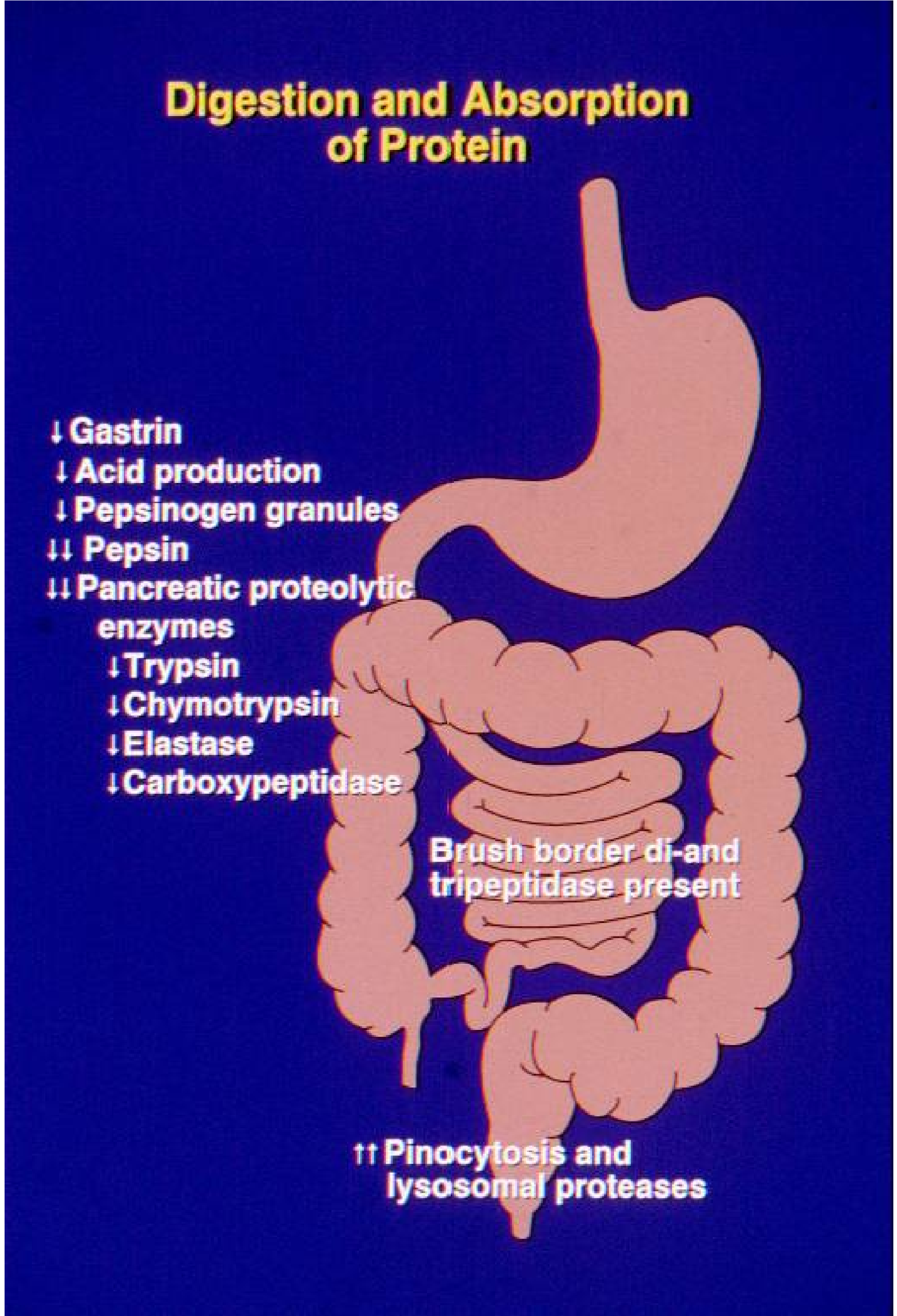

Amylase
665
2.0
1.5
1.0
0.5
Amylase (I.U/kg/50 min)
Trypsin
765
300
200
100
Trypsin (µg/kg/50 min)
Lipase
1464
300
200
100
Lipase (I.U./kg/50 min)
Birth
24 hrs PC
1wk
1 mo
children (9m-13y)

Zoppi,.1972.


LACTASE
SUCRASE
μ Moles/min/g Protein
Number of Samples
Age (Weeks)
<1yr

Digestion & Absorption- CHO

- Pancreatic amylase very low even at term.
- Brush border lactase levels are 25% of term by 25 wks gestation.
- Sucrase-isomaltase at 50% term levels by 20 wks gestation.
- Glucoamylase at 50% term levels by 28 wks gestation.
- In term infant, 30% of CHO is not absorbed in small bowel but is salvaged in colon by SCFA absorption.


Digestion and Absorption
of Protein
↓ Gastrin
↓ Acid production
↓ Pepsinogen granules
↓↓ Pepsin
↓↓ Pancreatic proteolytic enzymes
↓ Trypsin
↓ Chymotrypsin
↓ Elastase
↓ Carboxypeptidase
Brush border di-and tripeptidase present
↑↑ Pinocytosis and lysosomal proteases

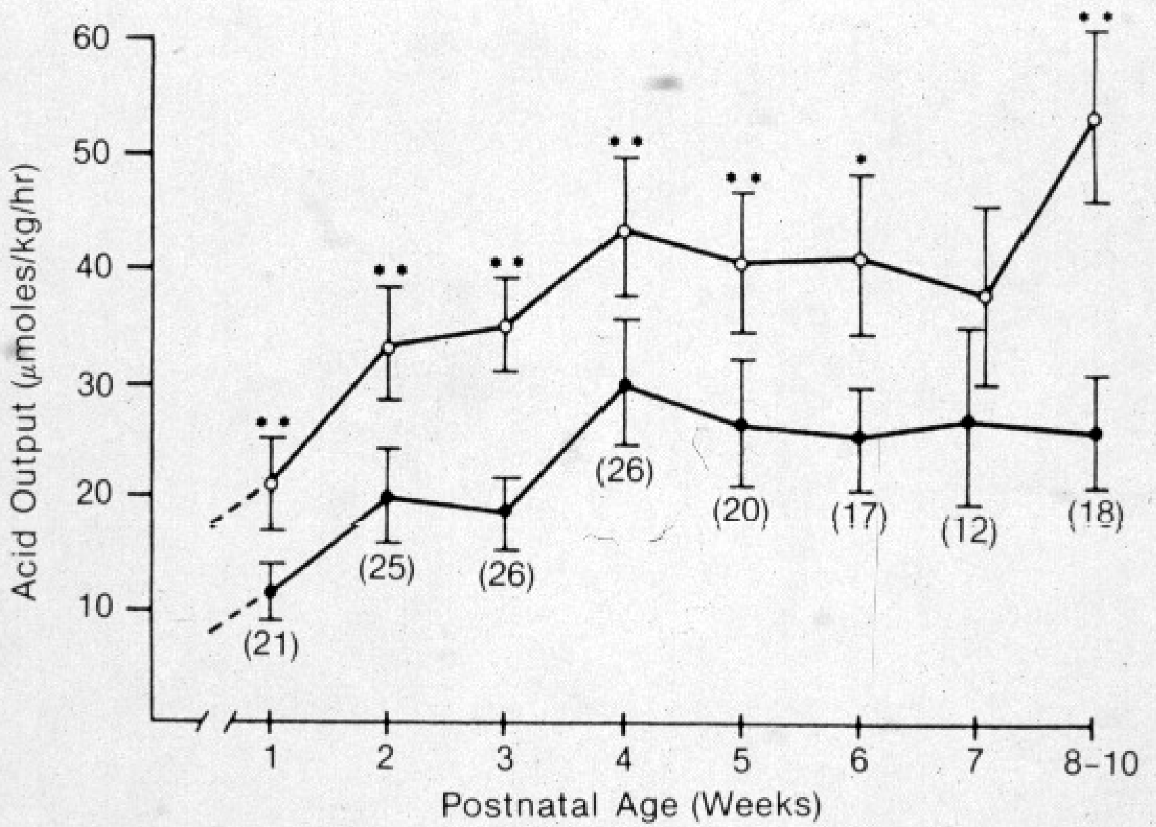
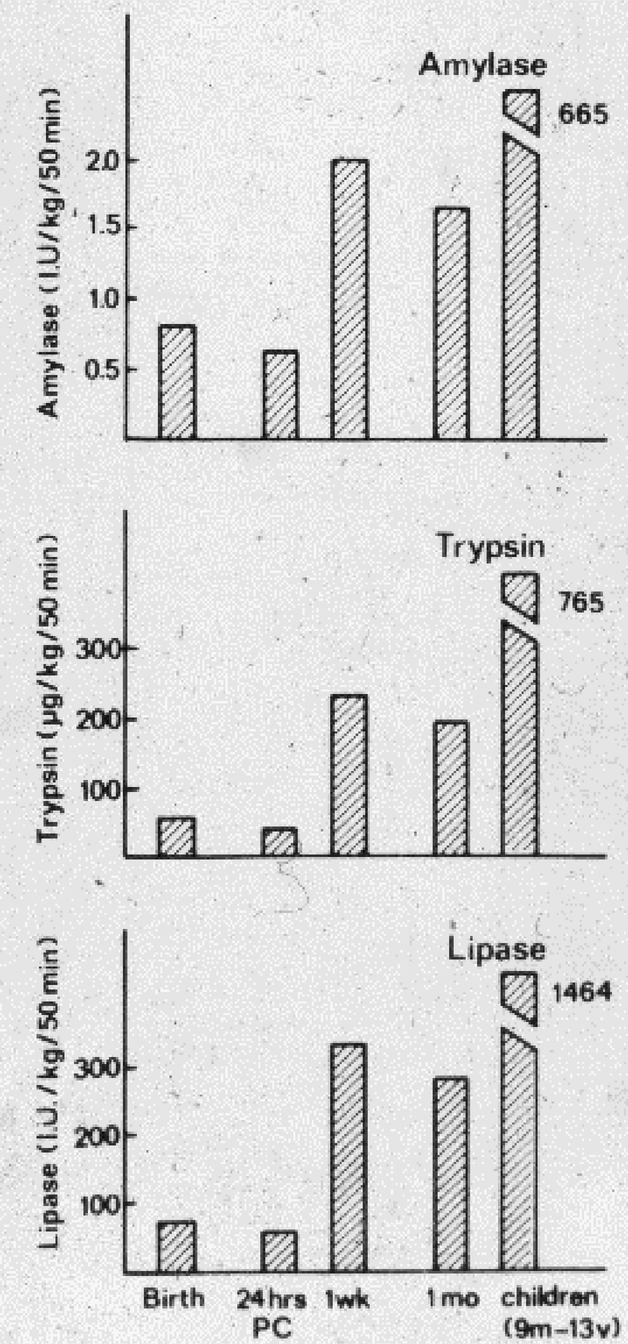


FIGURE 67–1. *Basal acid output (●) and pentagastrin-stimulated acid output (○) in preterm infants. Number of subjects studied at each age is given in parentheses. *P <0.05. **P <0.01. (From Hyman, P. E., Clarke, D. D., and Everett S. L.: Gastric acid secretory function in preterm infants. J. Pediatr. 106:468, 1985.)*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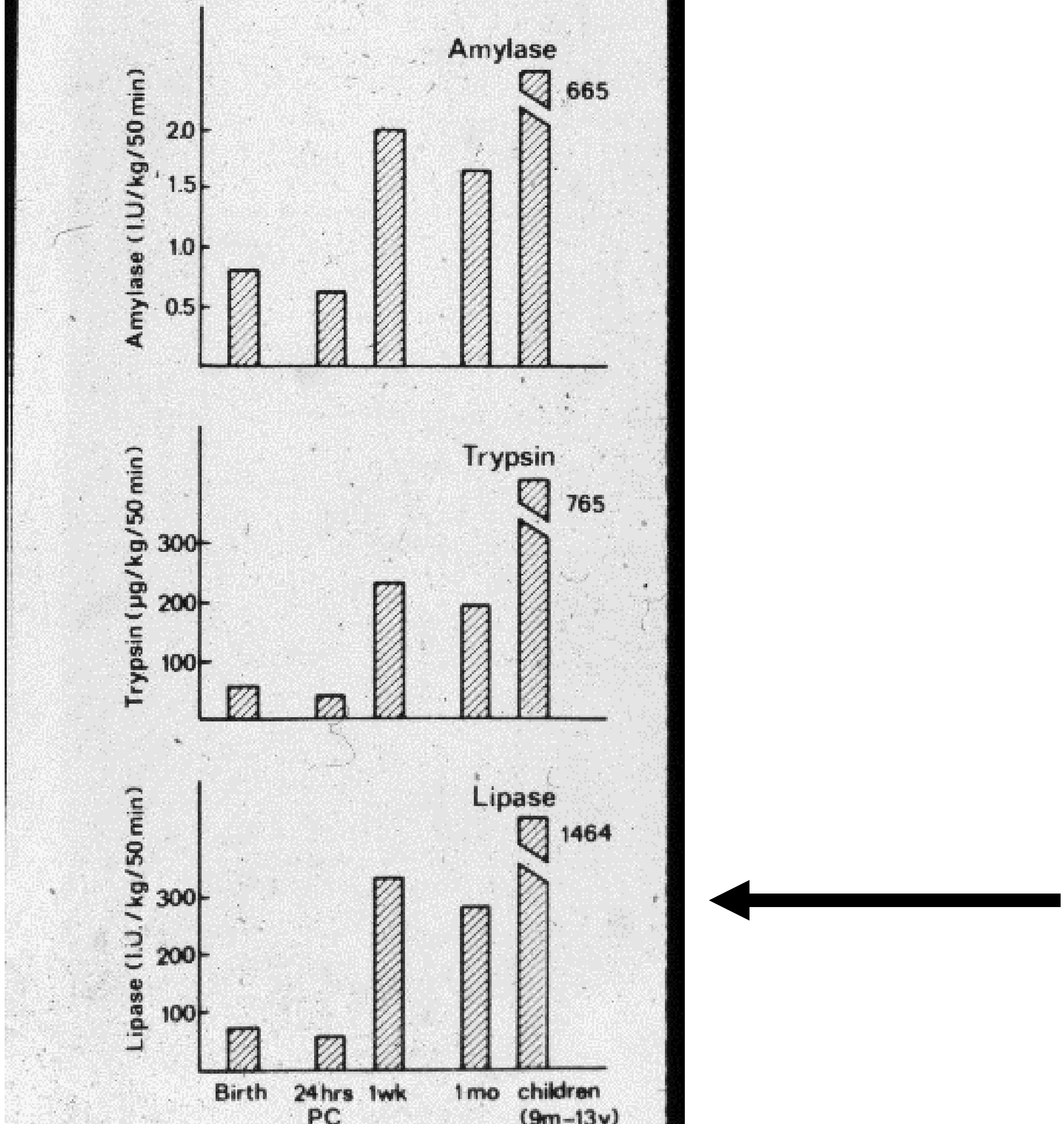
Lipase
1464
Lipase (I.U./kg/50 min)
300
200
100
Birth
24 hrs PC
1wk
1 mo
children (9m-13y)

Zoppi,.1972.

Digestion & Absorption-Protein

- Trypsin and chymotrypsin at term levels by 25 wks gestation.
- Mucosal transport mechanisms and dipeptidases are present in preterm infants.
- Protein digestion is not limited by absorption or digestion in the preterm infant.
- Uptake of intact protein may occur

Digestion and Absorption of Fat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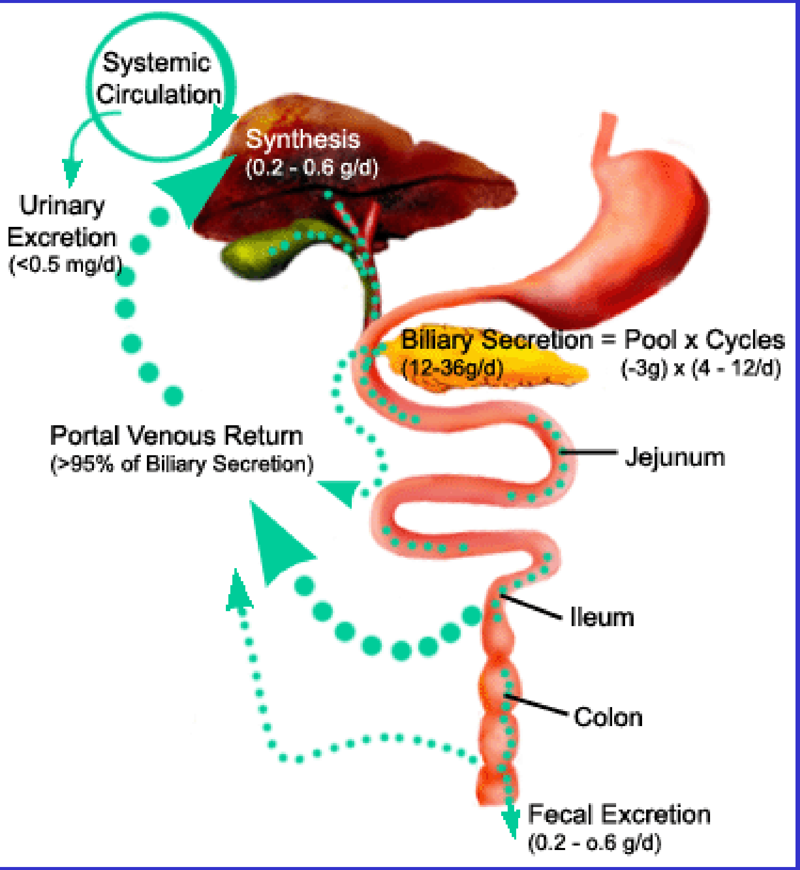
Birth
24 hrs PC
1wk
1 mo
children (9m-13y)

Zoppi,.1972.

Bile Acids



- Synthesis is lower in preterm.
- Bile acid reabsorption is lower in preterm.
- Duodenal bile acid concentration usually below CMC for a few weeks.

Digestion & Absorption-Fat

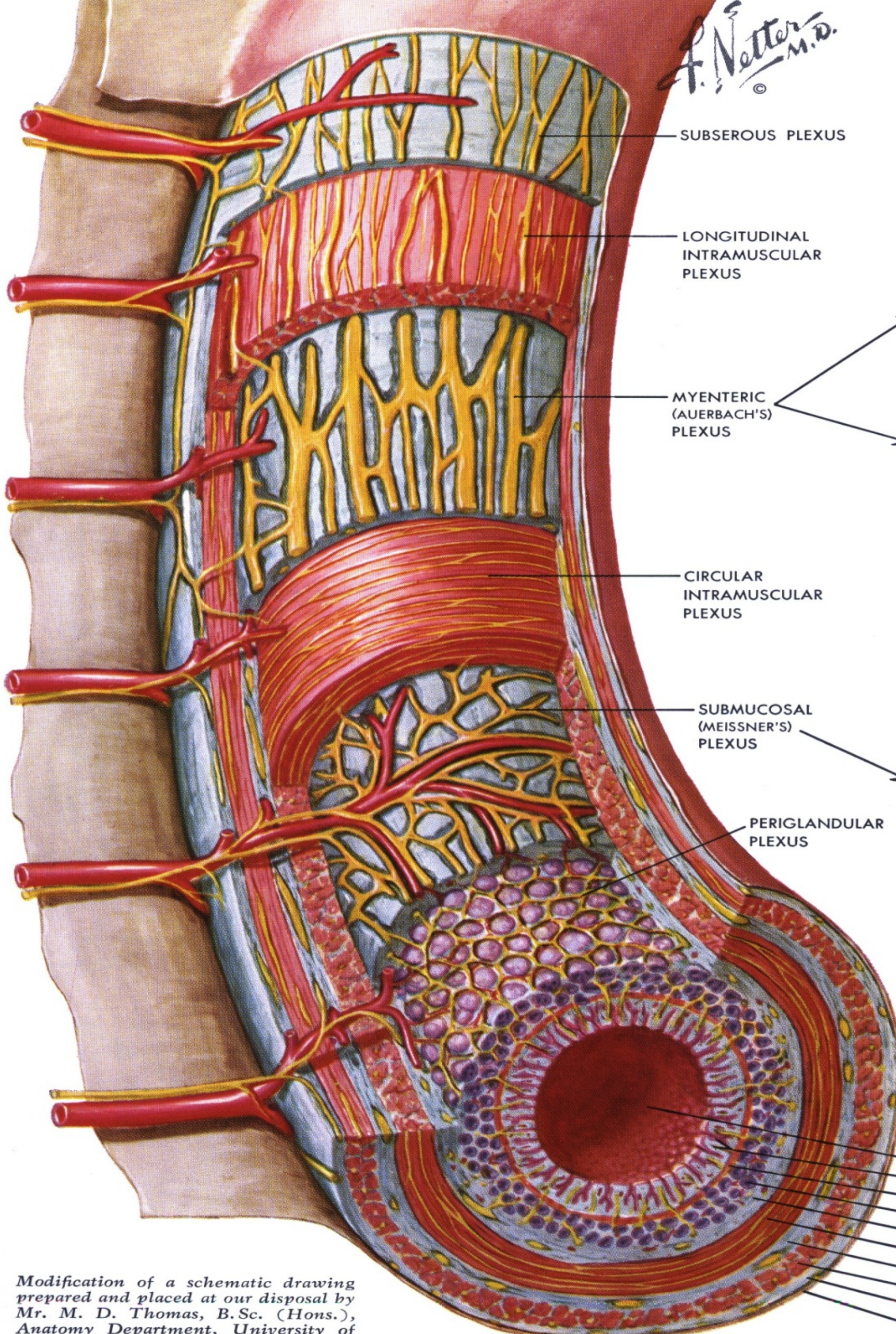
- Even at term pancreatic lipase is very low .
- Bile acid luminal concentrations are only 25% of term at 32 to 36 wks gestation.
- Despite this, 80-90% of fat absorbed in preterm and term newborn.
- Gastric lipase (present by 26 wks gestation) and bile-salt stimulated lipase in breast milk play important roles in fat digestion in the preterm infant.

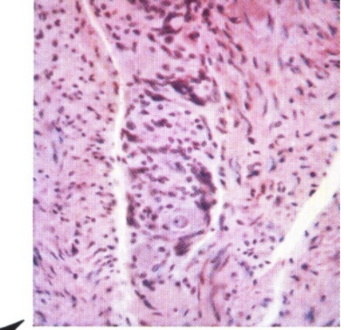
Summary
Mucosal/Hormonal Function

- Lactase may not be fully functional until 32 wk gestation, but CHO malabsorption not a major concern for the preterm infant
- Protein absorption not a major concern for the preterm infant; macromolecules may be taken up by pinocytosis

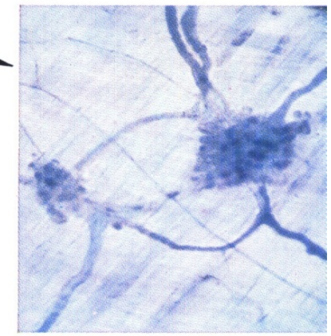
Summary
Mucosal/Hormonal Function

- Fat absorption ranges from 40-90%, reflecting immaturity of intraluminal processing, but fat malabsorption not a major concern for the preterm infant
- Fasting plasma concentrations of GI hormones low (or high) in unfed preterm infants but postprandial release is brisk when preterm infants receive small feedings

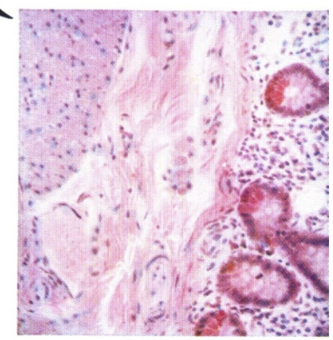




MYENTERIC PLEXUS (CROSS SECTION
HEMATOXYLIN–EOSIN, X 200)

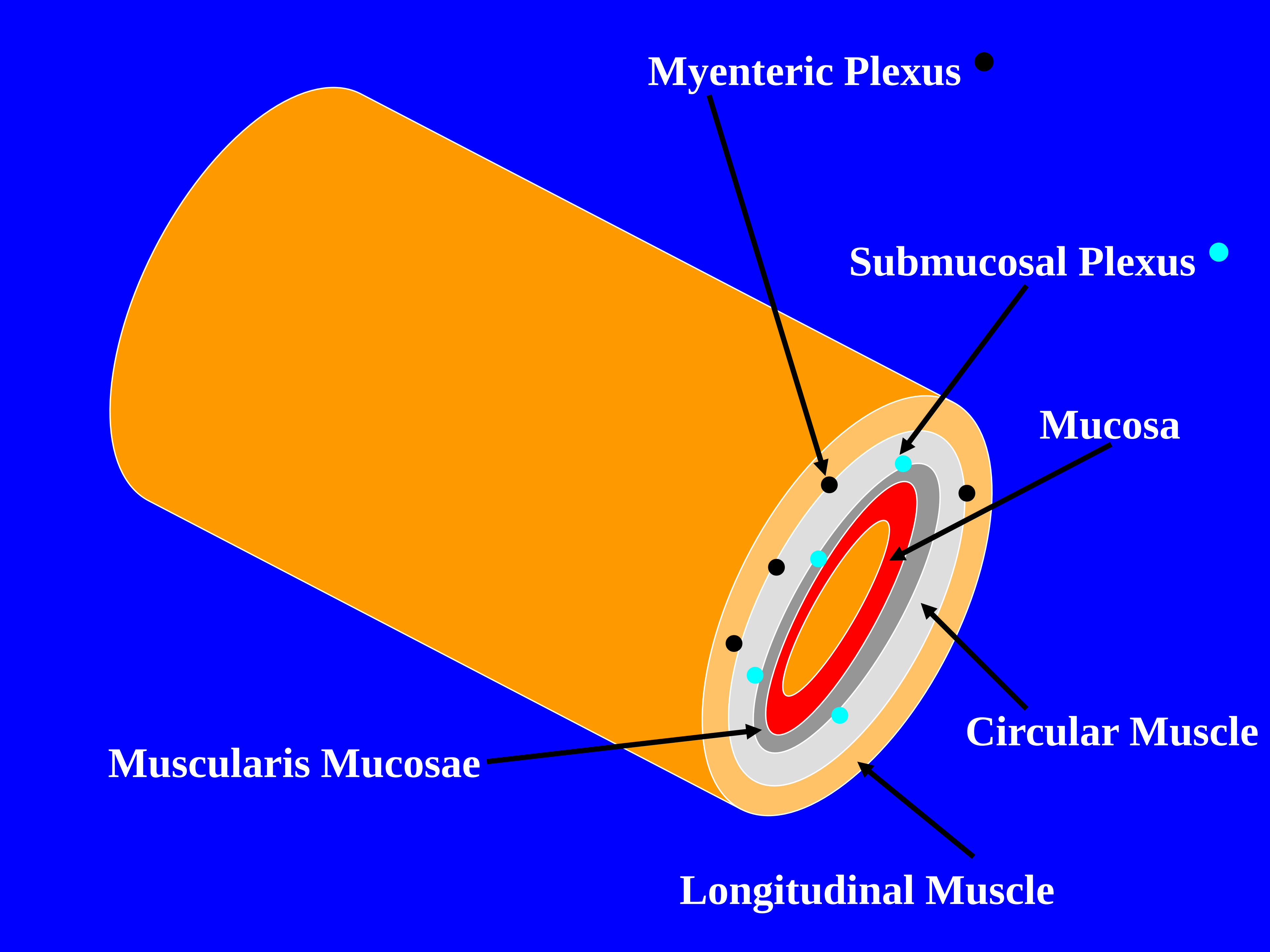


MYENTERIC PLEXUS (PARALLEL SECTION; METHYLENE BLUE, X 200)



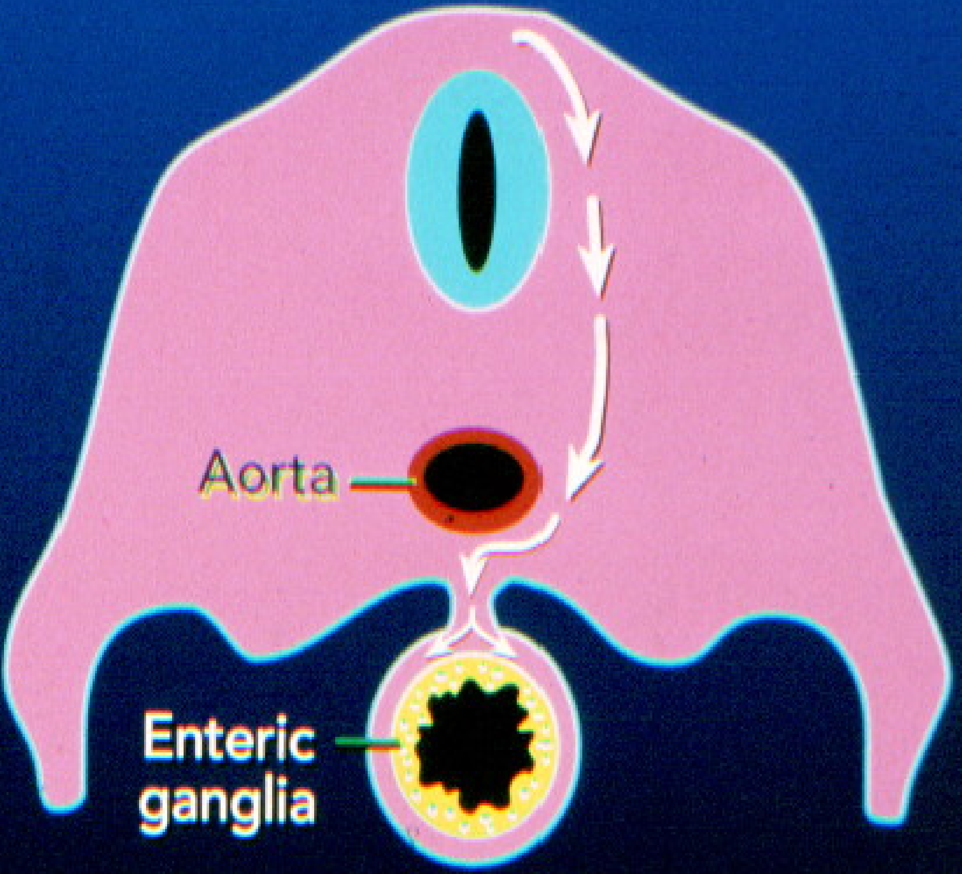
SUBMUCOSAL PLEXUS (LONGITUDINA
SECTION; HEMATOXYLIN–EOSIN, X 200

Modification of a schematic drawing prepared and placed at our disposal by Mr. M. D. Thomas, B.Sc. (Hons.), Anatomy Department, University of Manchester, England

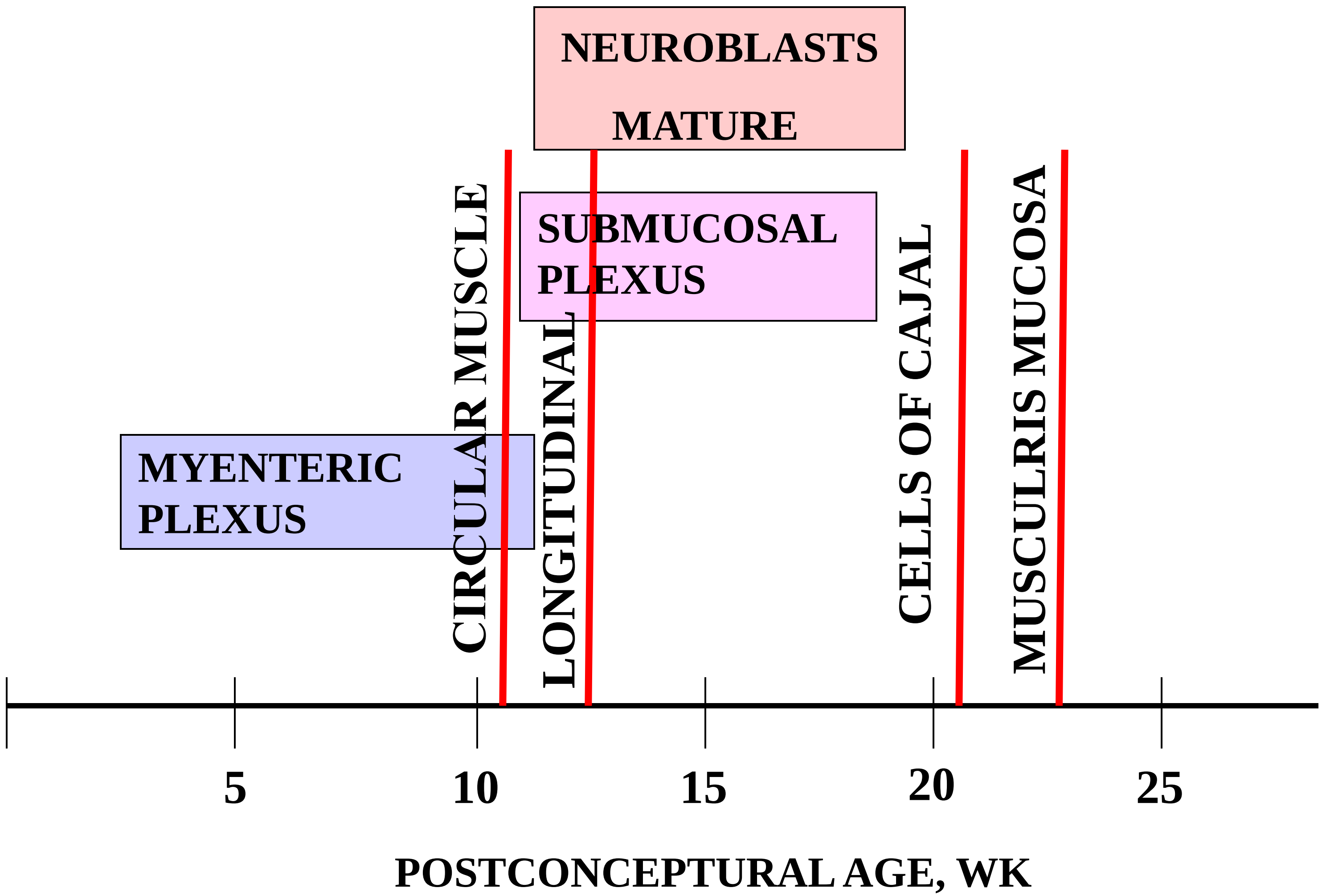

Myenteric Plexus
Submucosal Plexus
Mucosa
Circular Muscle
Muscularis Mucosae
Longitudinal Muscle

Neural Crest Cells Populate the Developing Gut and Give Rise to Enteric Ganglia

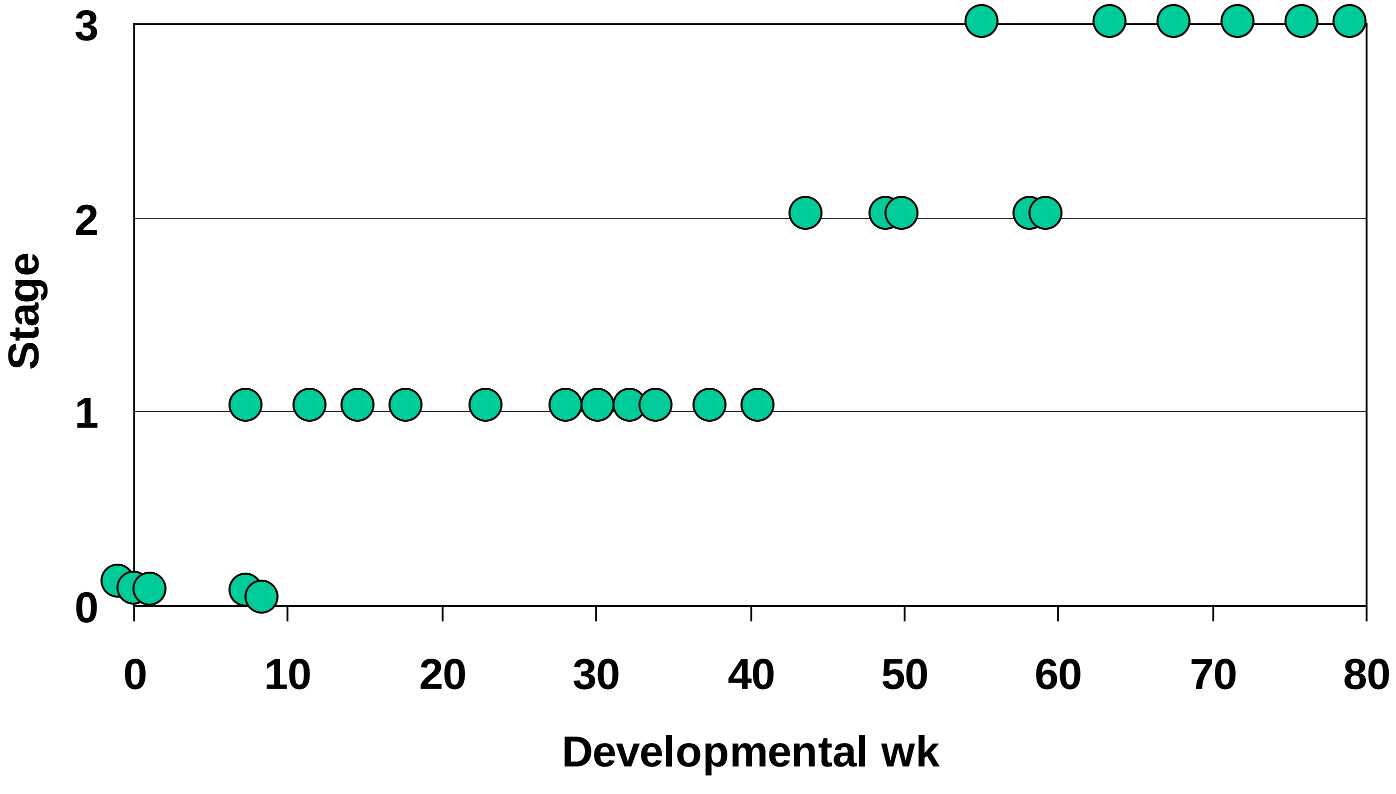
- A subpopulation of the neural crest cells which migrate through the embryo from the lateral edges of the neural plate gives rise to the enteric ganglia
- Neural crest cells from the occipitocervical (vagal) region populate the entire gut
- Neural crest cells from the sacral region populate the distal gut



Ontogeny of Fetal Intestine



Maturation of Enteric Nervous System NOS



Adapted from Khen, Pediatr Res 56:975,2004

Regulation and Modulation of Motor Function

- Myogenic
- Neural
- Chemical

Myogenic Control

- Pacesetter potential related to ocillatory changes in myocyte membrane potential
- Frequency of oscillation decreases in cephalocaudal manner, resulting in differences in contraction rate
  - Duodenum 12/min
  - Jejunum 10/min
  - Ileum 8/min
  - Colon 5/min

Neural Control

- Intrinsic neural regulation
  - Refers to nerves located within the GI tract
  - Is the major source of neural regulation
  - 2500 nerve cells/mm of gut length
- Extrinsic neural regulation
  - CNS
  - ANS

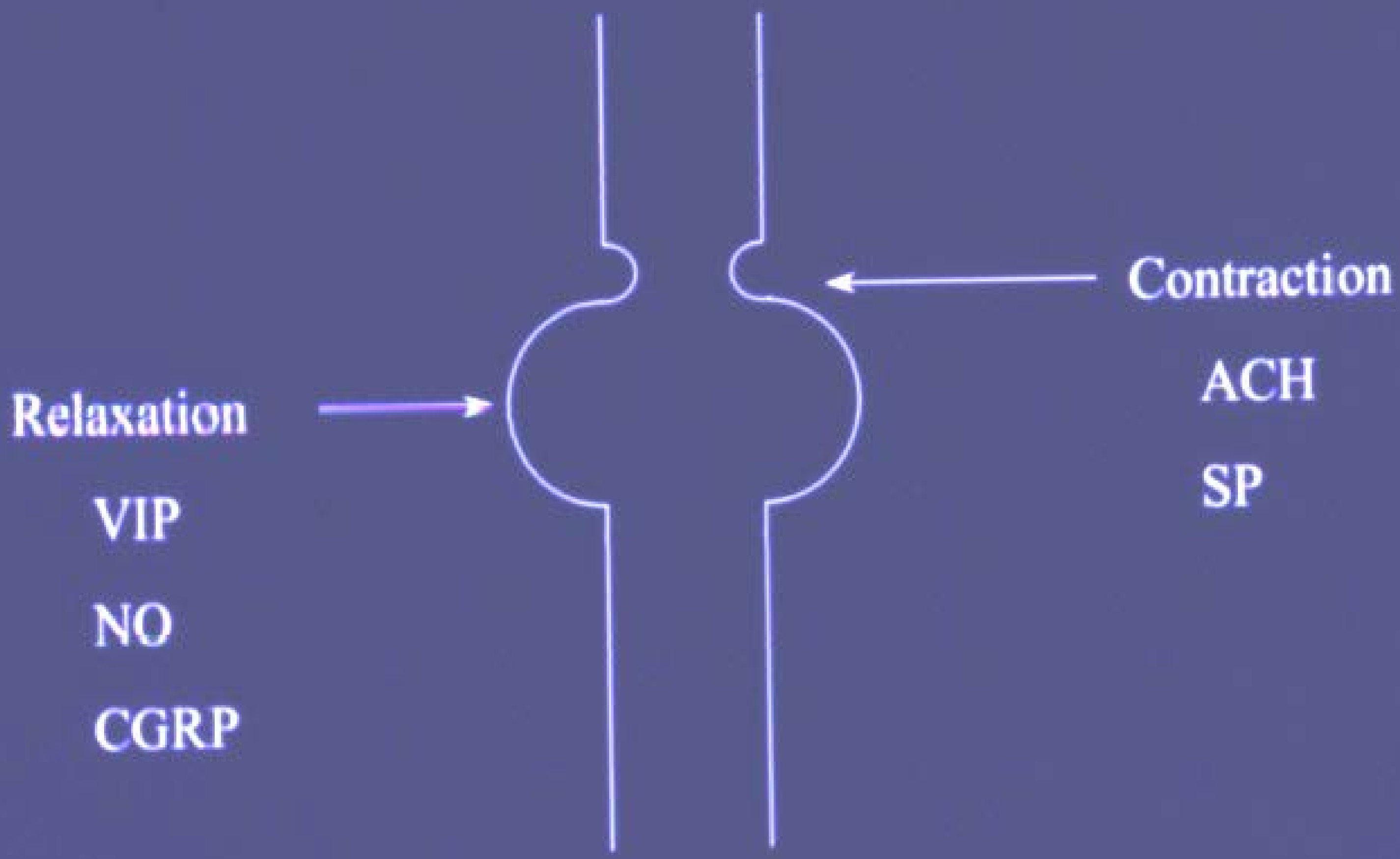
Chemical Control

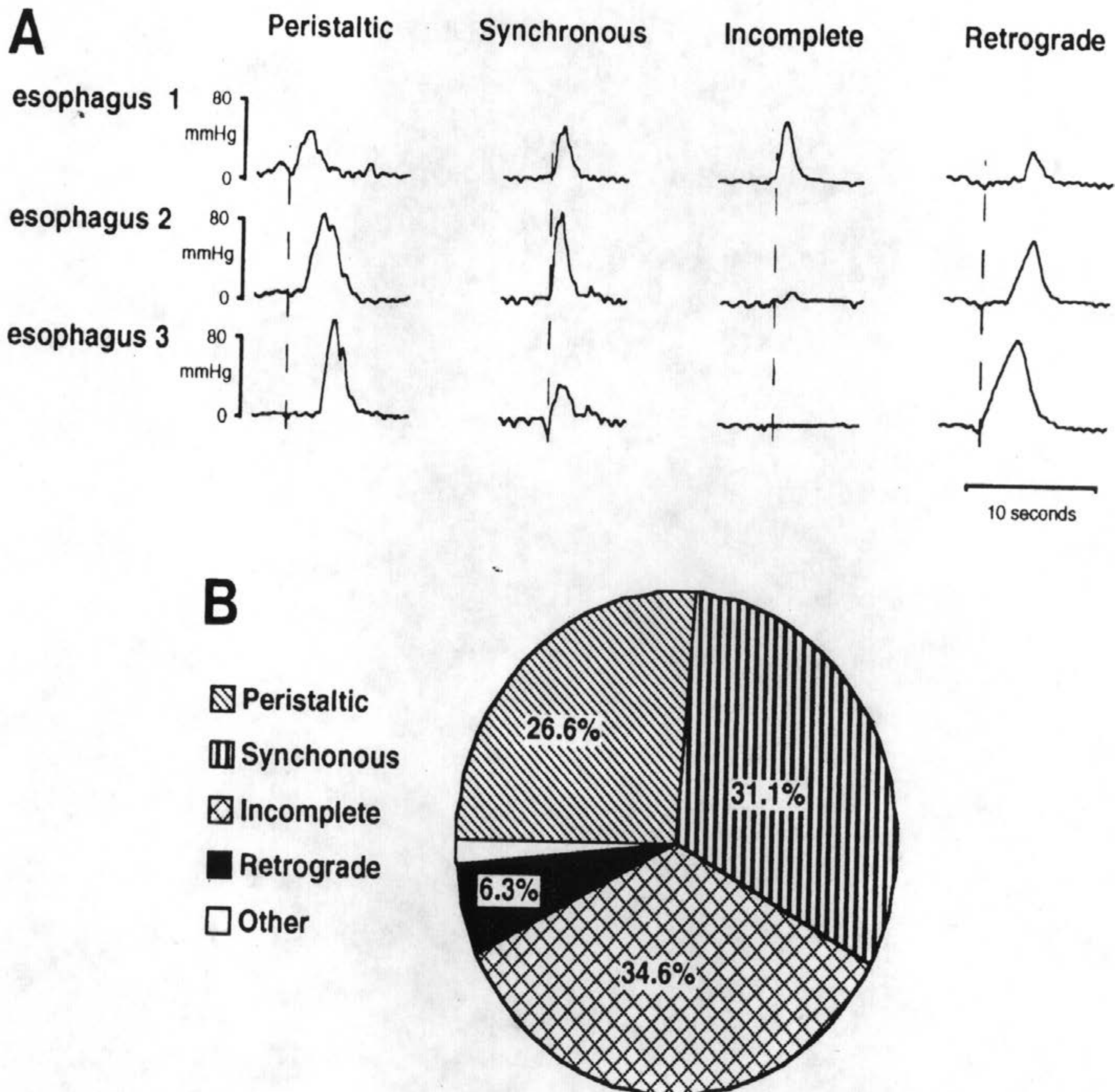
- Endocrine (motilin, PYY)
- Paracrine (VIP)
- Neurocrine (Acetylcholine, NO)

Aspects of Motor Function in the Preterm Infant

- Suck and swallow
- Esophageal function
- Gastric emptying
- Small intestinal function
- Colon and Rectal function

Peristaltic Reflex




A
Peristaltic
Synchronous
Incomplete
Retrograde
esophagus 1
esophagus 2
esophagus 3
80
mmHg
0
10 seconds
B
Peristaltic
Synchonous
Incomplete
Retrograde
Other
26.6%
31.1%
6.3%
34.6%

Omari, 1995

Maturation of Esophageal Peristalsis in Preterm Infants

- High resolution manometry recorded in healthy infants on full feedings
  - 16 preterm infants (32.9±1.6 wk)
  - 14 term infants (38.9±1.6 wk)
- Pressure responses recorded at 3 segments above LES
  - 1= upper esophagous
  - 2= mid esophagous
  - 3=lower esophagous

Staiano, Gastroenterol 132: 1718, 2007

Findings

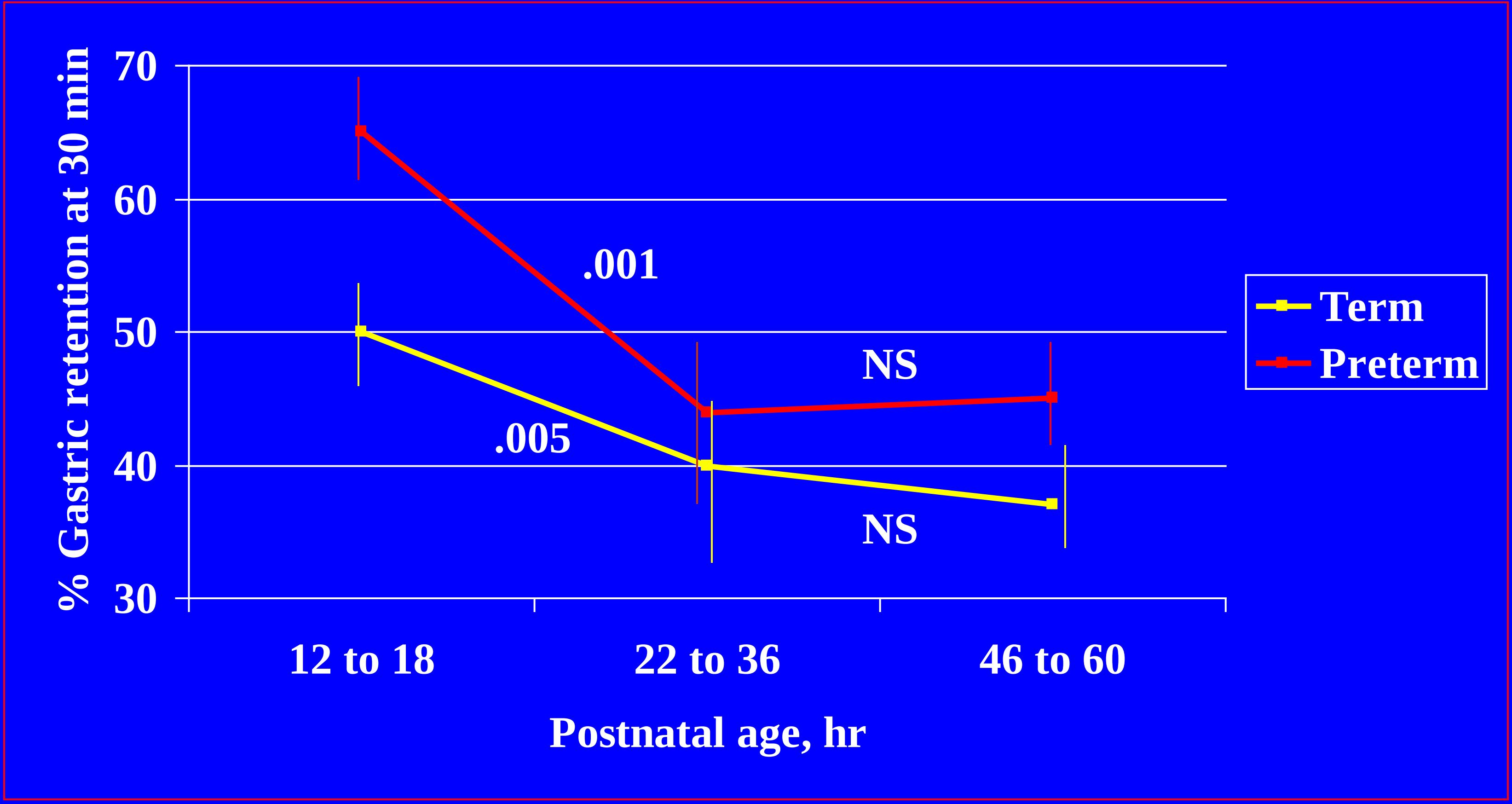
- Segment 2 more mature than segments 1 and 3 in preterm and term infants
- Segment 2 more mature in term than preterm infants
- Approximately 55% of swallows propagated down esophagus in term, implying further maturation during infancy

Staiano, Gastroenterol 132: 1718, 2007

Lower Esophageal Sphincter Function

- Lower esophageal sphincter tone lower in preterm and term infants compared to adults
- Tone related to gestational age
- LES function appears to be intact in preterm infants

Gastric Emptying in Term and Preterm Infants



Modified from Siegel and Lebenthal, 1981

Gastric Emptying

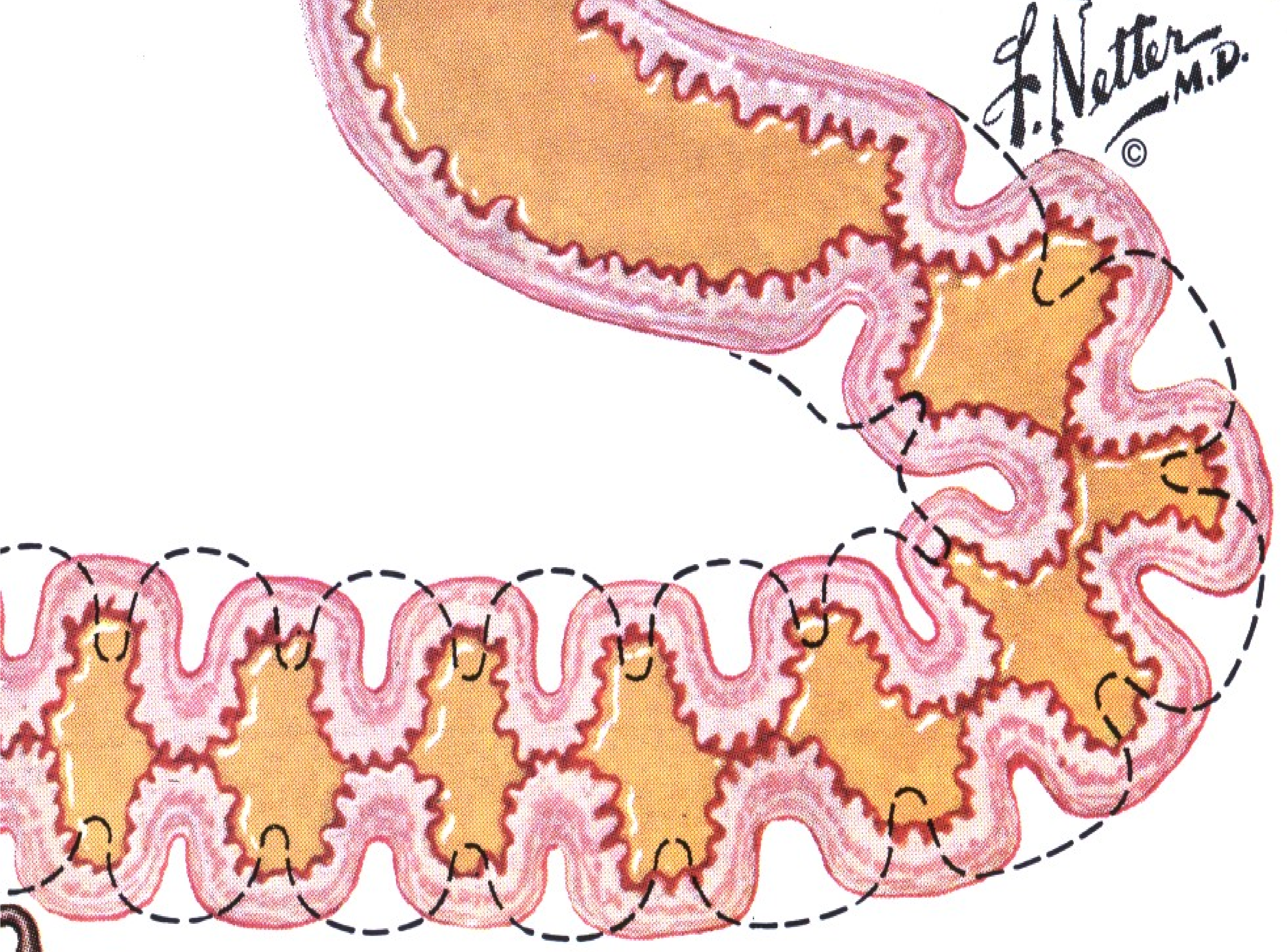
- Delayed in preterm infants compared to term infants
- Pattern of emptying consistent with liquid, i.e. curvilinear not linear
- Rates controlled by feedback from small intestine

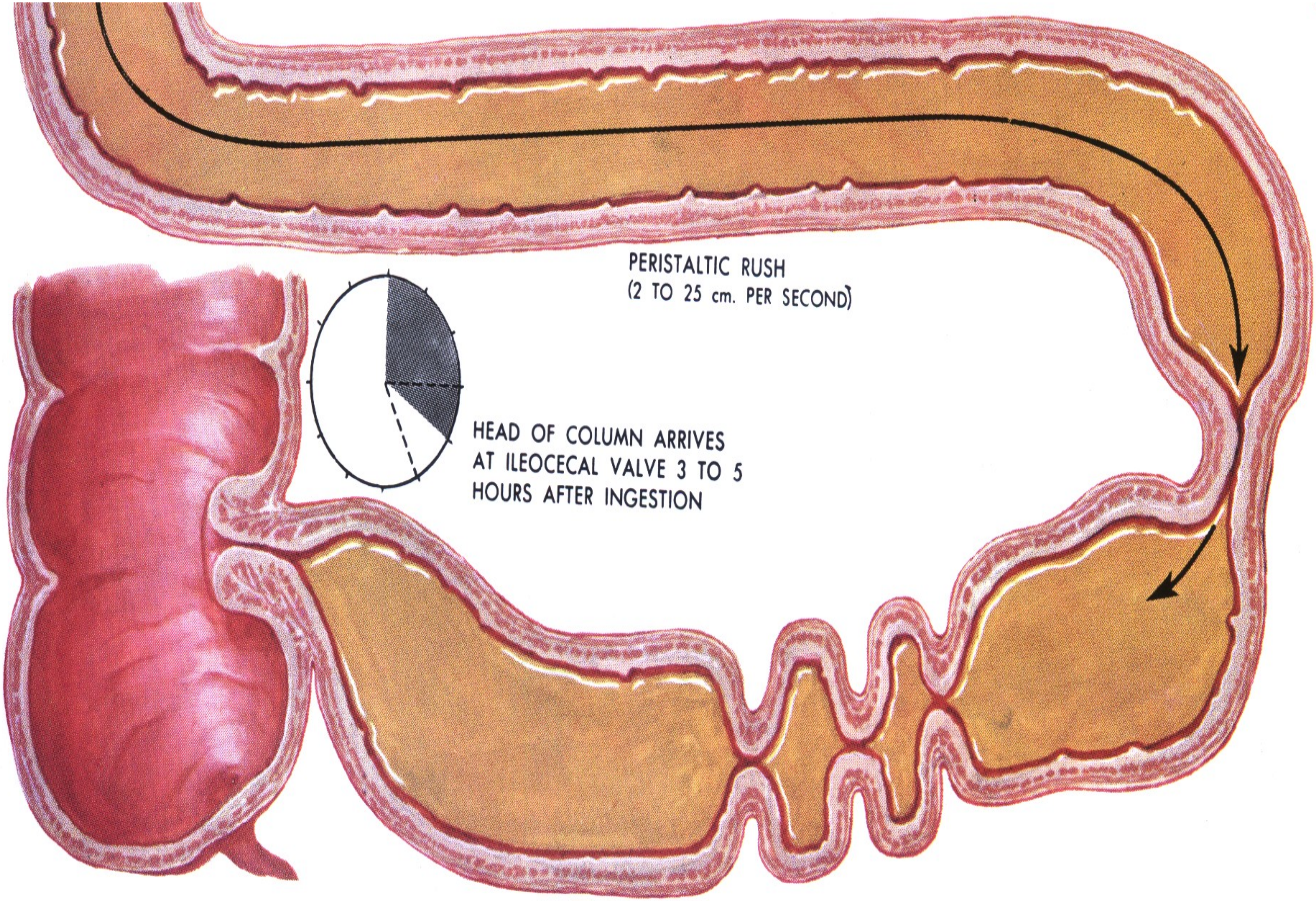
Factors That Delay Gastric Emptying in Preterm Infants

- Fat
- Glucose
- Acid
- Increased osmolality
- Decreased osmolality
- Increased caloric density
- Decreased caloric density

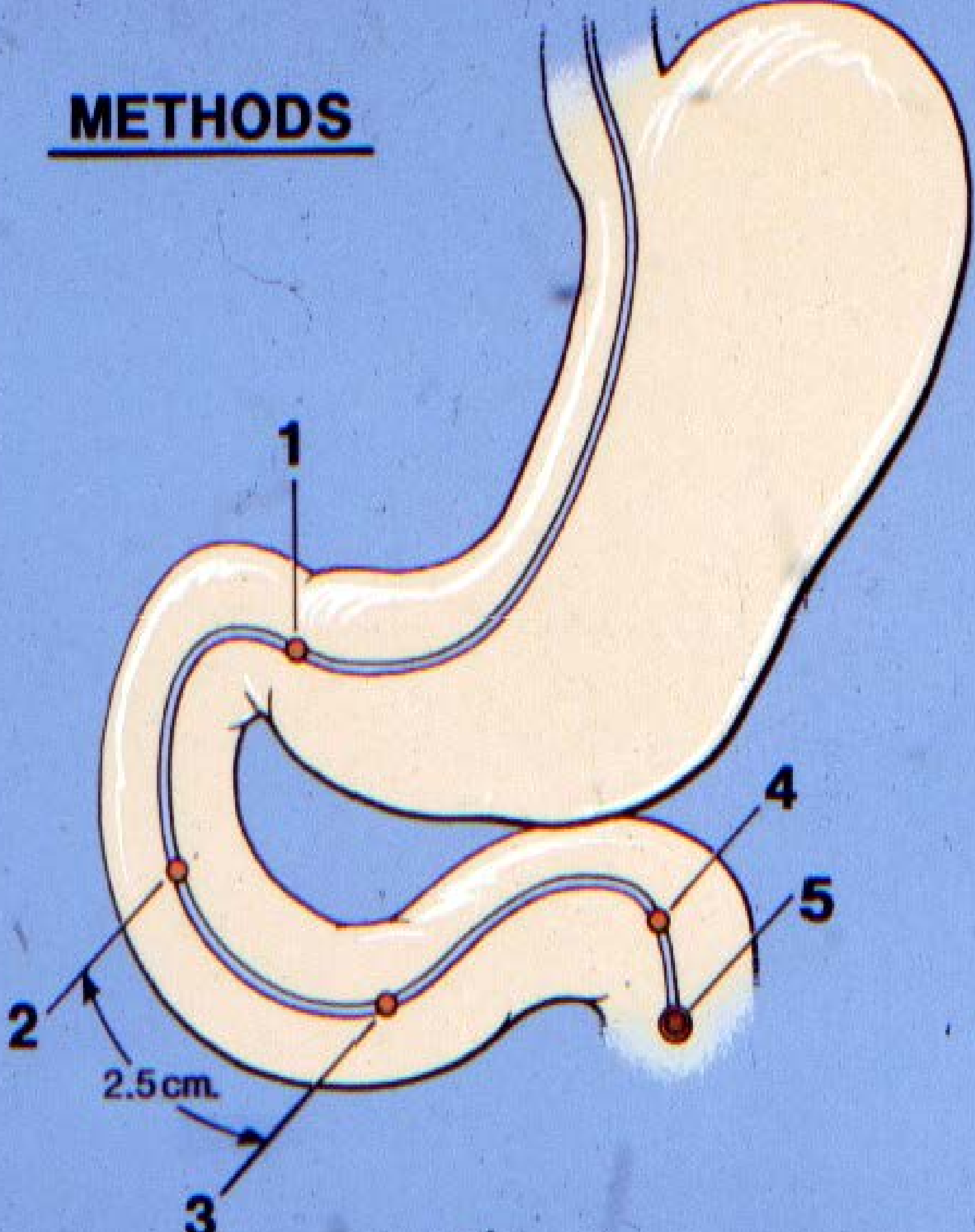
Small Intestinal Motor Function

- Duodeno-anal transit is delayed in preterm infants, ranging from 2 to 7 days during the first postnatal wk
- Small intestinal motor patterns are more immature in neonates than children and adults


F. Netter M.D.
©


PERISTALTIC RUSH
(2 TO 25 cm. PER SECOND)
HEAD OF COLUMN ARRIVES
AT ILEOCECAL VALVE 3 TO 5
HOURS AFTER INGESTION

METHODS

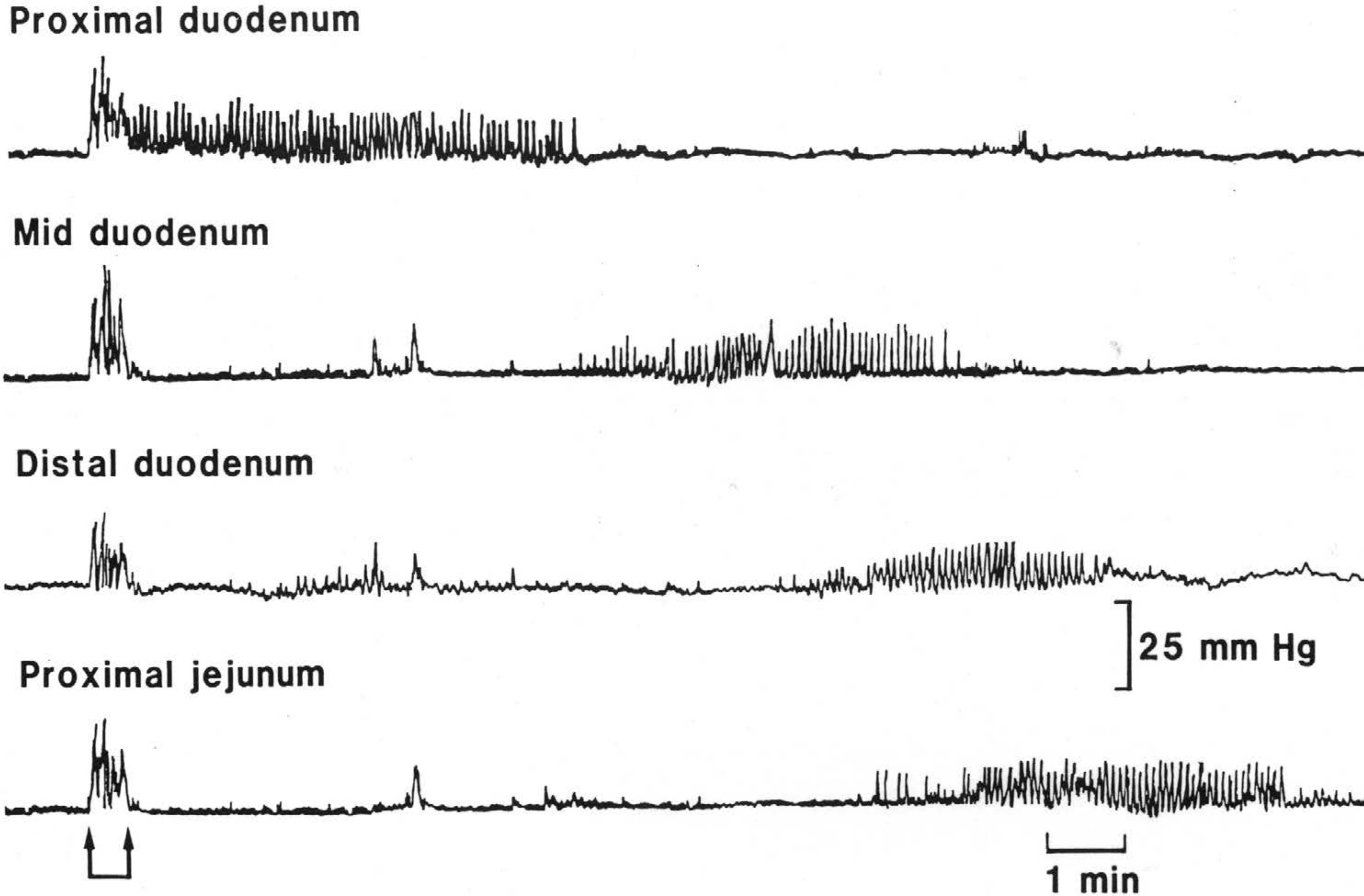


Multilumen Manometric and Feeding Tube

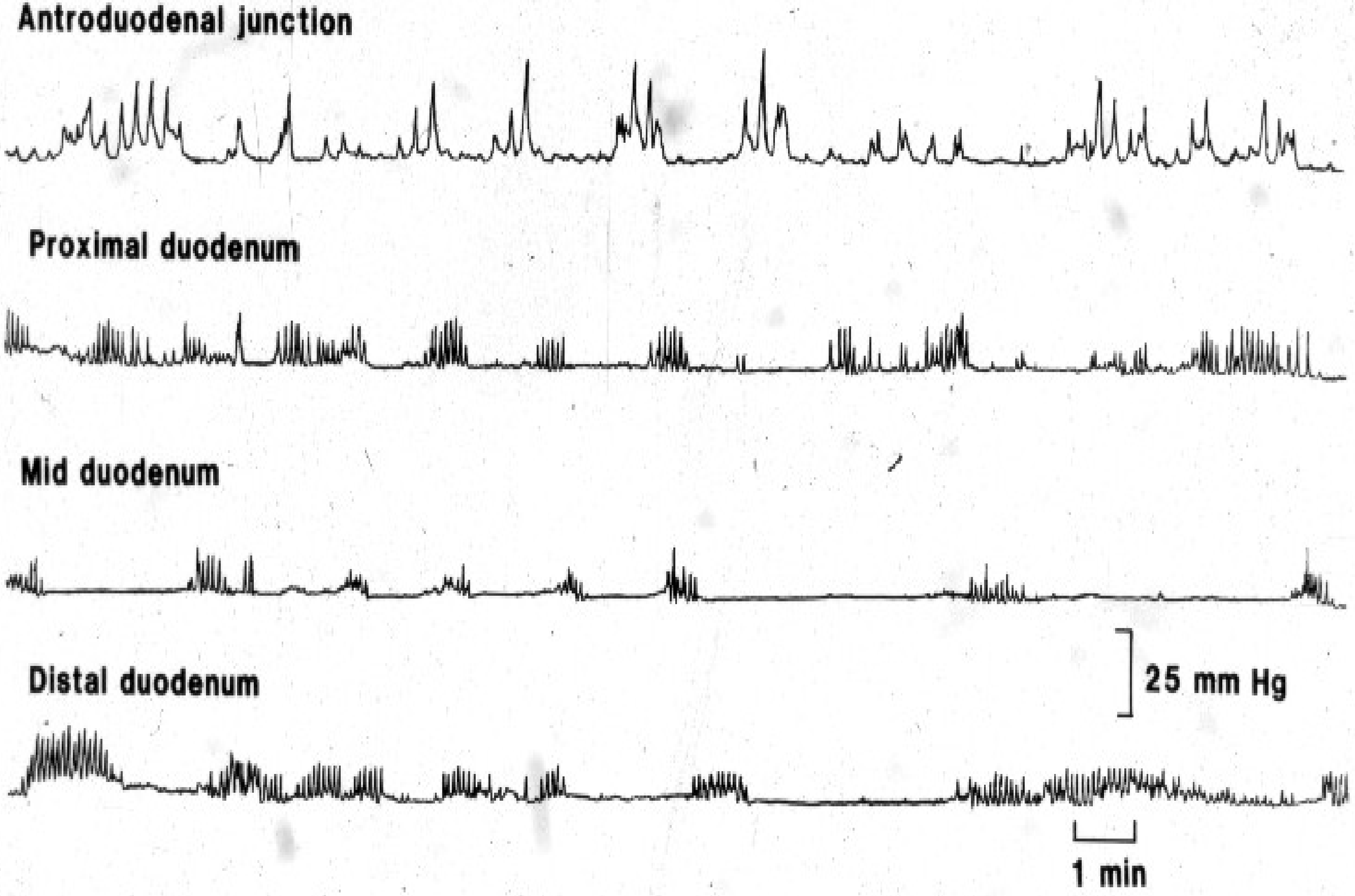
4 Recording Ports (1-4)

1 Feeding Port (5)

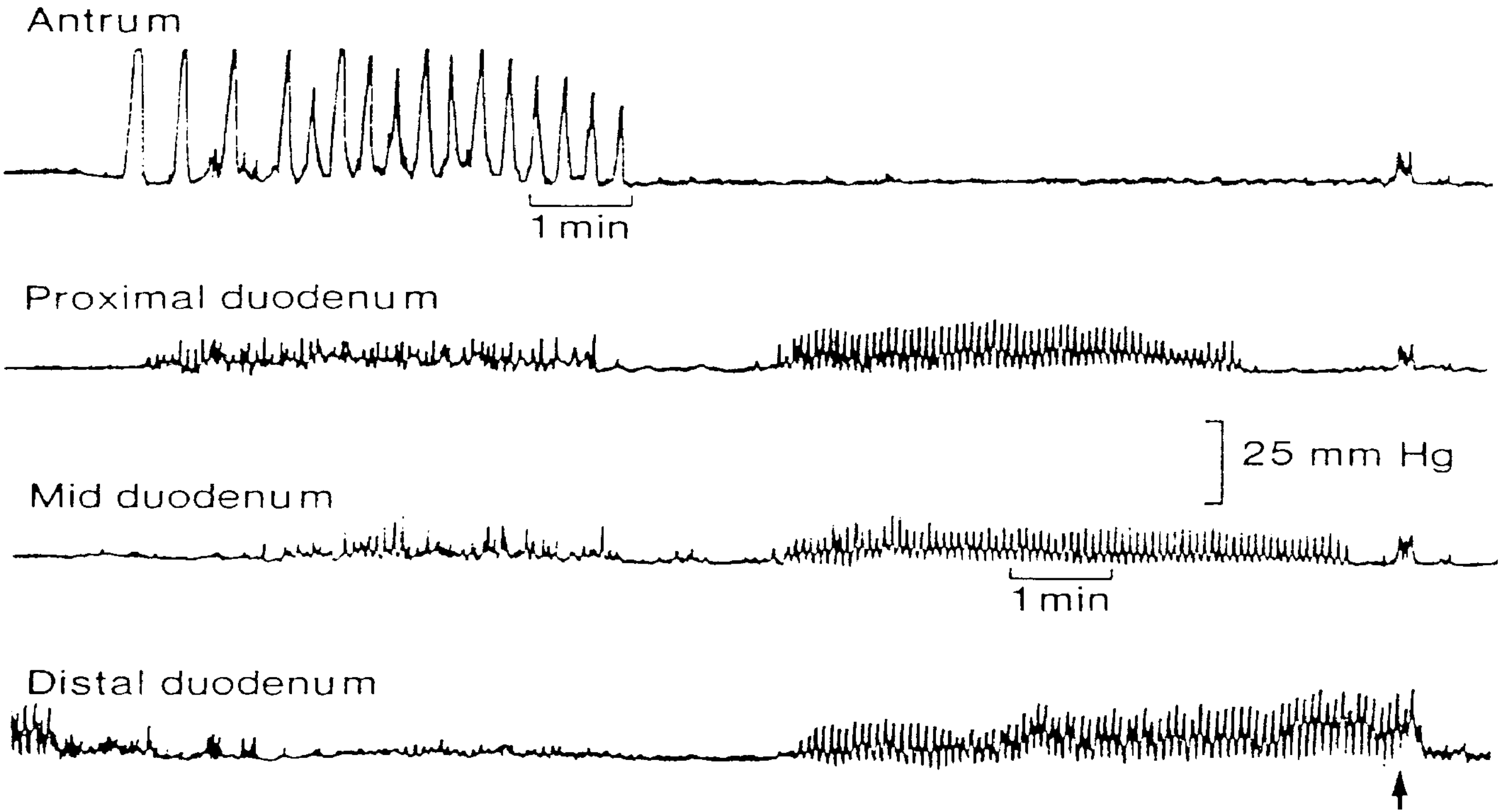
MIGRATING MOTOR COMPLEX (MMC) IN A TERM INFANT



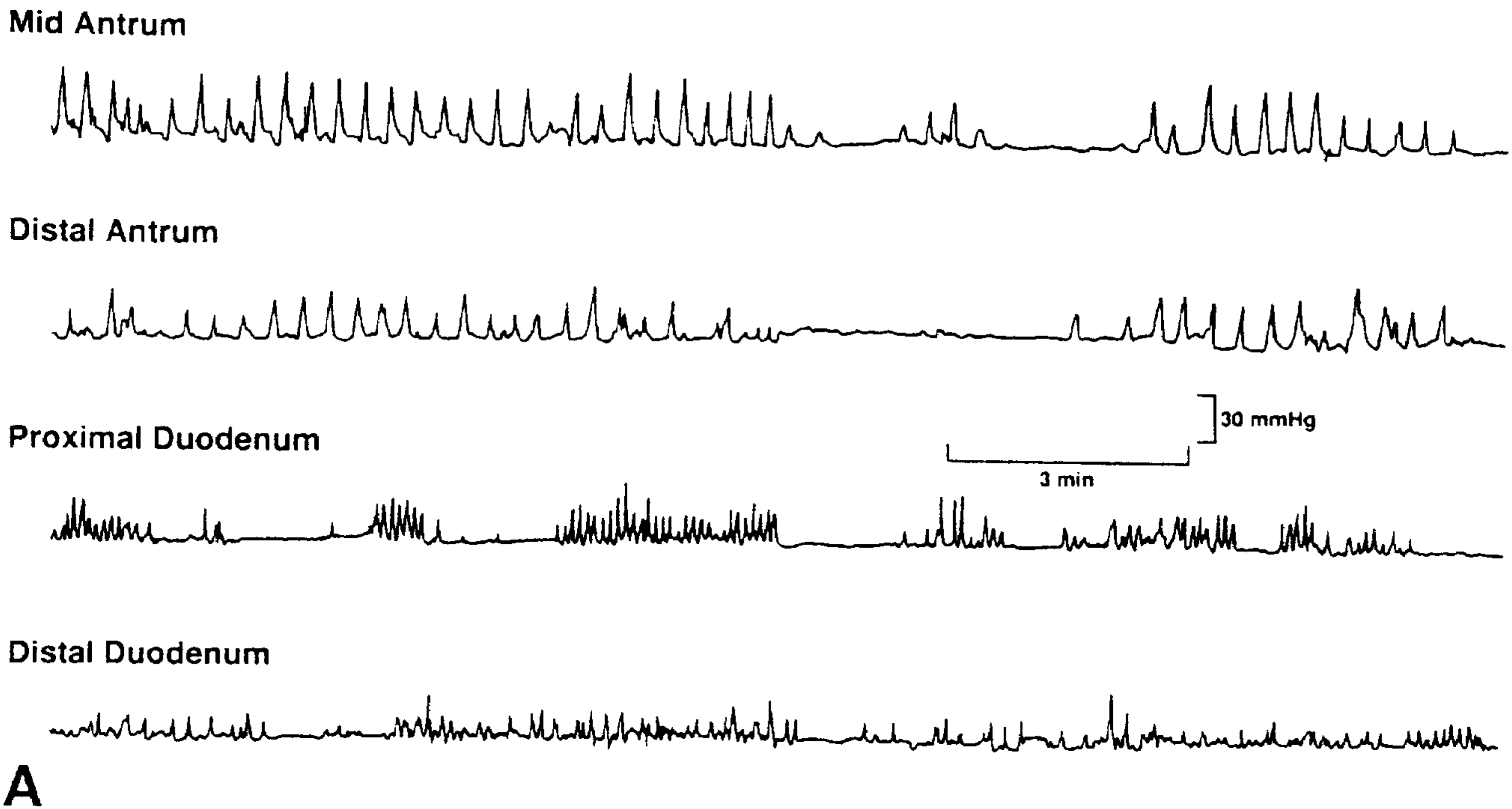
CLUSTER ACTIVITY IN AN UNFED PRE-TERM INFANT



MMC in an MEN Fed Infant



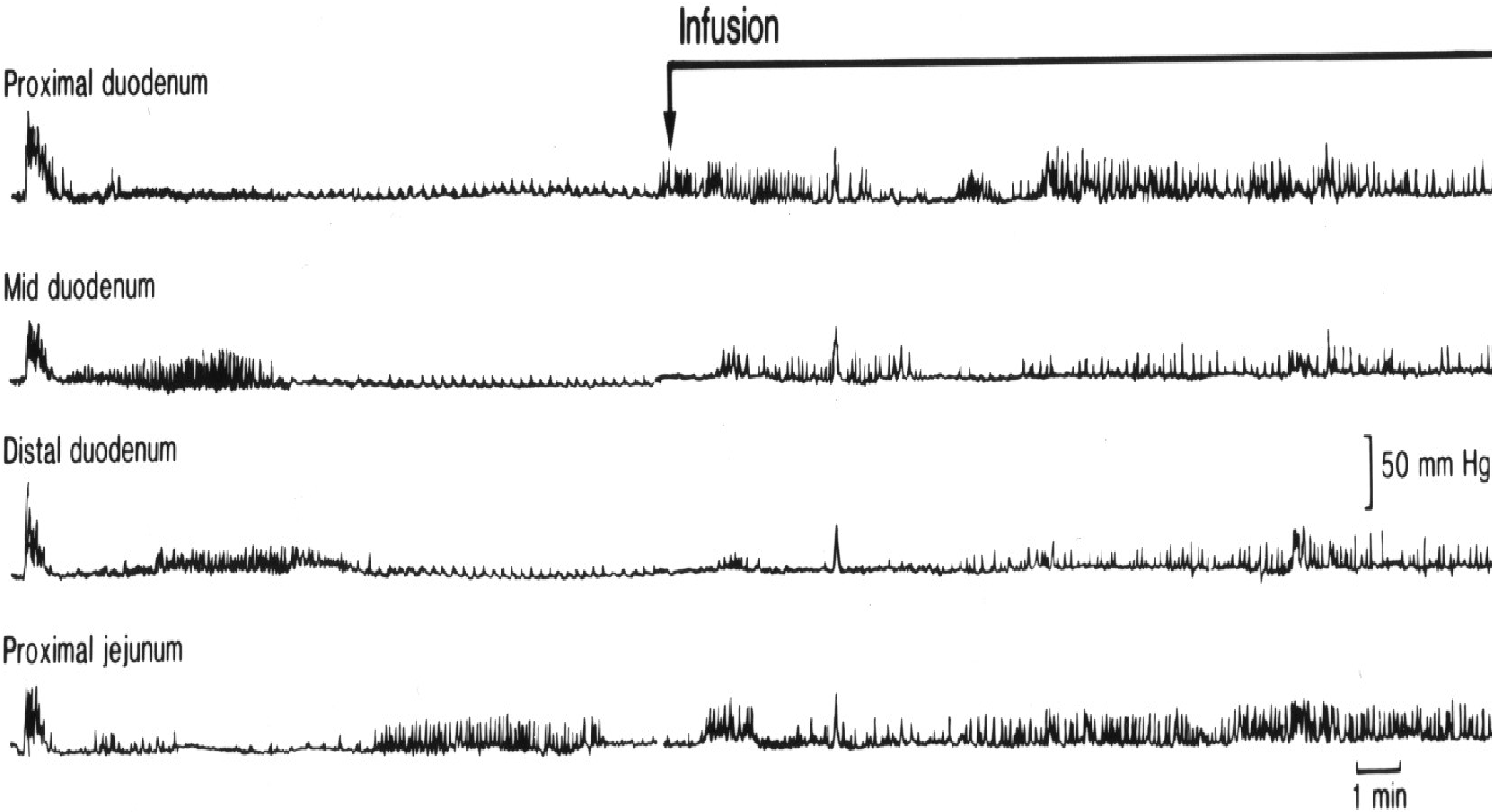
MMC's Absent in an Unfed Infant



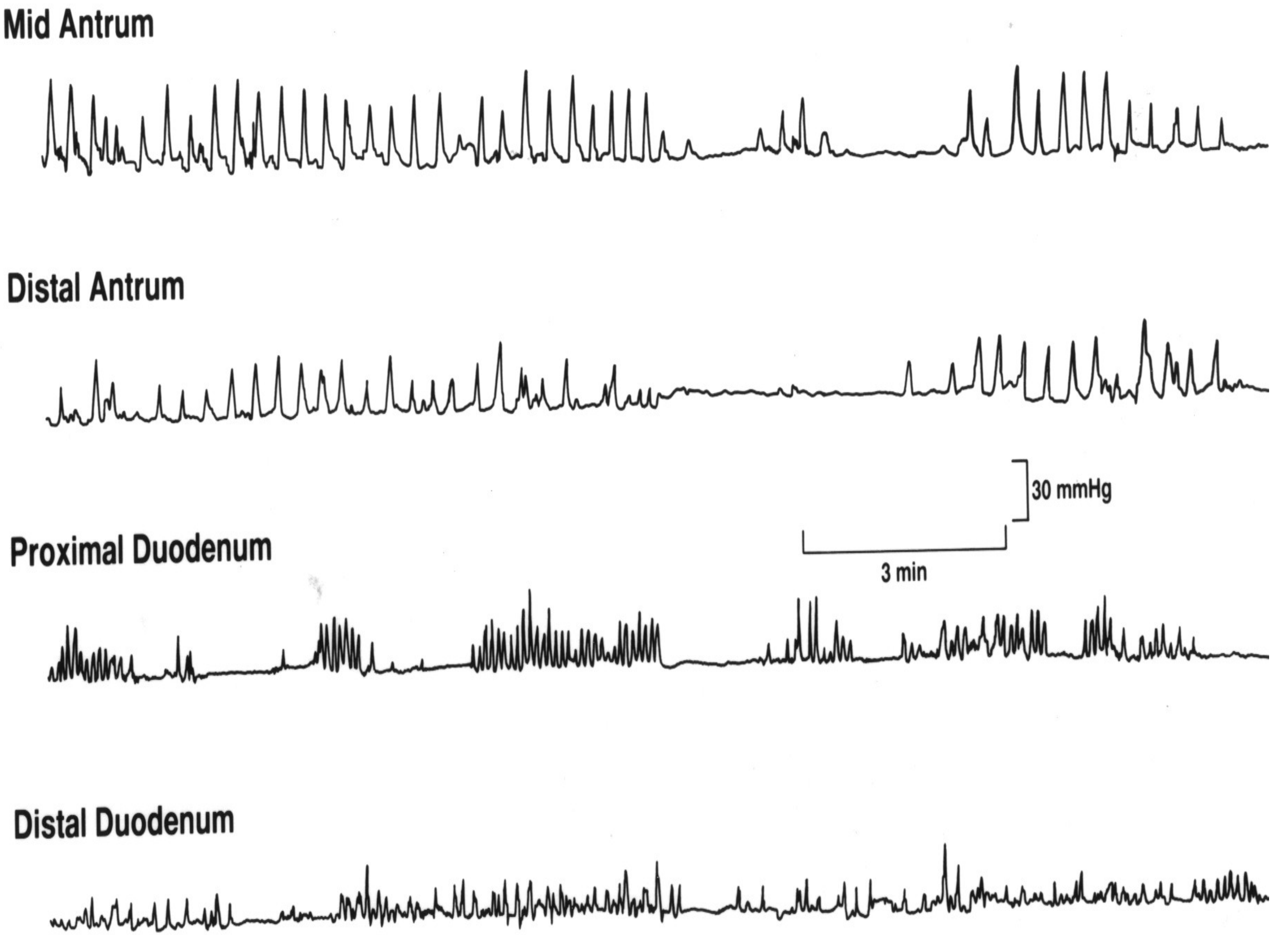
Clinical Outcomes

- When compared to infants fed late, infants fed early
  - Had more mature motor patterns
  - Had higher plasma concentrations of gastrointestinal hormones
  - Reached full enteral feedings sooner
  - Had less feeding intolerance

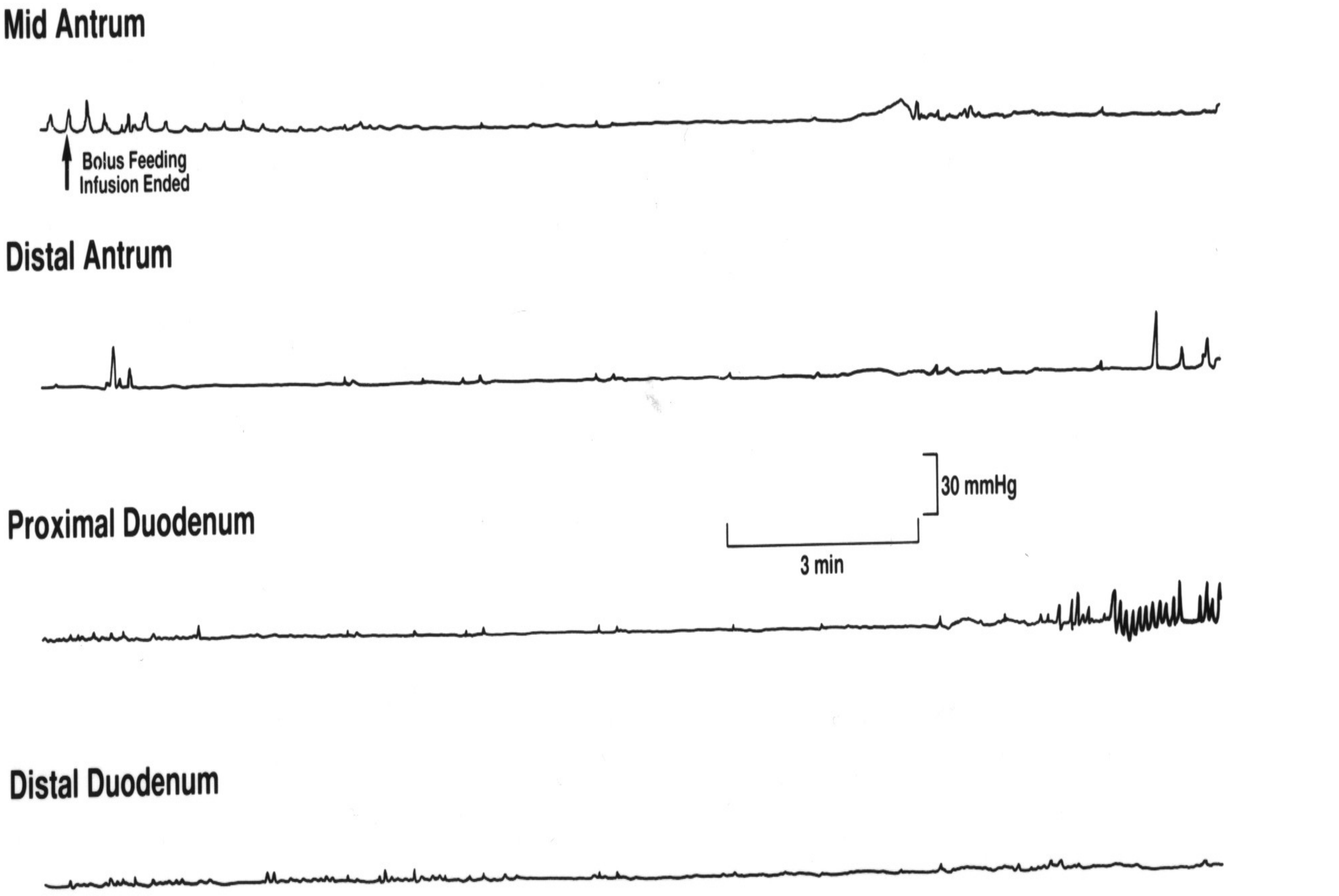
CHANGE IN SMALL INTESTINAL MOTOR ACTIVITY IN A TERM INFANT IN RESPONSE TO INFUSION OF MILK



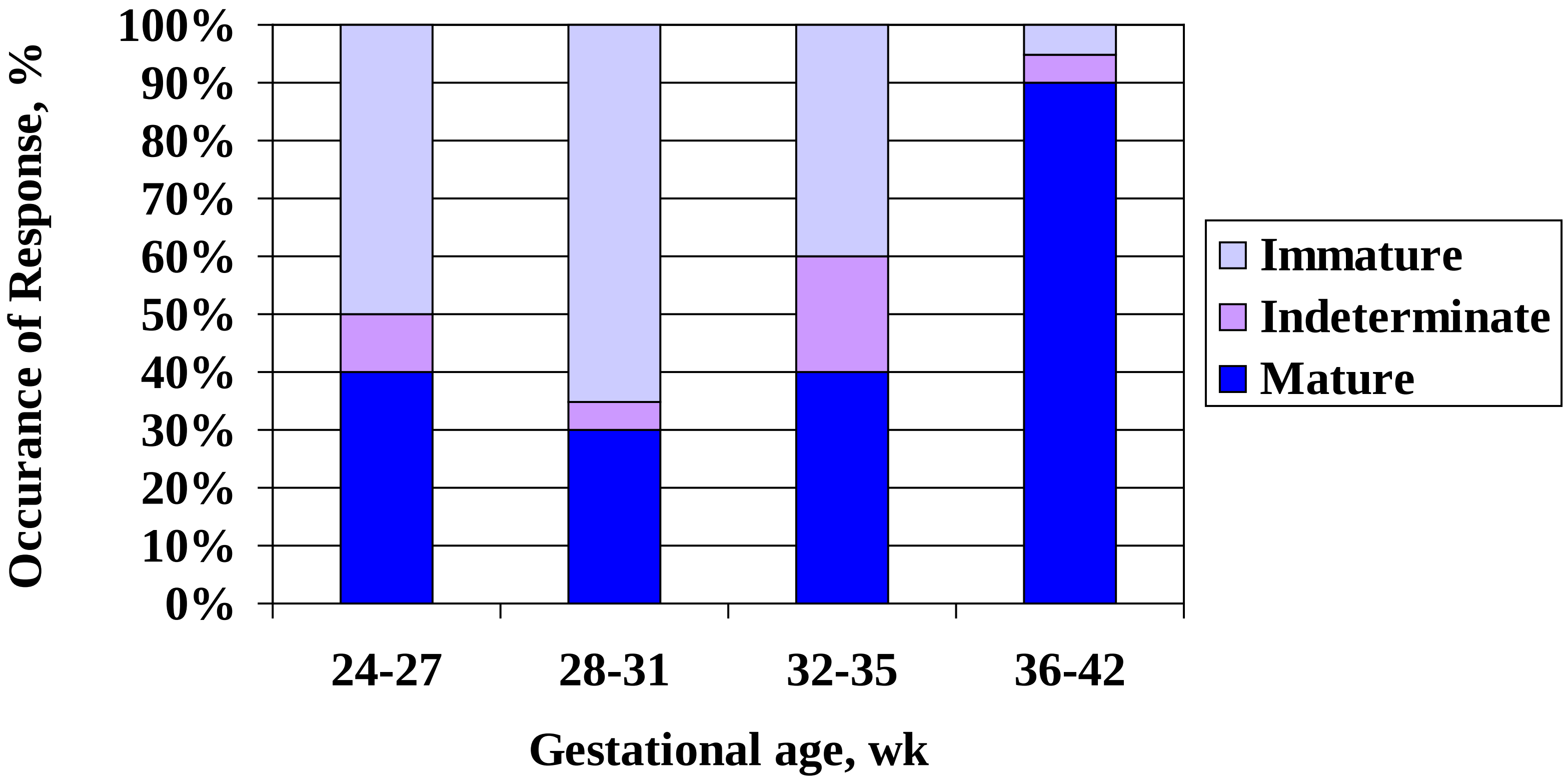
MATURE MOTOR RESPONSE TO FEEDING



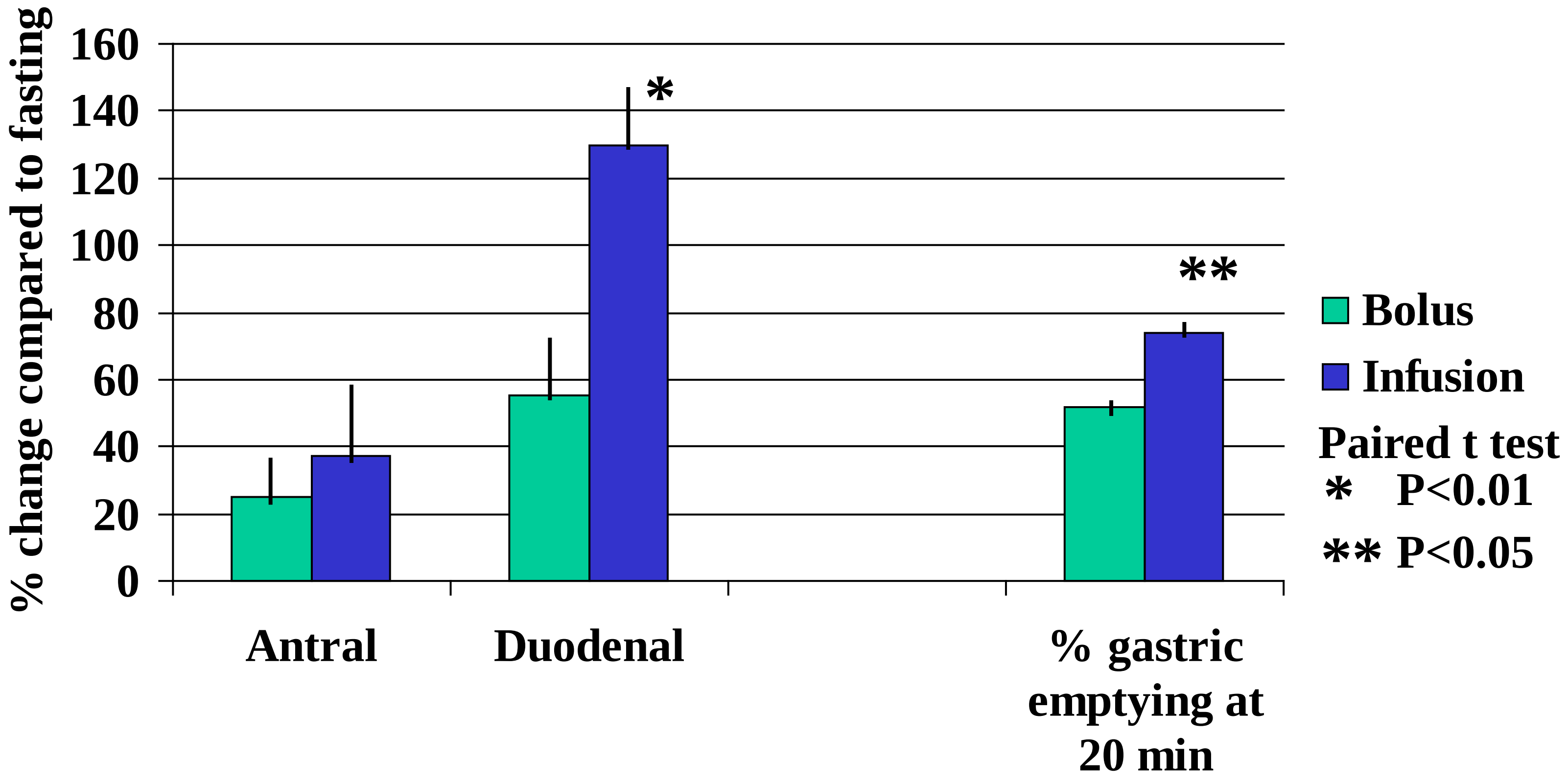
IMMATURE MOTOR RESPONSE TO FEEDING



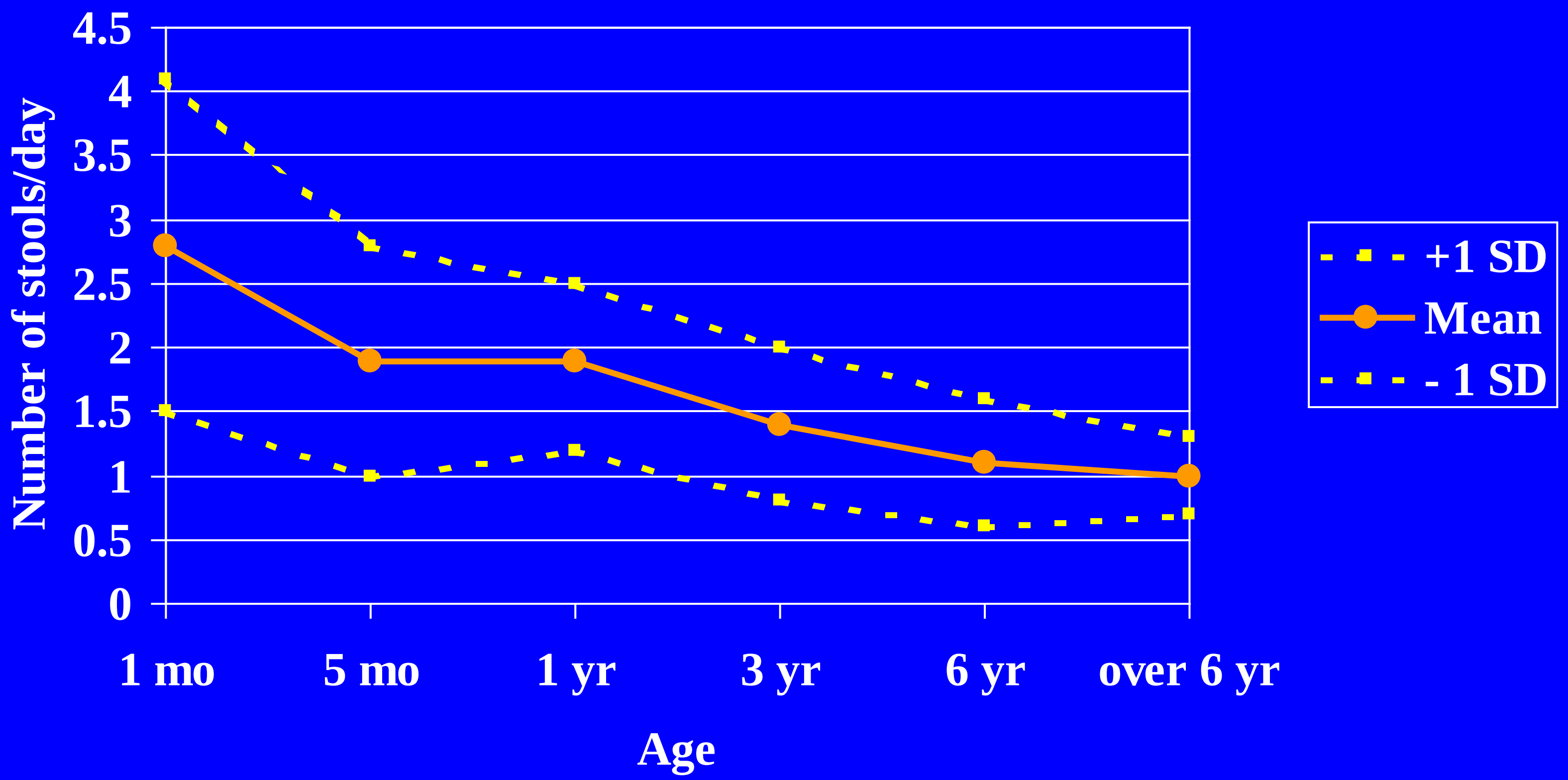
Presence of Motor Response to Feeding in Infants



Changes in Antral and Duodenal Motor Contractions and Gastric Emptying in Response to Feeding



Number of Stools per Day as a Function of Age

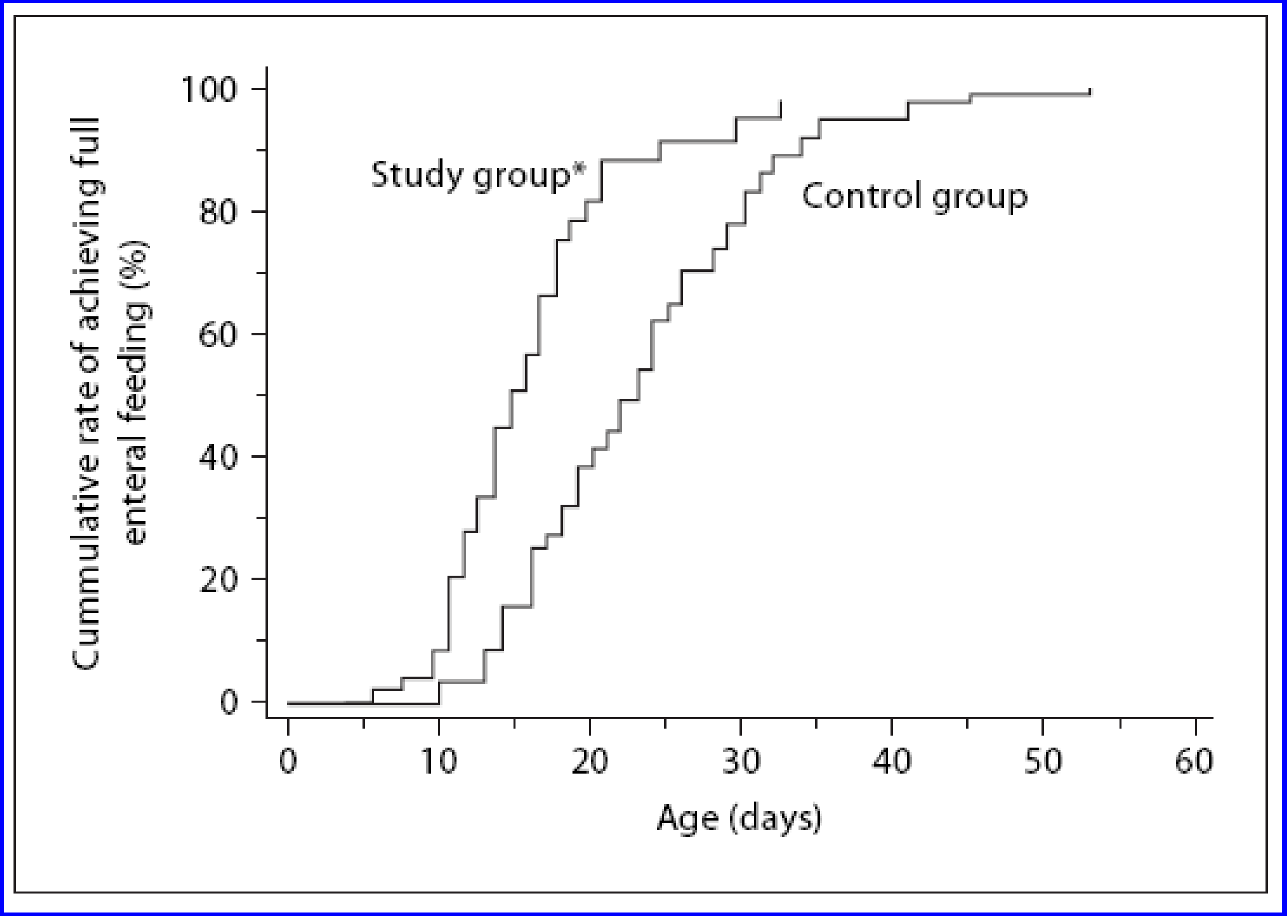


Modified from Fontana, Acta Paediatr Scand 78: 862, 1989

Passage of Meconeum

- Delayed in about 20% of infants with birth weights < 1500 g (Jhaveri, 1987 and Wang, 1994)
- Delayed up to 10 days in infants with birthweights < 1250 g (Meetze, 1993)
- Delay inversely related to gestational age (Weaver, 1993)

Induction of Early Meconium Evacuation Promotes Feeding Tolerance in VLBW Infants



Cumulative rate of achieving full enteral feeding according to the Cox proportional hazard model (* $p < 0.001$).

Shim et al. *Neonatology*. 2007;92:67.

Additional Findings
The Study Group

- Passed meconeum sooner (1.4 vs 3.7 d) $P<.001$
- Had fewer days with central catheter (17.6 vs 24.4 d) $P<.001$
- Lower incidence of sepsis (3 vs 12%) $P=.02$
- More likely to achieve full enteral feedings sooner
  - if <1500 g Hazard ratio 2.9 (1.8 to 4.8 CI)
  - If < 1000 g Hazard ratio 4.6 (1.9 to 11.1 CI)

Shim Neonatology 92: 67, 2007

Take Home Messages

- Maturation of intestinal absorptive function progresses throughout fetal life and early infancy
- Maturation of motor function progresses throughout fetal life and infancy
- Feeding problems may be related to immaturity of either or both
- Adaptation of feeding practices and/or nutrient content may optimize immature intestinal function