Core Lecture:
Colorectal Motility Disorders

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Colorectal Motility Disorders

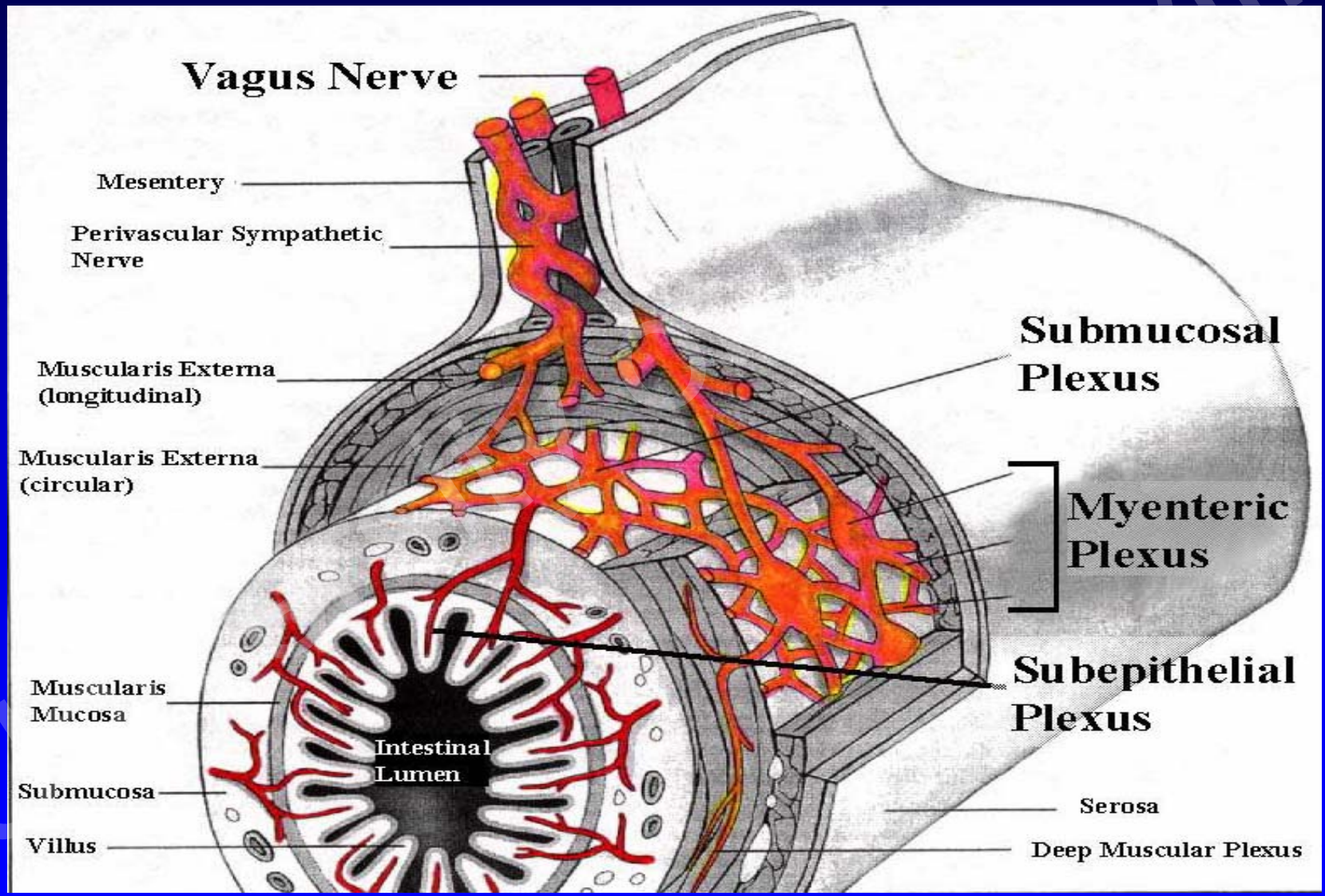
- Normal anatomy and physiology
- Diagnostic evaluation
- Common colorectal motility disorders
  - Irritable bowel syndrome
  - Constipation
    - Colonic inertia
    - Obstructive defecation
  - Fecal incontinence

Differences in the GI Tract

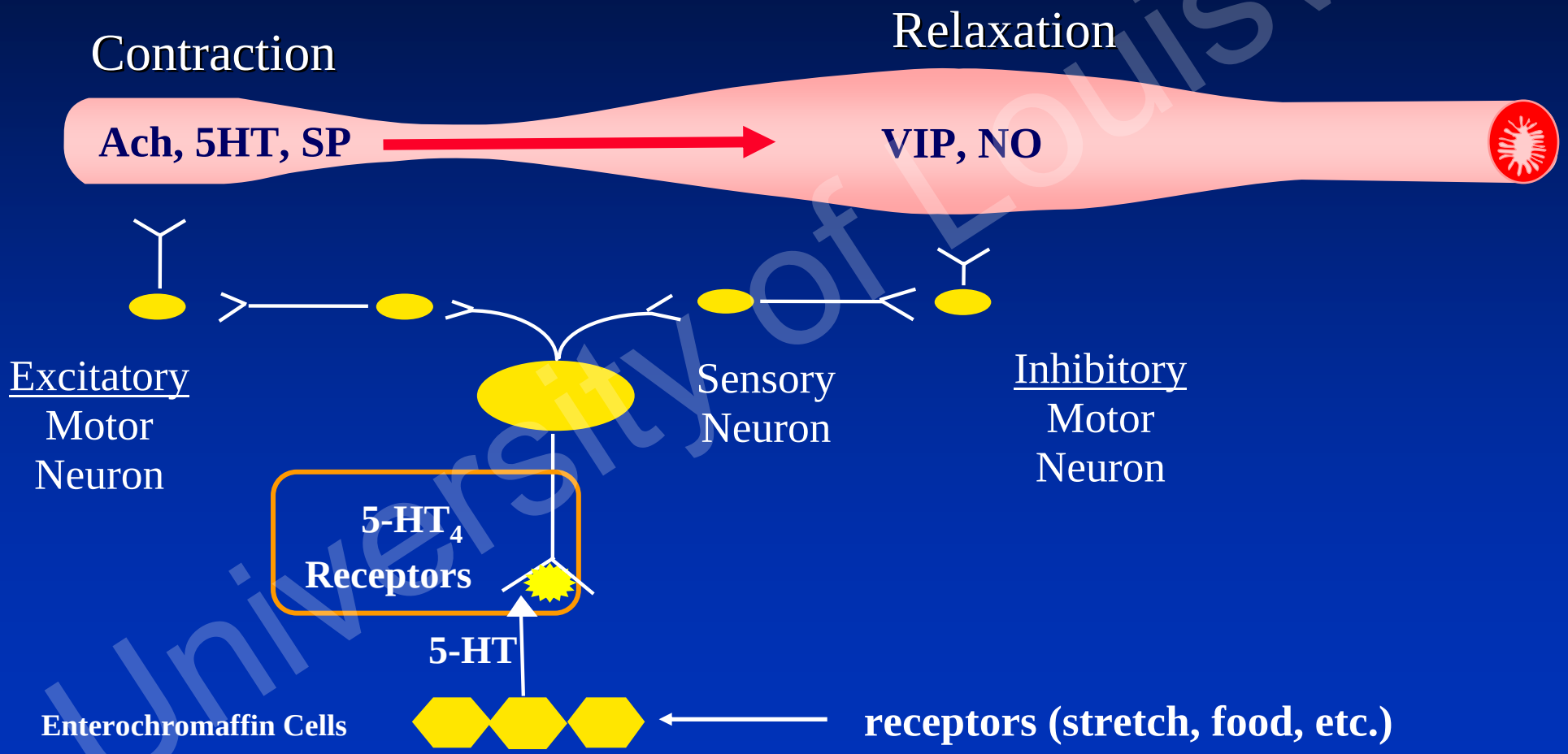
	Embryonic origin	ANS dependence	ENS dependence
Oropharynx to mid duod.	Foregut	+++	++
Small bowel to prox. colon	Midgut	++	+++
Colon to rectum	Hindgut	+	+++

ANS (autonomic nervous system); ENS (enteric nervous system)

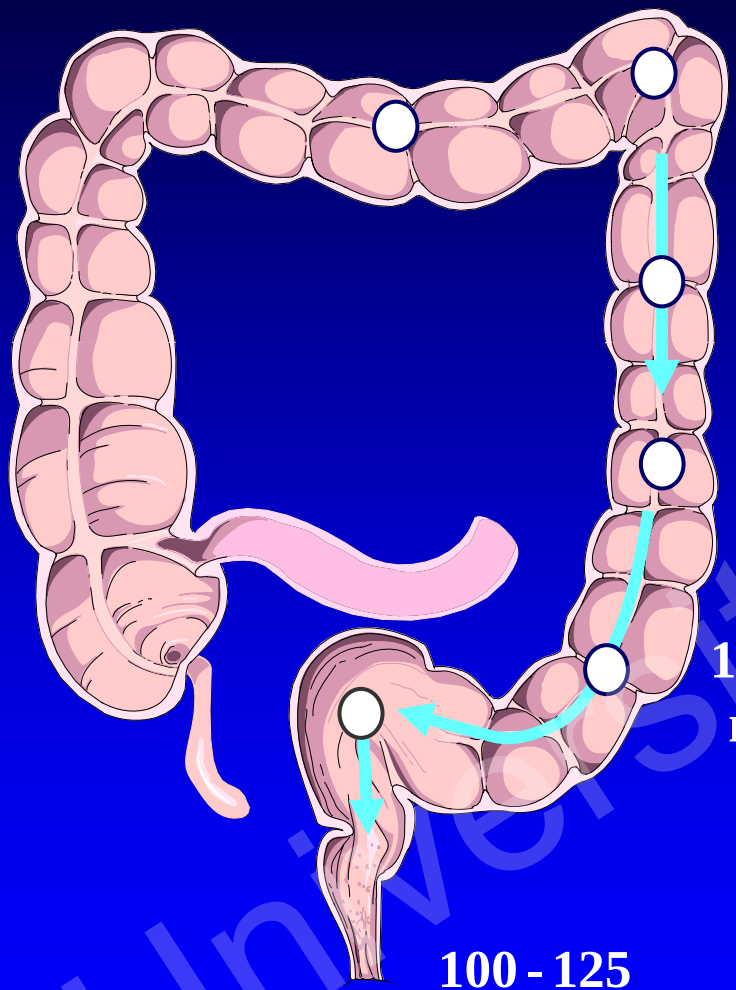
Enteric Nervous System (ENS)



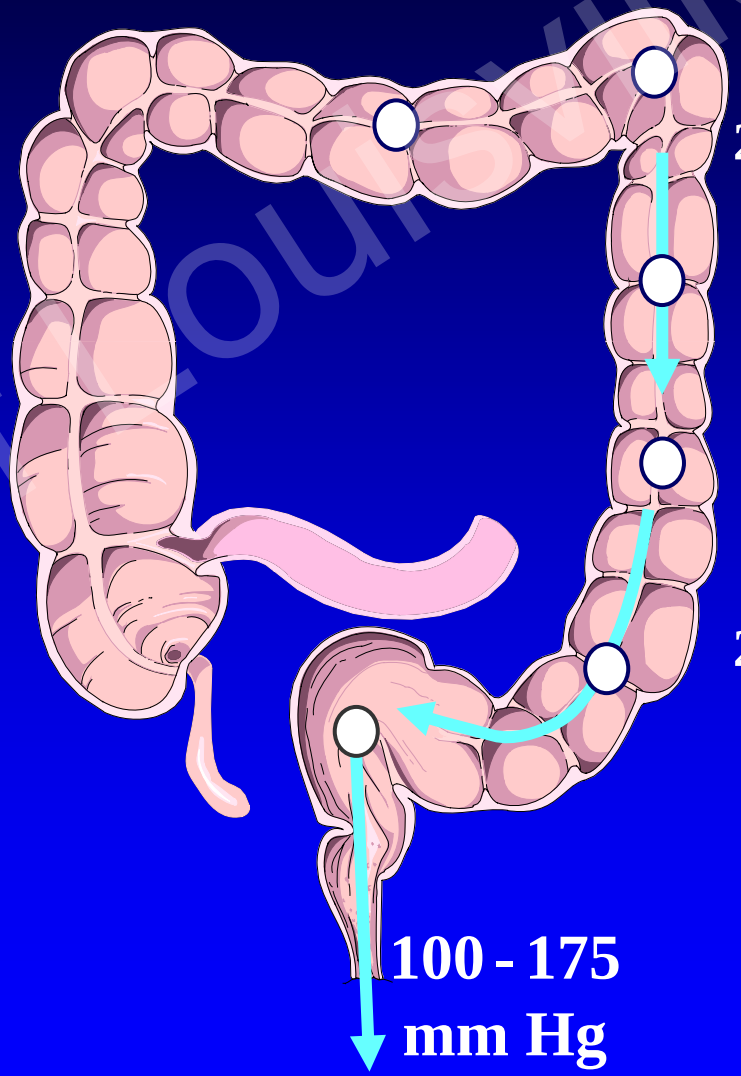
Enteric Nervous System: Peristalsis



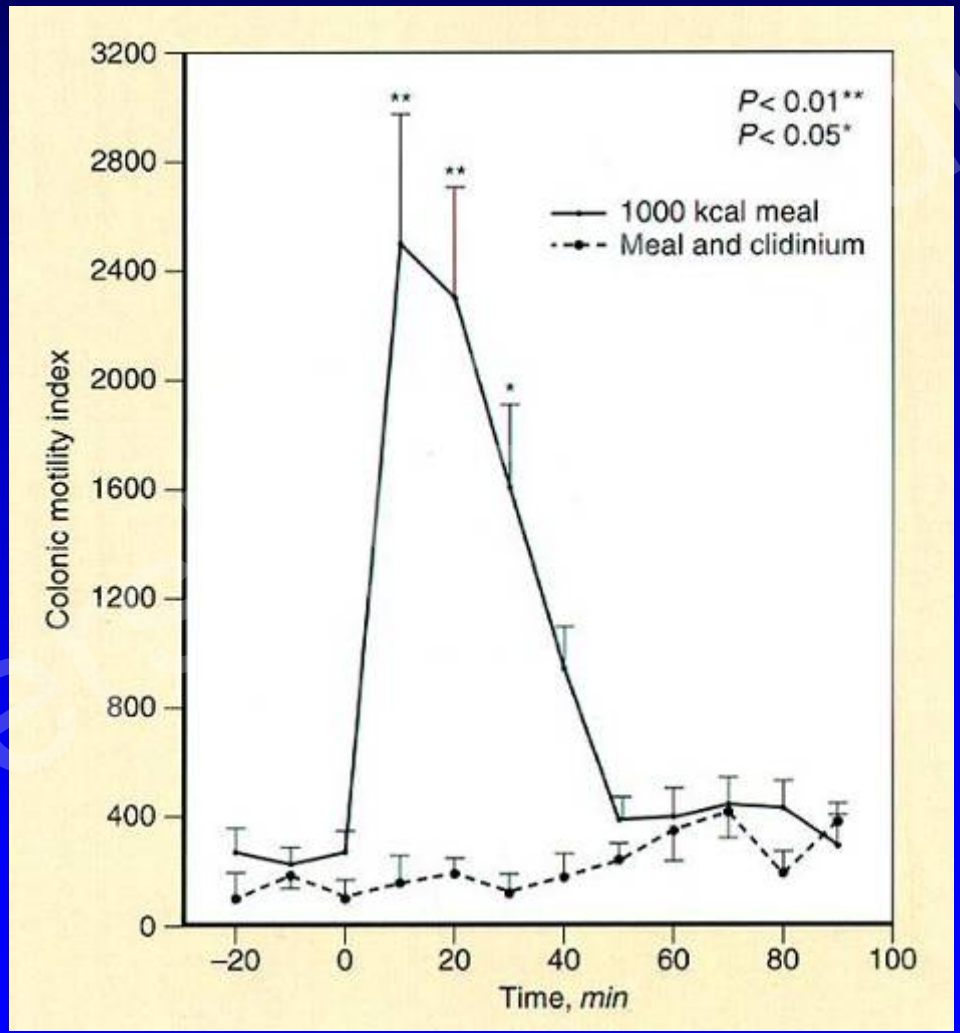
Normal



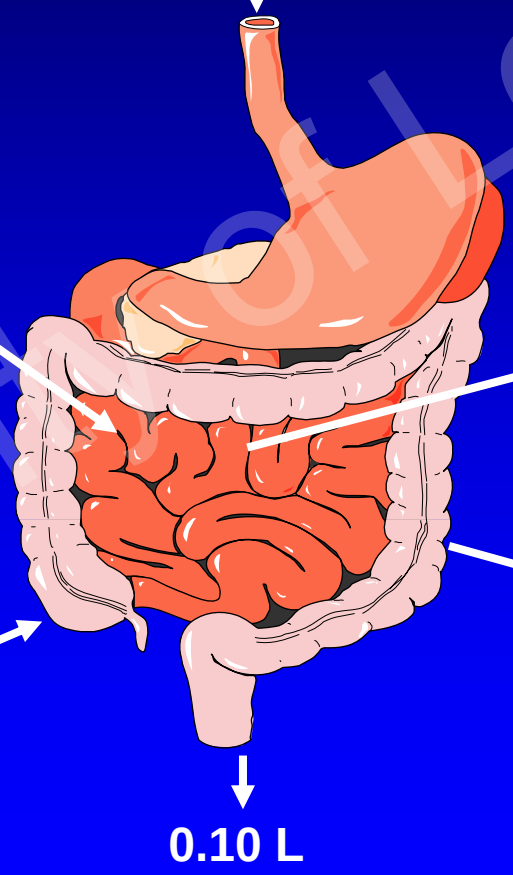
Irritable Bowel Syndrome



Gastro-Colonic Reflex



Daily Intestinal Fluid Balance



SECRETION

Endogenous secretions

Saliva	1.5 L
Stomach	2.5 L
Bile	0.5 L
Pancreas	1.5 L
Intestines	1.0 L
Total	~ 7.0 L

2 L Dietary intake

ABSORPTION

Small intestine absorbs ~ 7.0 L

2L enters the colon

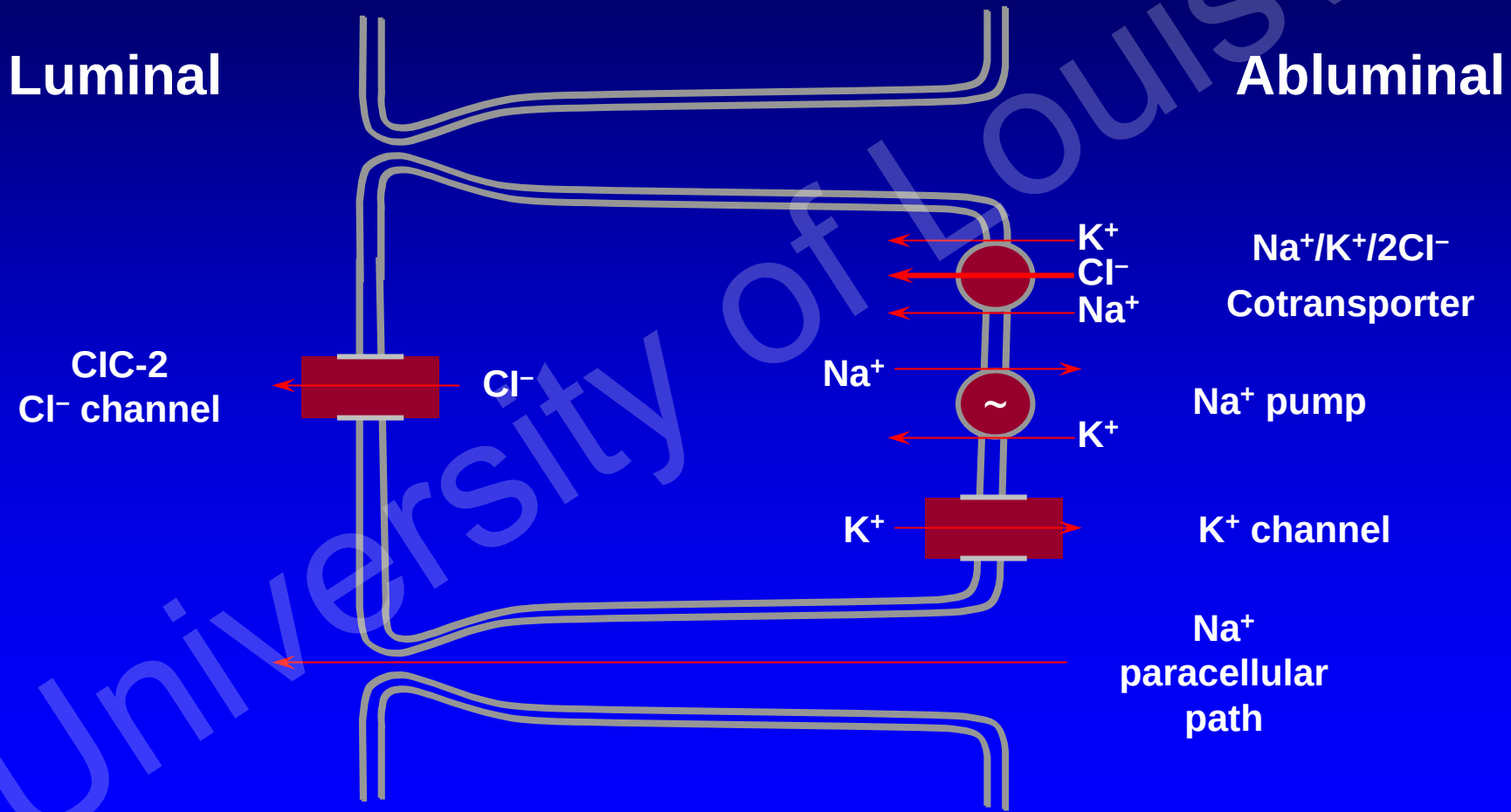
Colon and rectum absorb ~ 1.9 L

Total ~ 9.0 L

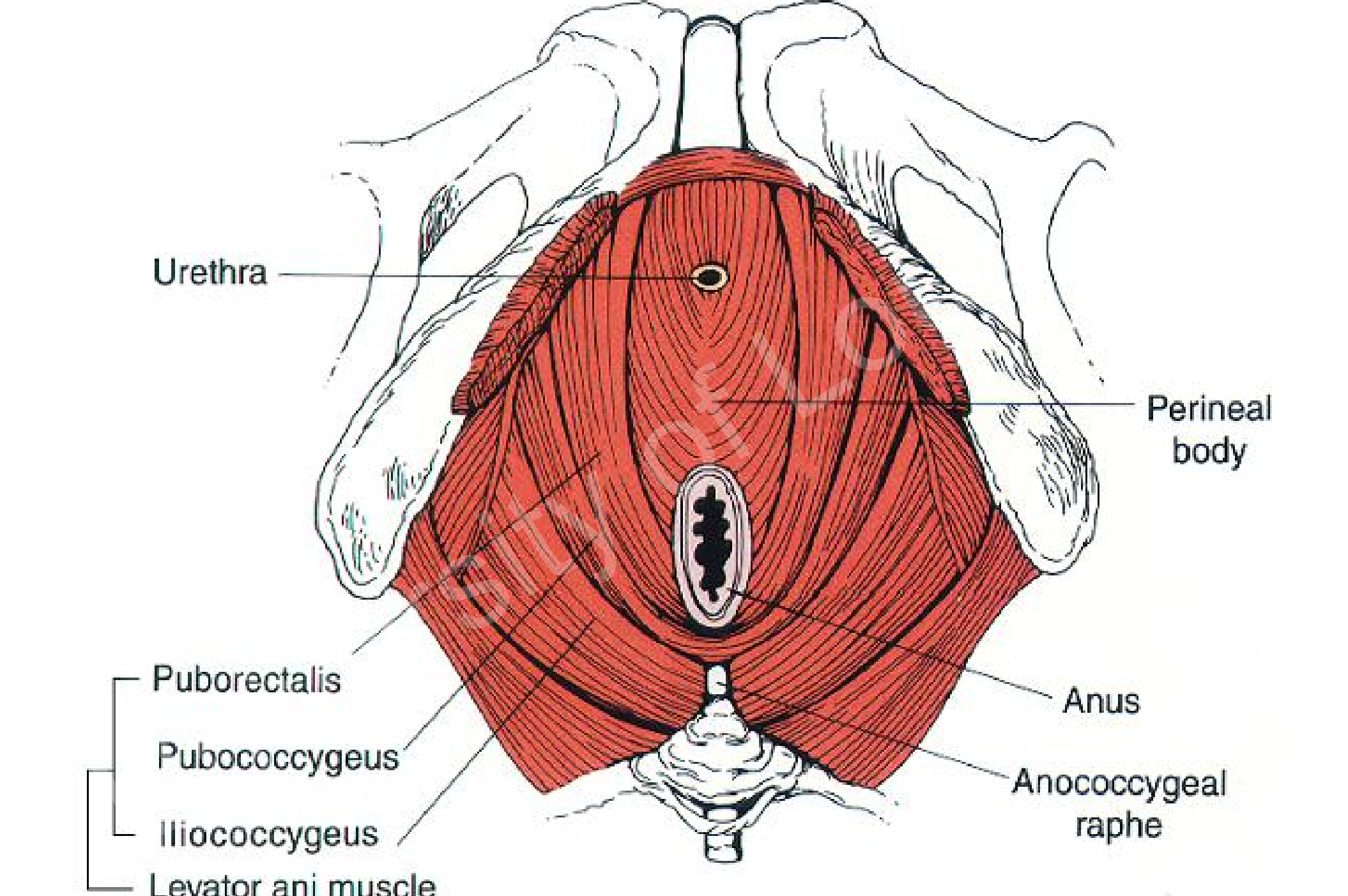
0.10 L

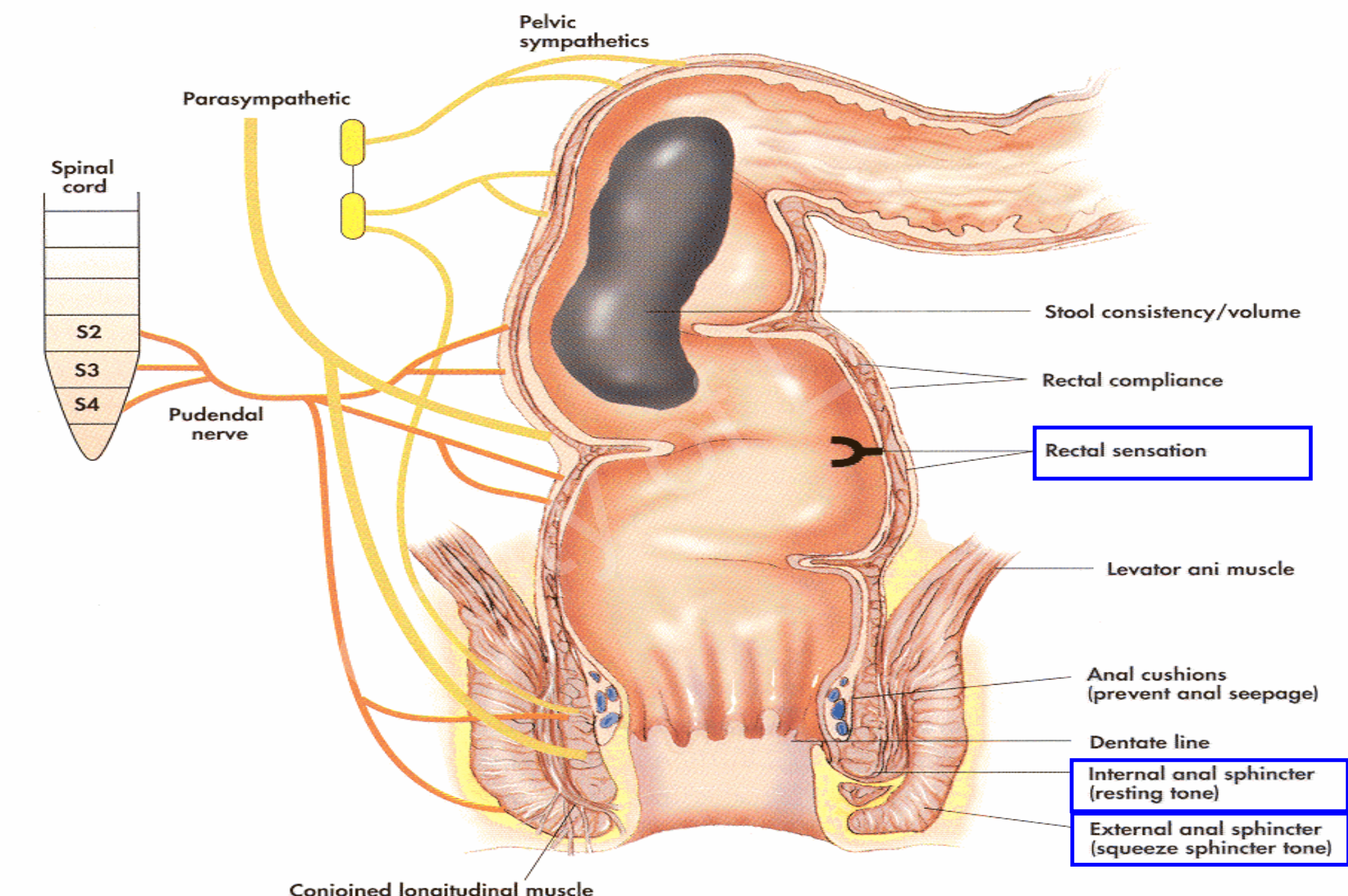
Data from Montrose MH, et al. In: *Textbook of Gastroenterology*. 3rd ed. 1999;1:320-355.

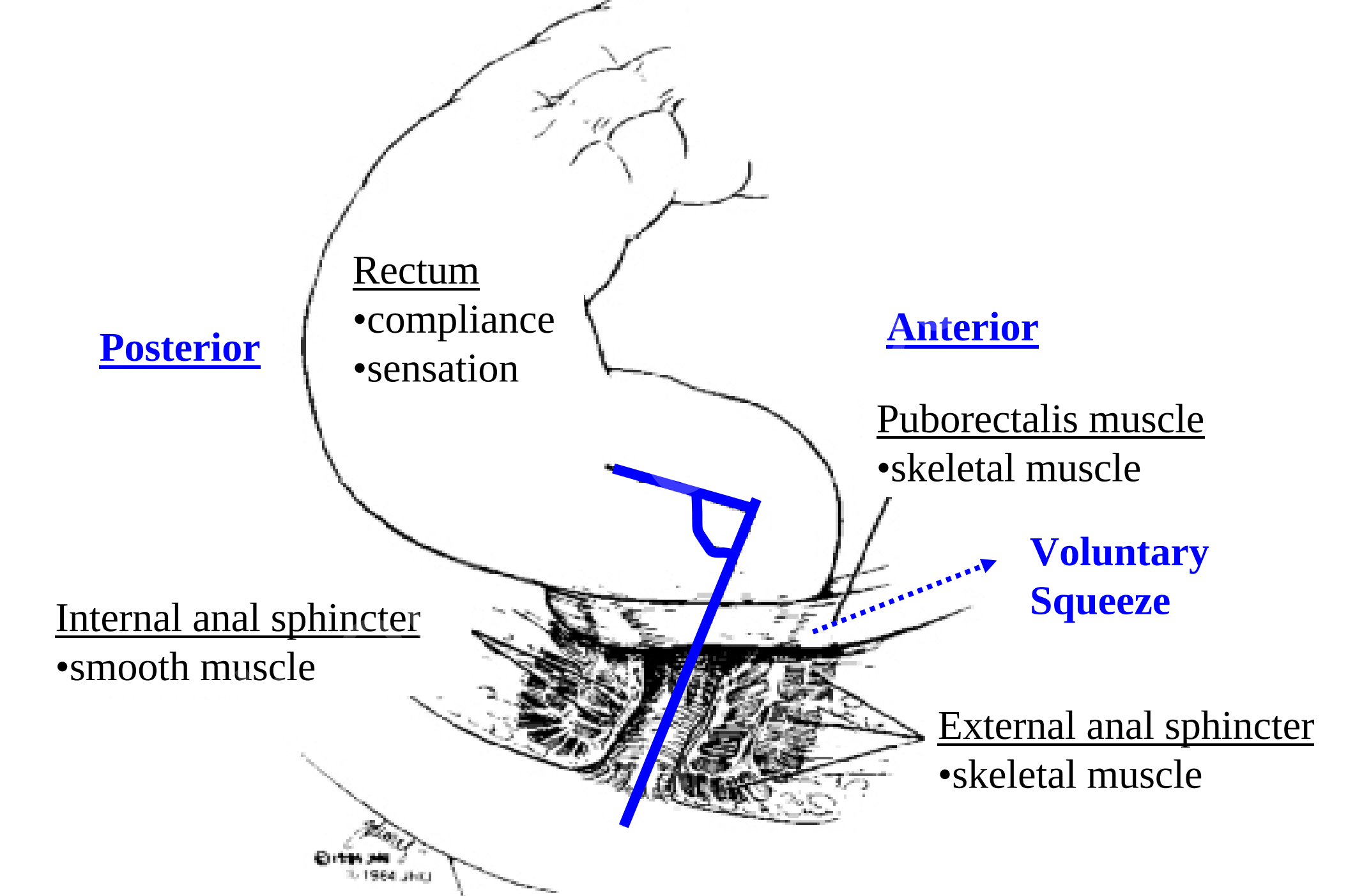
Intestinal Expression of ClC-2 Chloride Channels



Adapted from Cuppoletti J, et al. *Am J Physiol Cell Physiol*. 2004;287:C1173-C1183.


Urethra
Perineal body
Puborectalis
Pubococcygeus
Iliococcygeus
Levator ani muscle
Anus
Anococcygeal raphe


Pelvic sympathetics
Parasympathetic
Spinal cord
S2
S3
S4
Pudendal nerve
Stool consistency/volume
Rectal compliance
Rectal sensation
Levator ani muscle
Anal cushions (prevent anal seepage)
Dentate line
Internal anal sphincter (resting tone)
External anal sphincter (squeeze sphincter tone)
Conjoined longitudinal muscle


Rectum
•compliance
•sensation
Posterior
Anterior
Puborectalis muscle
•skeletal muscle
Voluntary
Squeeze
Internal anal sphincter
•smooth muscle
External anal sphincter
•skeletal muscle

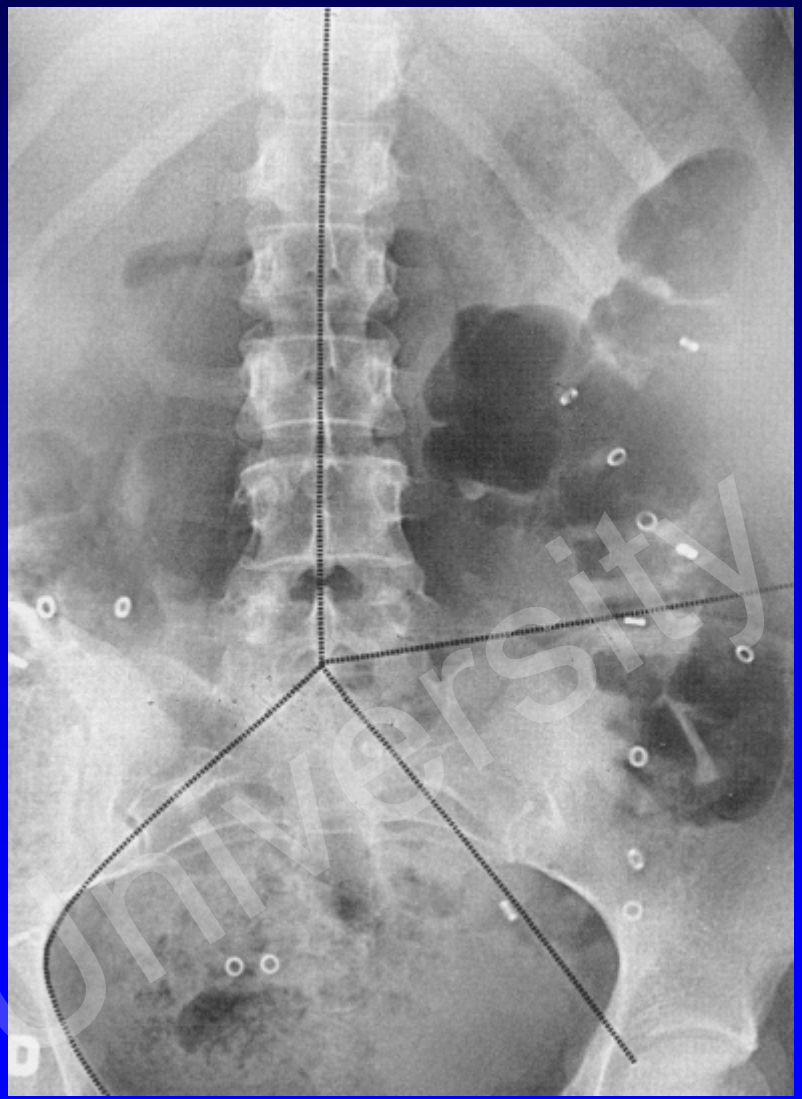
Diagnostic Evaluation

- Colon
  - Colonic Sitzmarkers
  - Smart Pill transit
  - Barium enema
  - Colonic manometry
- Rectum and Pelvic Floor
  - Anorectal manometry
  - Anal EMG
  - Anal ultrasound
  - Pudendal nerve testing (St. Marks test)
  - Defecating proctogram
  - Pelvic functional MRI

Radiopaque Transit Markers

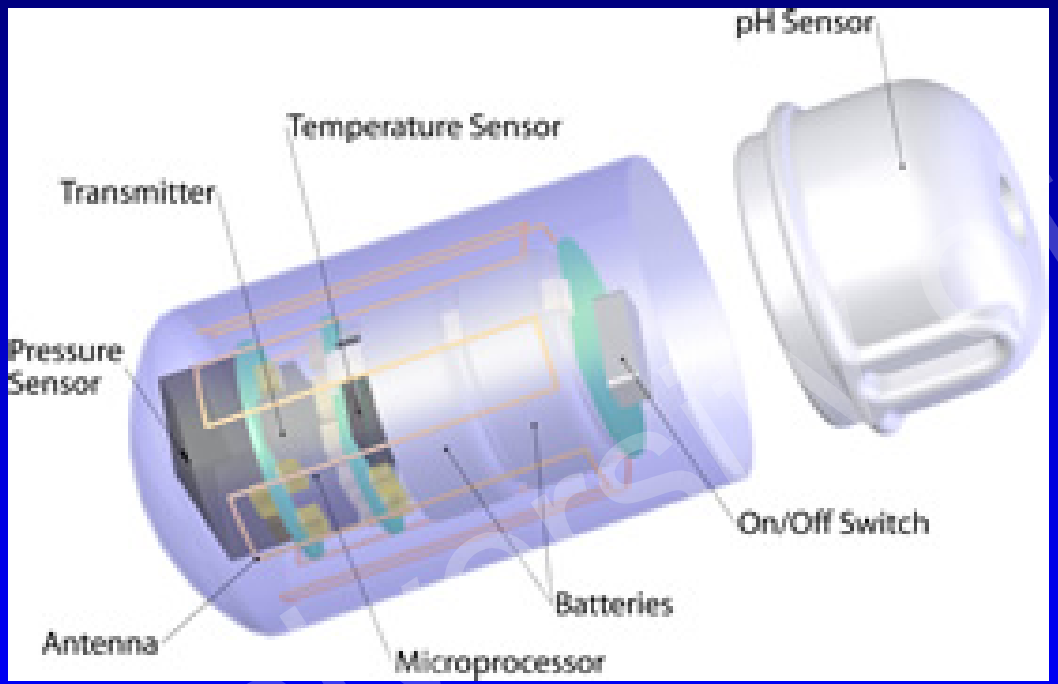
- *Sitzmark* capsule
  - 24 markers in capsule
  - Avoid laxatives
  - Abdominal x-ray
    - Normal: day 5 (≤4 markers), day 7 (none)

Colonic Inertia



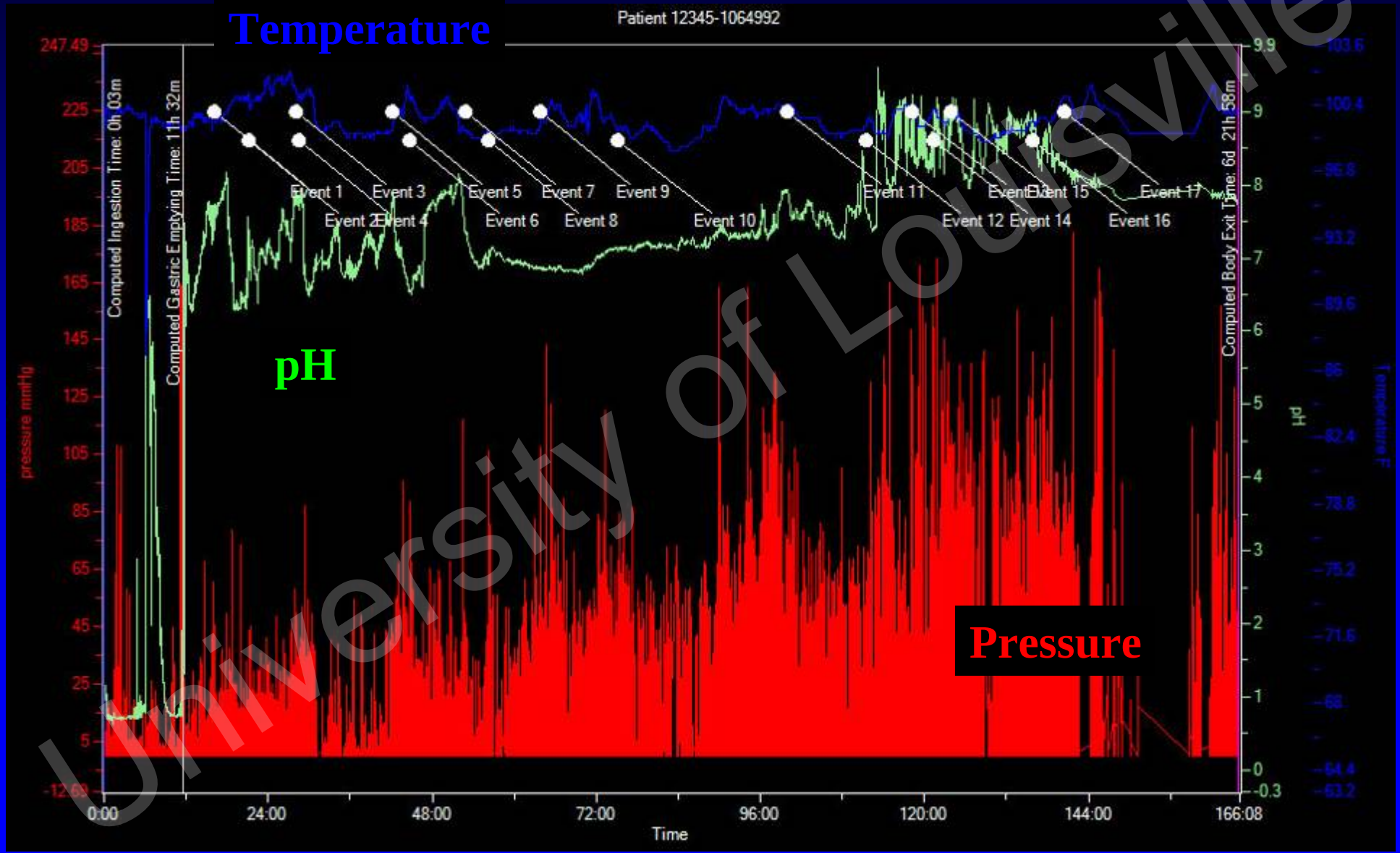
Obstructive Defecation

Case Presentation (cont.)



- Patient underwent Smartpill® Wireless Capsule:
  - Pressure
  - pH
  - Temperature

SmartPill (Whole Gut)



Test Summary

Clinical Data | Descriptive Data | Properties

Patient Information

Patient Name		ID	1064992	Test Date	9/7/2007

Transit Times (hr:min)

Computed Transit Times		Physician Defined Transit Times	
Gastric Emptying Time (greater than 4.0 hours suggests delay)	11:28	Gastric Emptying Time	n/a
Small/Large Bowel Transit Time	154:25	Small/Large Bowel Transit Time	n/a
Total GI Transit Time (normal male: 26hrs 24min) (normal female: 35hrs 24min)	165:54	Total GI Transit Time	n/a

Event Times

	Computed		Physician Defined	
	Clock Time	Elapsed Time	Clock Time	Elapsed Time
Capsule Ingested at:	9/7/2007 4:40 PM	0:03	n/a	n/a
Capsule Left Stomach at:	9/8/2007 4:09 AM	11:32	n/a	n/a
Capsule Left Body at:	9/14/2007 2:35 PM	165:58	n/a	n/a

Gastric pH Values

High	6.5
Low	0.6

Close

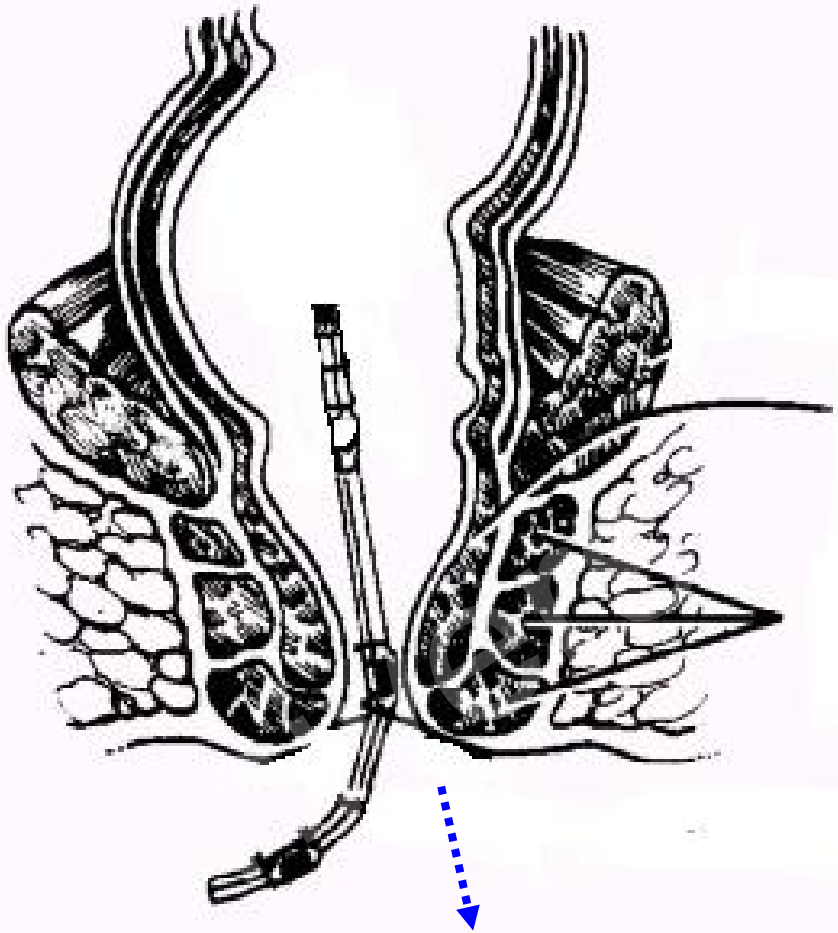
Indications for Anorectal Manometry

- Fecal incontinence
- Fecal urgency
- Unexplained diarrhea
- Symptoms of obstructive defecation
- Pre-op subtotal colectomy for severe colonic inertia

Different Methods to Perform Anorectal Manometry

- Manometry catheter
  - Solid-state, water-perfusion, air-coupled
- Methods
  - Stationary, station pull through, rapid through
- Pressure sensors
  - Vector, circumferential, high-definition manometry

Anorectal Manometry: Station Pull-Through Technique



Internal anal sphincter

External anal sphincter

Resting pressure:
70-85% of IAS

Squeezing pressure:
70-85% of EAS


Polygram 98
File Go Insert Tools Help
HOME
STUDIES
PATIENTS
PROTOCOLS
EQUIPMENT
PERSONNEL
ARCHIVES
AFT - [ARM 9/29/2005 13:24]
STUDY DETAILS
EQUIPMENT
CAPTURE
REVIEW
REPORT
PROTOCOL
Markers
AIR
Sensory Threshold
Stimulation Pull
Tools
Text
Re(5)
Sq(5)
Posterior
Right
Anterior
Left
mmHg
2.0
1.0
150
100
50
0
Resting Pressure
Squeezing Pre...
00:02:20
00:02:30
00:02:40
00:02:50
00:03:00
Start
11:48 AM

File Go Help

HOME | STUDIES | PATIENTS | PROTOCOLS | EQUIPMENT | PERSONNEL | ARCHIVES

AFT - [ARM 9/29/2005 13:24]

- STUDY DETAILS
- EQUIPMENT
- CAPTURE
- REVIEW
- REPORT
- PROTOCOL

Comments and Interpretation

Equipment Used
4 ch radial anorectal [Polygraf ID]

Protocol Comments

ARM - Fixed Position Catheter Results

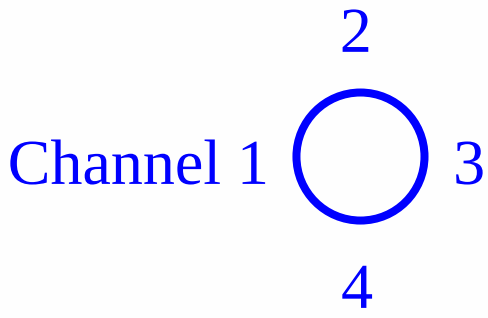
ARM - Station Pull Results

Mean Resting Pressure

Location (cm)	Channel 1 Posterior mmHg	Channel 2 Right	Channel 3 Anterior	Channel 4 Left
6.0	1.1	2.2	9.9	5.5
5.0	1.0	0.8	2.0	2.2
4.0	4.4	3.7	5.9	1.5
3.0	19.7	12.7	8.3	15.7
2.0	45.7	50.9	28.4	43.2
1.0	49.5	58.5	49.9	55.3
0.0	3.7	8.6	6.4	14.5

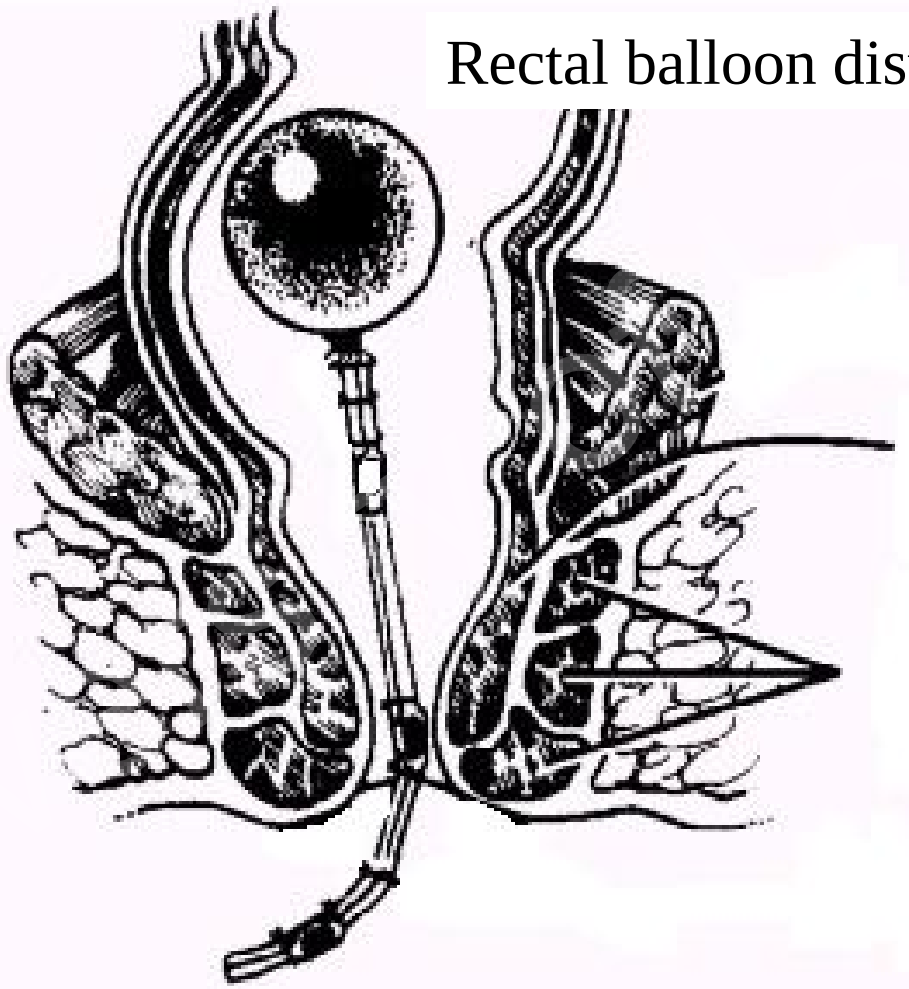
Pressure Increase during Squeeze

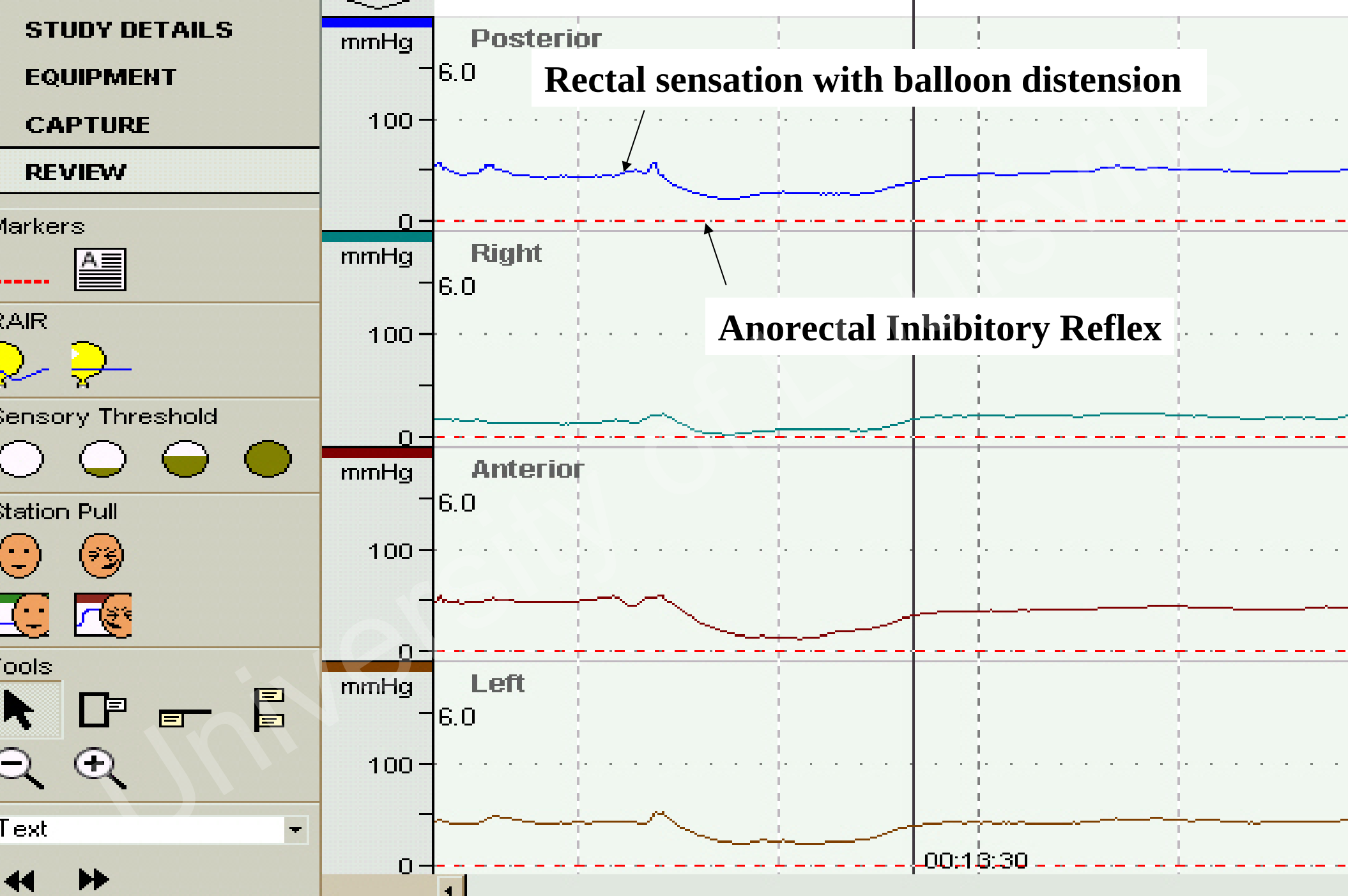
Location (cm)	Channel 1 Posterior mmHg	Channel 2 Right	Channel 3 Anterior	Channel 4 Left
6.0	38.1	42.4	33.5	26.6
5.0	31.5	31.7	36.8	33.6
4.0	76.1	66.2	62.7	77.5
3.0	119.7	82.4	55.0	86.8
2.0	150.7	172.2	133.1	154.2
1.0	146.5	173.4	158.8	161.2
0.0	18.2	22.9	17.8	33.2



Start | Polygram 98 | ARM tracing - Paint | 11:52 AM

Anorectal Manometry




STUDY DETAILS
EQUIPMENT
CAPTURE
REVIEW
Markers
AIR
Sensory Threshold
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ools
Text
mmHg
Posterior
6.0
100
0
Rectal sensation with balloon distension
mmHg
Right
6.0
100
0
Anorectal Inhibitory Reflex
mmHg
Anterior
6.0
100
0
mmHg
Left
6.0
100
0
00:18:30

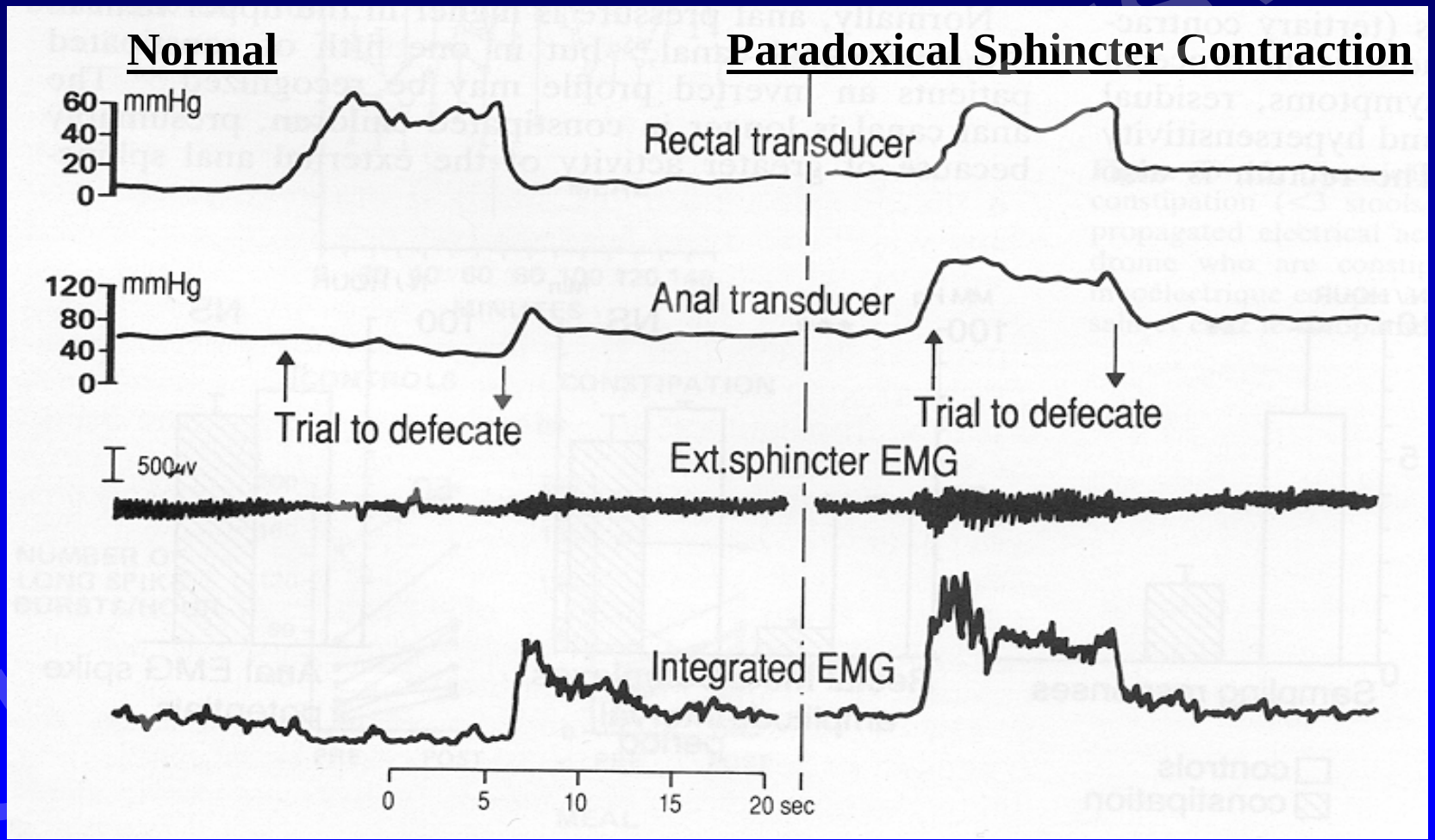
Anorectal Manometry

- Useful to identify functional defect
  - Resting pressure: approx 80% external anal sphincter
  - Squeeze pressure: approx 80% internal anal sphincter
  - Balloon sensation: sensory
  - Recto-anal inhibitory reflex: reflex relaxation
- Can direct therapy
  - Kegel exercises and biofeedback
  - Surgical repair

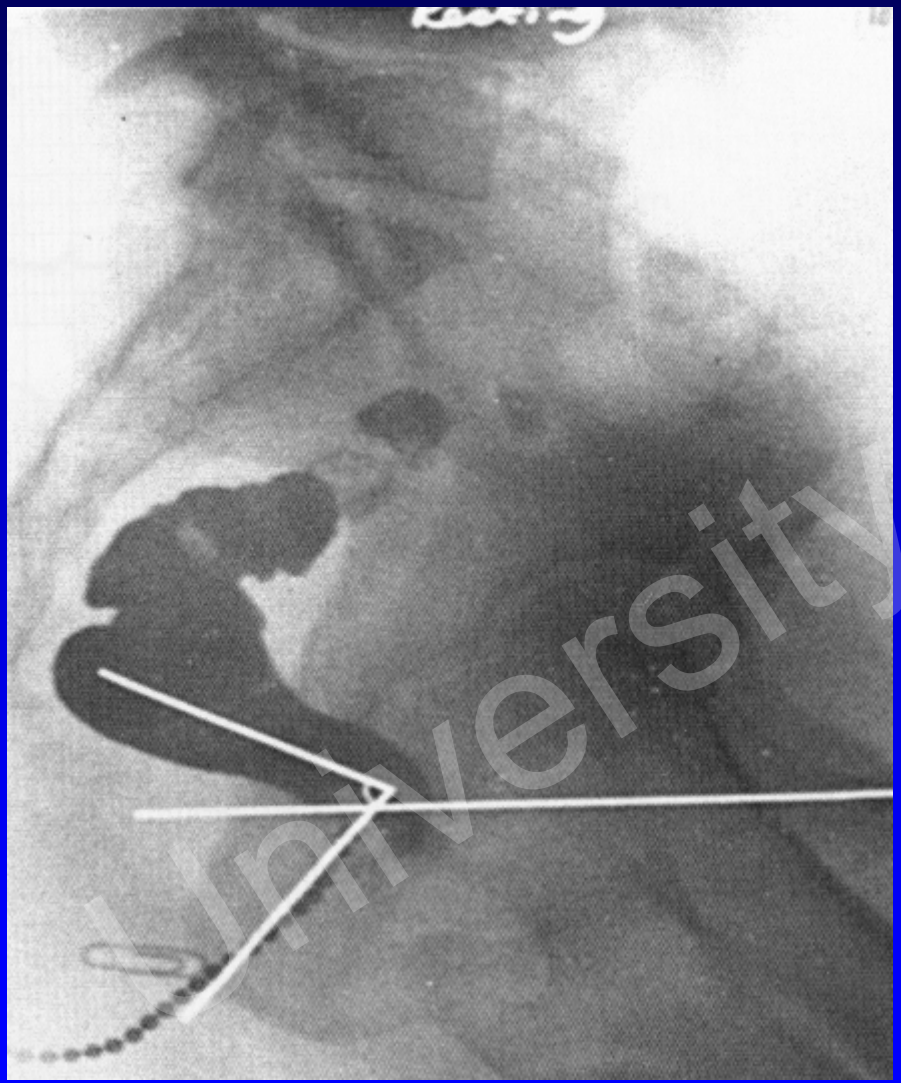
Anorectal Manometry

	Measurement	Disease states
Resting pressure	– 70-85% internal anal sphincter – parasympathetic motor (S2-S4)	Diabetes, autonomic neuropathy
Squeeze pressure	–70-85% external anal sphincter –pudendal motor (S2-S4)	OB trauma, excessive straining, perineal descent
Rectal sensation threshold	–central & spinal sensory –parasympathetic sensory (S2-S4)	Spinal cord injury, multiple sclerosis, caudal equina
Anorectal inhibitory reflex	– sphincter relaxation reflex with balloon distension – myenteric plexus	Hirschsprung

Anorectal Manometry and EMG in Paradoxical Sphincter Contraction

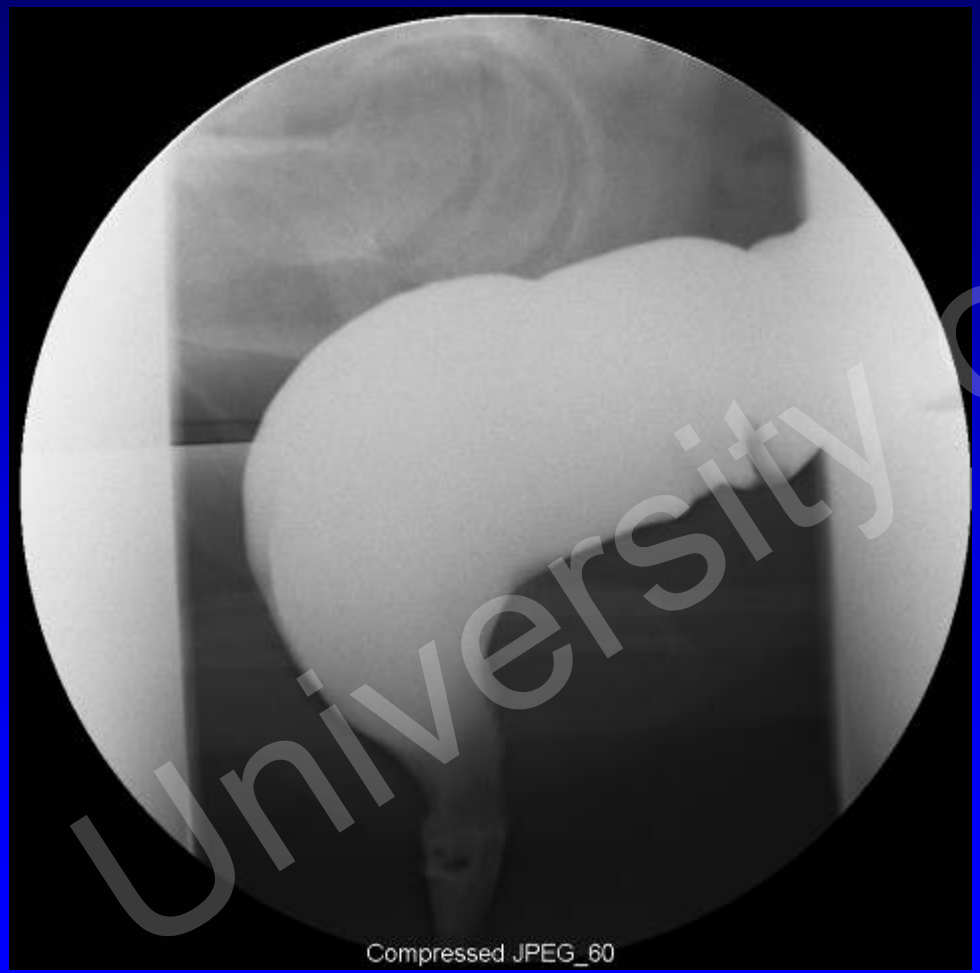


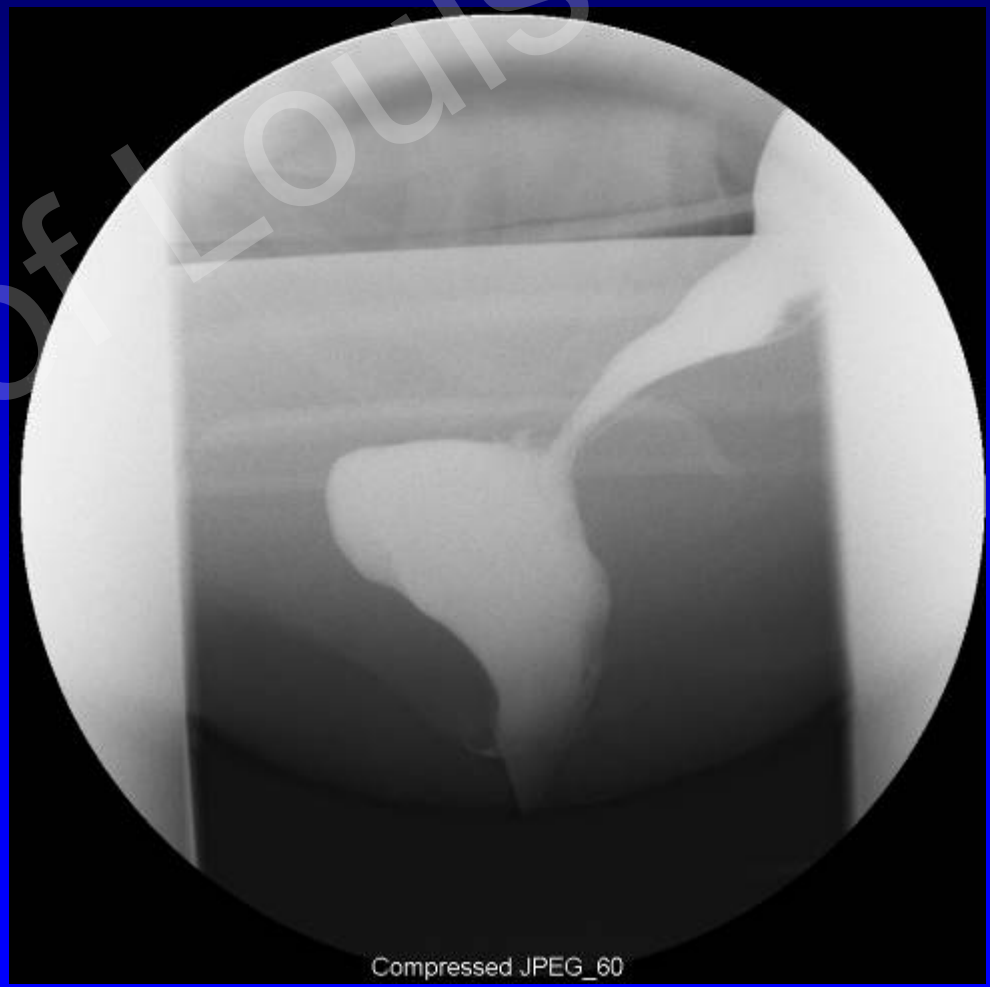
Defecating Proctogram



- To look for anatomical defect in pelvic floor
- Operator dependent
- May not be physiologic
- Clinical correlation is needed for anatomic defect

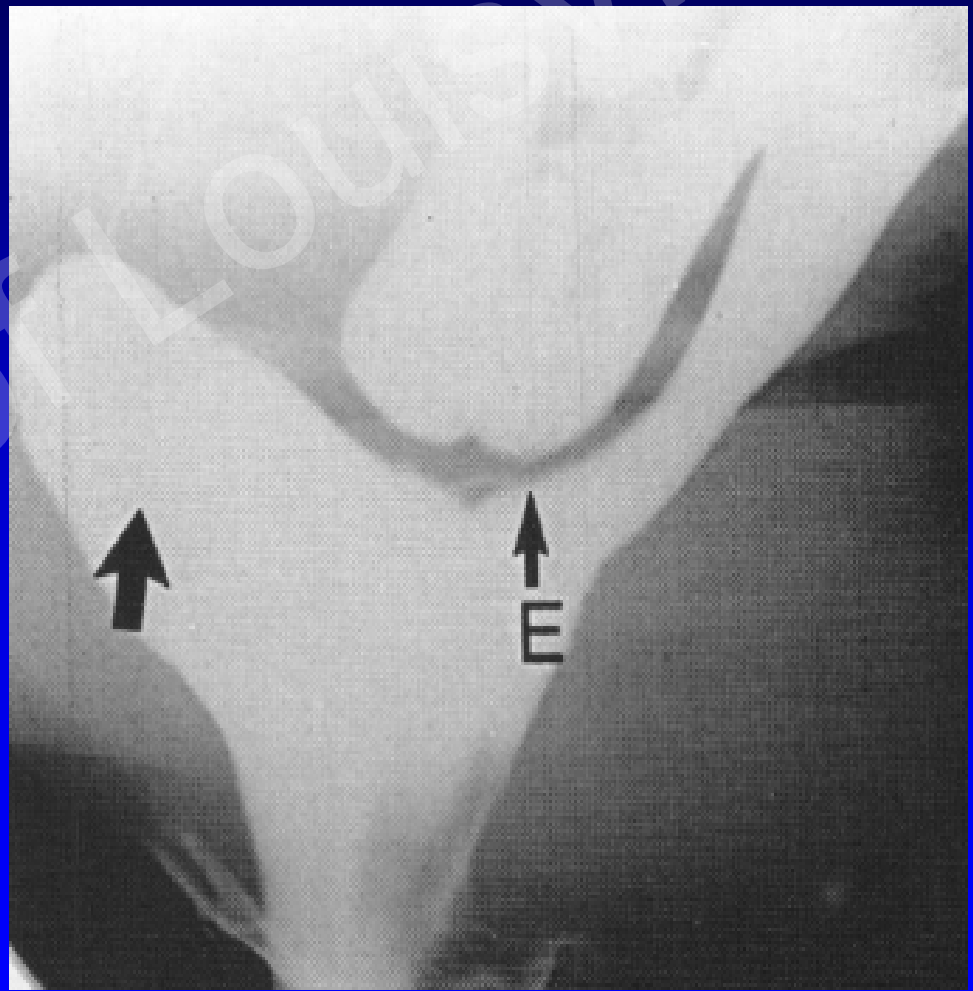
Anterior Rectocele





Rectocele

Rectocele and Enterocele



Patient with Multiple Sclerosis

Irritable Bowel Syndrome

Clinical Spectrum of IBS

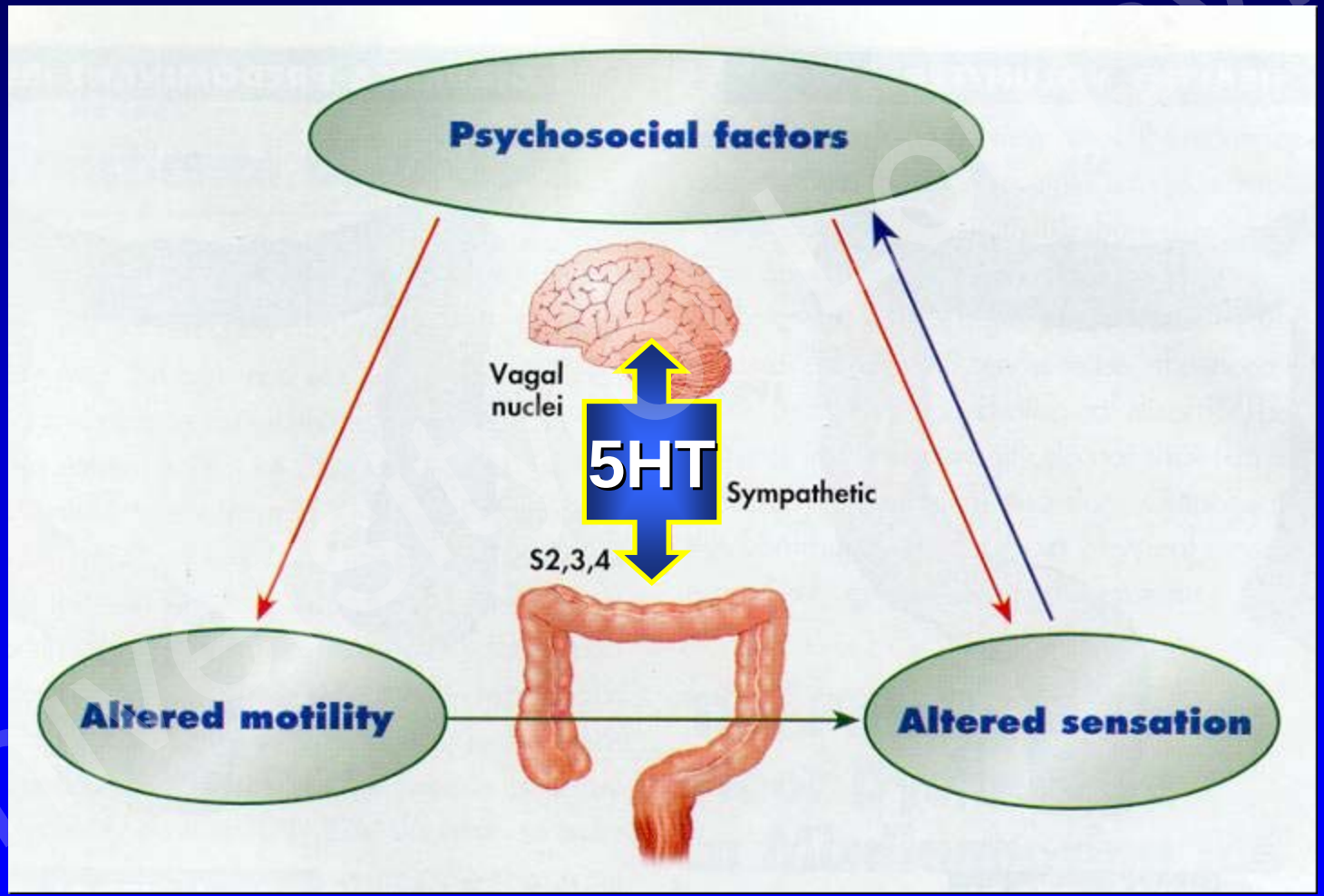
	Mild	Moderate	Severe
Prevalence	70%	25%	5%
Practice type	Primary	Specialty	Referral
Altered gut physiology	+++	++	+
Symptoms constant	0	++	+++
Psychosocial difficulties	0	+	+++
Health care use	+	++	+++

IBS: A Technical Review for Practice Guideline Development. Gastroenterol 1997;112:2120-2137

Rome III Definition of IBS

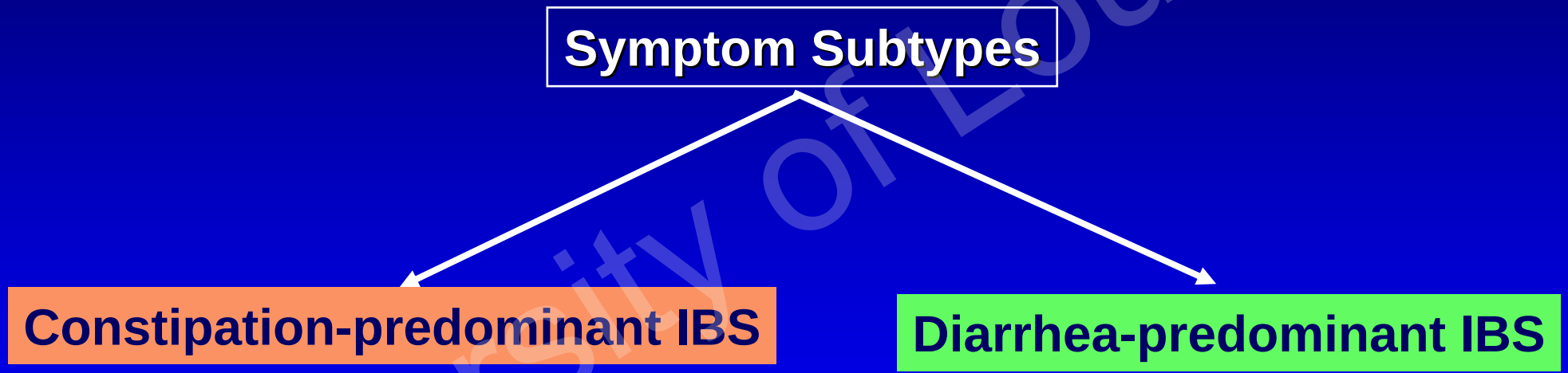
- Recurrent abdominal pain or discomfort at least 3 days per month in past 3 months with 2 or more of the following:
  - Improvement with defecation
  - Onset associated with a change in frequency of stool
  - Onset associated with a change in appearance of stool
- Symptom onset at least 6 months prior to diagnosis

Multifactorial Causes in IBS



Coulie B, Camilleri M. Clin Perspect Gastroenterol 1999;2:329-338.

Symptoms of IBS

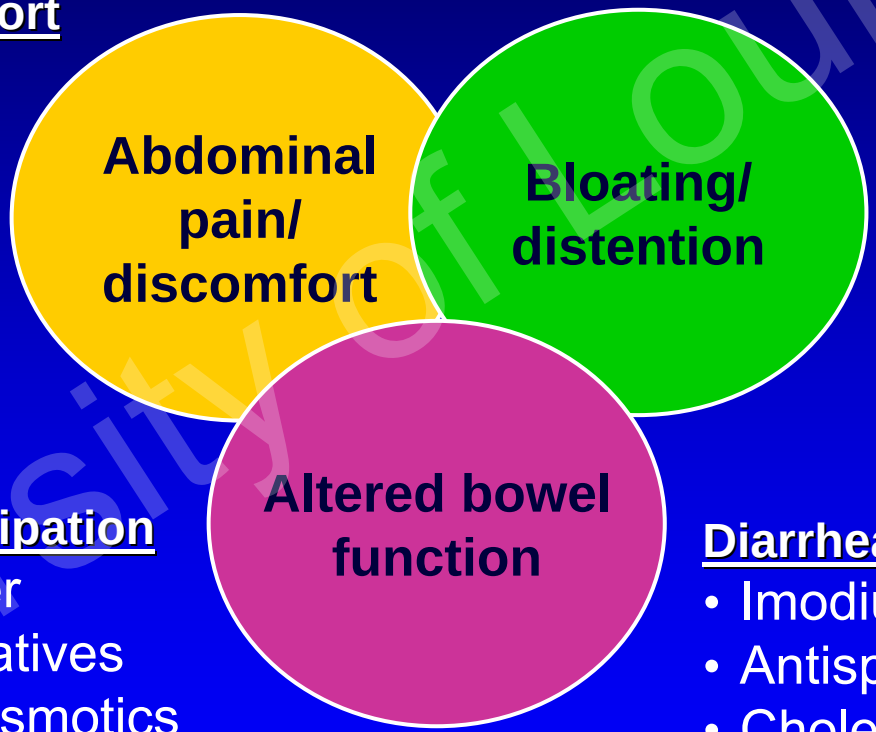


Differential Diagnosis of Diarrhea-Predominant IBS

- Malabsorption & dietary factors
  - Celiac disease, lactose intolerance, small intestinal bacteria overgrowth, pancreatic insufficiency
- Infection
  - Giardia, C. dif, Cryptosporidium
- Microcytic colitis
- Inflammatory bowel disease
- Weak anal sphincter
- Enhanced gastric-colonic reflex

Current Management of IBS

Abdominal pain/discomfort
- Antispasmodics
- Antidepressants

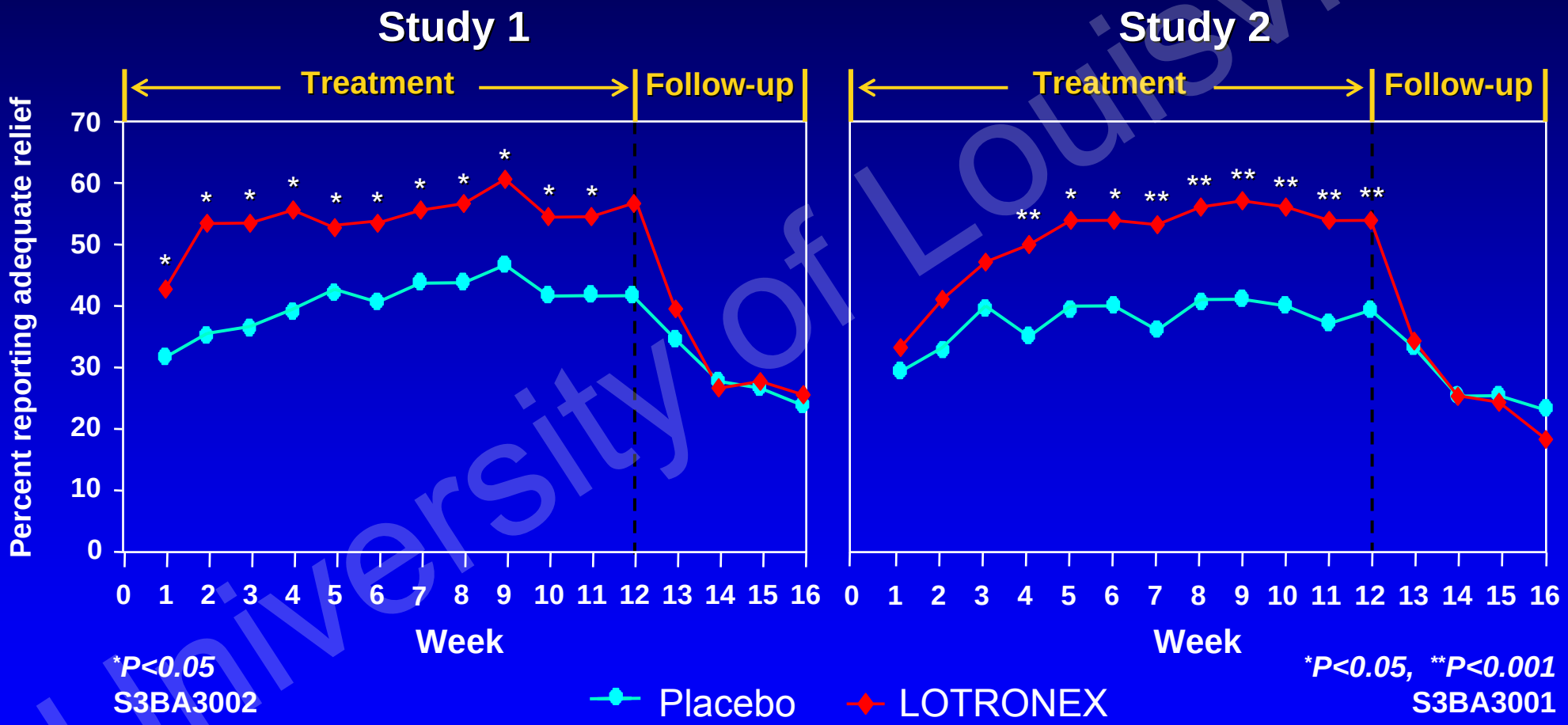


Bloating/distention
- Antiflatulents
- Antispasmodics
- Dietary modification
- Treat SIBO

Constipation
- Fiber
- Laxatives
  - Osmotics (Miralax)
  - Irritants

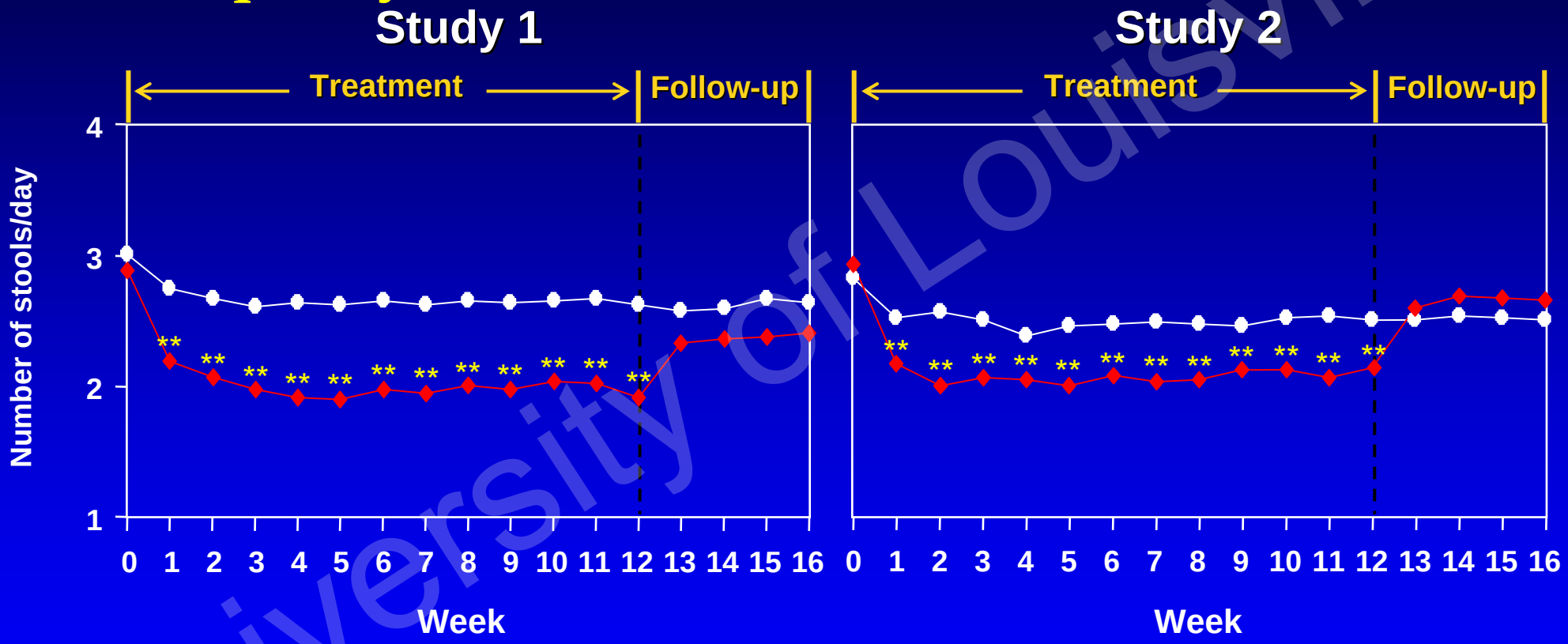
Diarrhea
- Imodium, lomotil
- Antispasmodics
- Cholestyramine
- Octreotide
- Lotronex

Clinical Trials With LOTRONEX™ (alosetron HCl): Effect on IBS Pain and Discomfort in Diarrhea-Predominant Female Patients



Reference: Data on file, Glaxo Wellcome Inc.
Please consult complete Prescribing Information.

Clinical Trials With LOTRONEX™ (alosetron HCl): Effect on Stool Frequency in Diarrhea-Predominant Female Patients



Reference: Data on file, Glaxo Wellcome Inc.
Please consult complete Prescribing Information.

Alosetron: Adverse Events in Clinical Trials

- Constipation (1 mg bid)
  - 28% in alosetron vs. 5% in placebo
- Cases of ischemic colitis have been reported
- Pulled off market by pharmaceutical company
- Available on a limited access program
  - Start at a lower dose: 0.5 mg qam

Differential Diagnosis of Constipation-Predominant IBS

- Colon cancer or obstruction
- Constipation

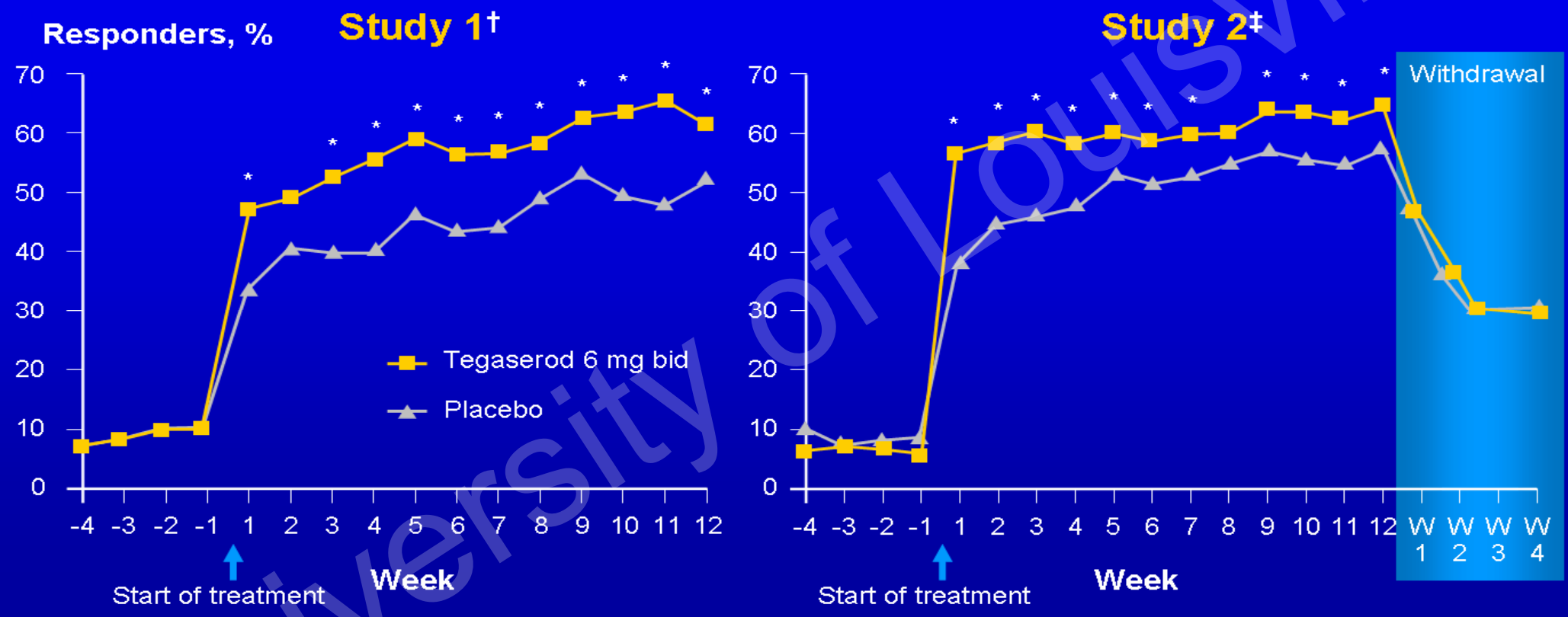
Symptoms of Chronic Constipation and IBS-Constipation are Similar

Symptoms >3 months	Chronic Constipation	IBS-C
Straining	+++	+++
Hard/lumpy stools	+++	+++
<3 BM/wk	+++	+++
Feeling of incomplete evacuation	+++	+++
Bloating/abdominal distension	++	+++
Abdominal pain/discomfort	+	+++

Chronic Constipation **IBS-C**

Thompson WG et al. *Gut.* 1999;45(suppl 2):II43-II47.
Drossman DA et al. *Gastroenterology.* 1997;112:2120-2137.

Tegaserod Demonstrated Relief Early and Throughout the Treatment Period



Efficacy beyond 12 weeks has not been studied. Response rates versus placebo were greater at Month 1 than at Month 3.

*$P<0.05$ vs placebo, ITT.

†Müller-Lissner SA et al. *Aliment Pharmacol Ther*. 2001;15:1655-1666.

‡Novick J et al. *Aliment Pharmacol Ther*. 2002;16:1877-1888.

Treatment of C-IBS

- Treat constipation
- Antispasmodic for pain

Fecal Incontinence

Prevalence of Fecal Incontinence

		Fecal Incontinence	Odds Ratio
Gender:	Female	2.9%	1.7 (1.2-2.4)
	Male	1.6%	
Age:	>65	7.1%	3.9 (2.7-5.6)
	<65	1.8%	
Physical Limitation:	Yes	6.6%	5.0 (3.6-7.0)
	No	1.7%	
Poor General Health:	Yes	11.5%	6.0 (4.1-8.3)
	No	1.7%	

Nelson et al. JAMA 1995;274:559-61. Survey of 6,959 adults.

Causes of Fecal Incontinence

- Multifactorial
  - Up to 80% of patients have more than 1 cause
- Major causes
  - Obstetric trauma
  - Anorectal causes
  - Neurologic causes

Obstetric Trauma

- Most common cause of fecal incontinence in women
- Injury to pudendal nerve or anal sphincters
- Risk factors
  - Forceps delivery, prolonged labor, large birth weight, twins, multiple pregnancy, breach delivery

Anorectal Diseases

- Disrupt continence barrier
  - Surgery: hemorrhoids, fistula, fissures, ileoanal anastomosis, low anterior resection
  - Anorectal cancer
  - Rectal prolapse
  - Descending perineum
- Impaired rectal sensation
  - Radiation, ulcerative colitis, Crohns

Neurological Disorders

- Can affect sensory and motor function
- Central
  - Multiple sclerosis, stroke, tumor, dementia
- Spinal
  - Cauda equina lesions (overflow)
- Autonomic
  - Diabetic neuropathy, polyneuropathy, amyloidosis

Clinical Presentation

- Presents as “diarrhea” and “fecal urgency”
- “Passive” incontinence vs. “Urge” incontinence
- Past medical history and ROS
  - OB
  - GU
  - Surgical
  - Neurologic

Clinical Presentation

- Associated syndromes
  - Irritable bowel syndrome, post-prandial diarrhea, acute diarrhea
- Post op
  - Cholecystectomy
  - Fundoplication
  - Colon resection
  - Vagotomy

Clinical Assessment of Fecal Incontinence

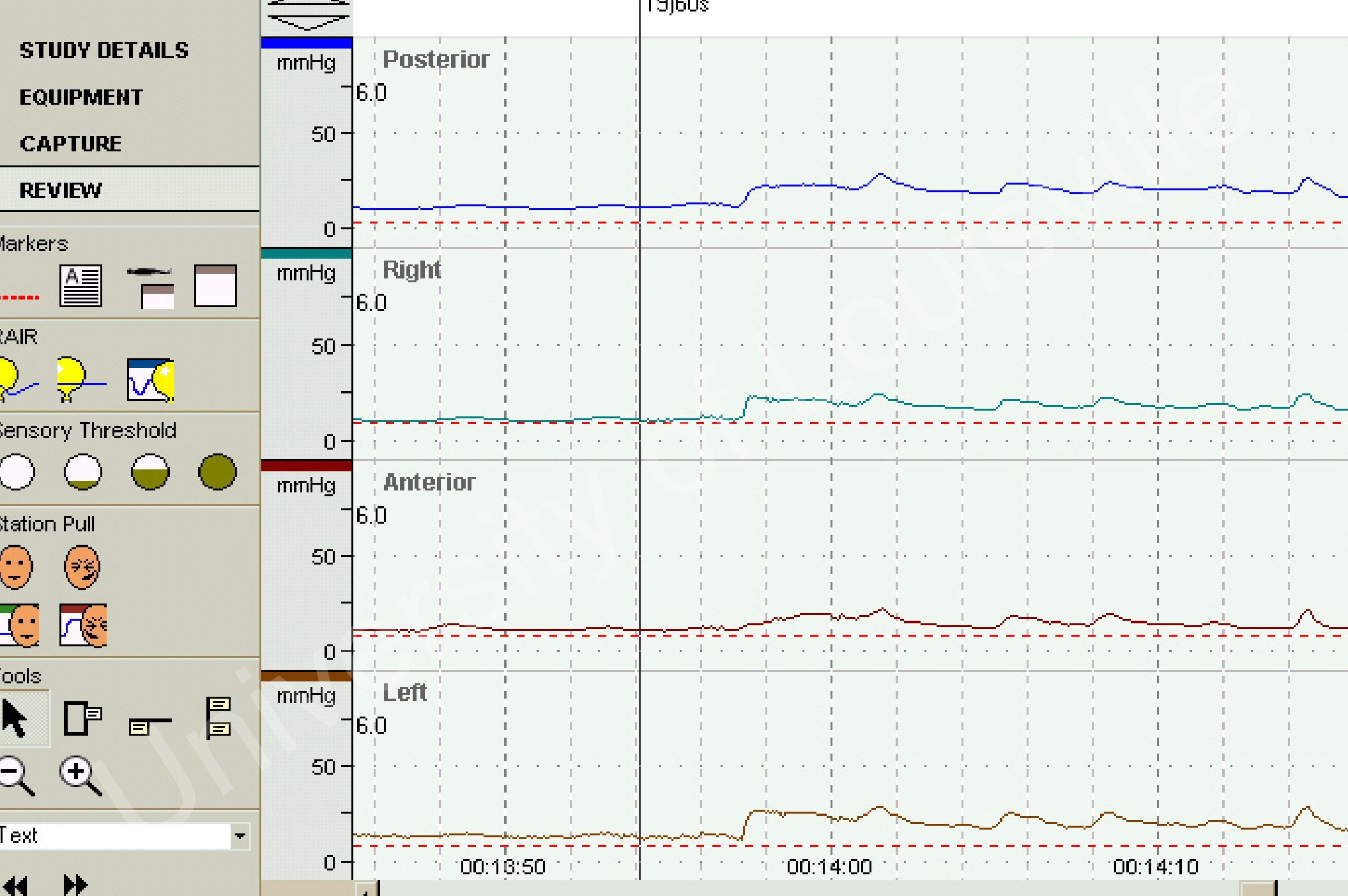
- Physical exam
- Sigmoidoscopy or colonoscopy
- Anorectal manometry
- Anal ultrasound
- Others

Pharmacologic Therapy for Fecal Incontinence

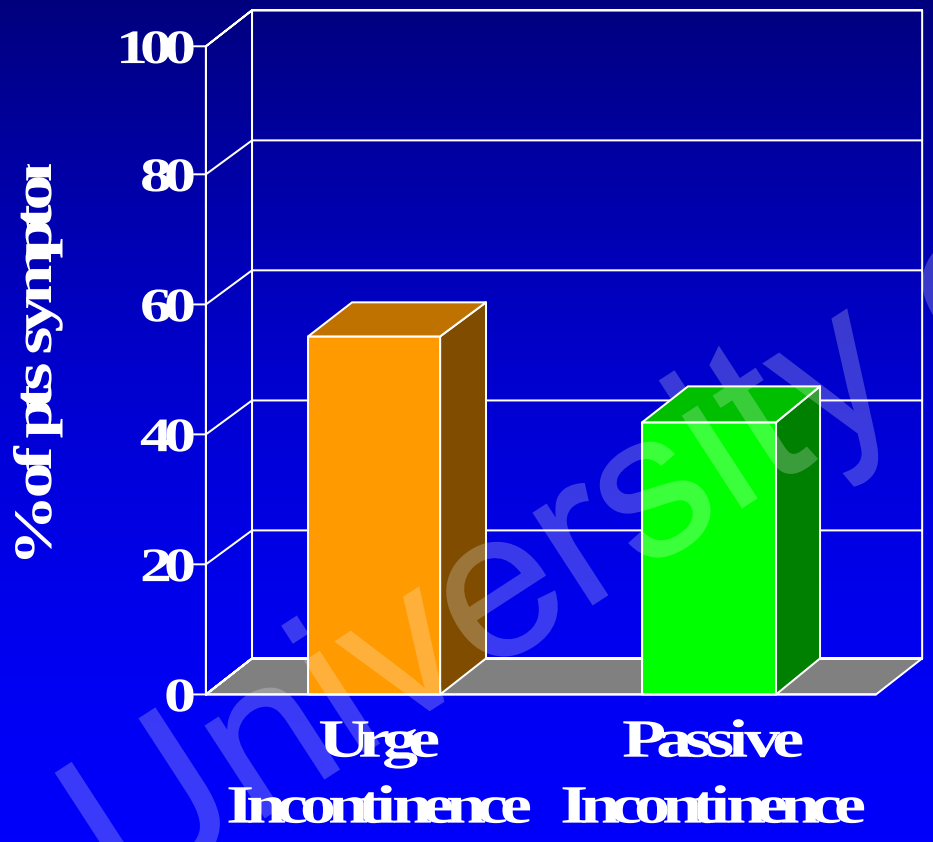
- Anti-diarrhea agents
  - Imodium®, Lomotil®
  - Cholestyramine
  - Lotronex
- Fiber supplement
- Octreotide for selected cases
- Can take before meals

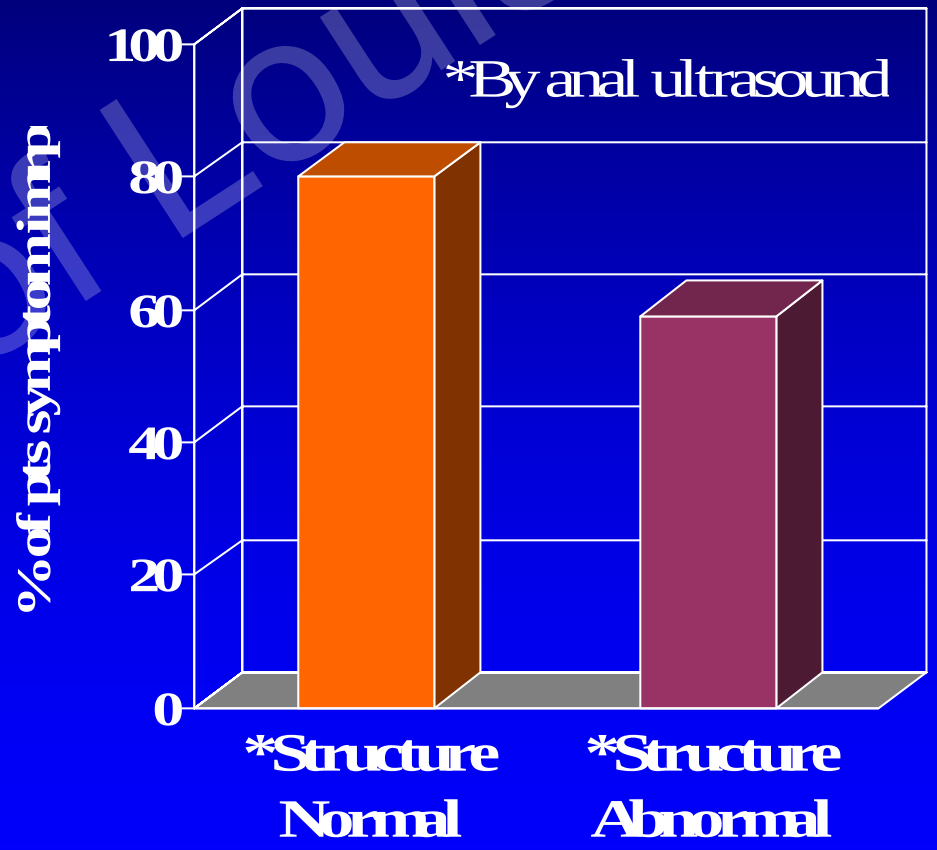
Biofeedback for Fecal Incontinence

- Visual & verbal reinforcement
- Maneuvers
  - Kegel exercises (voluntary squeezes)
  - Sensory conditioning
- Home “practice”


STUDY DETAILS
EQUIPMENT
CAPTURE
REVIEW
Markers
AIR
Sensory Threshold
Station Pull
Tools
Text
T9)60s
mmHg
Posterior
6.0
50
0
mmHg
Right
6.0
50
0
mmHg
Anterior
6.0
50
0
mmHg
Left
6.0
50
0
00:13:50
00:14:00
00:14:10

Biofeedback for Fecal Incontinence

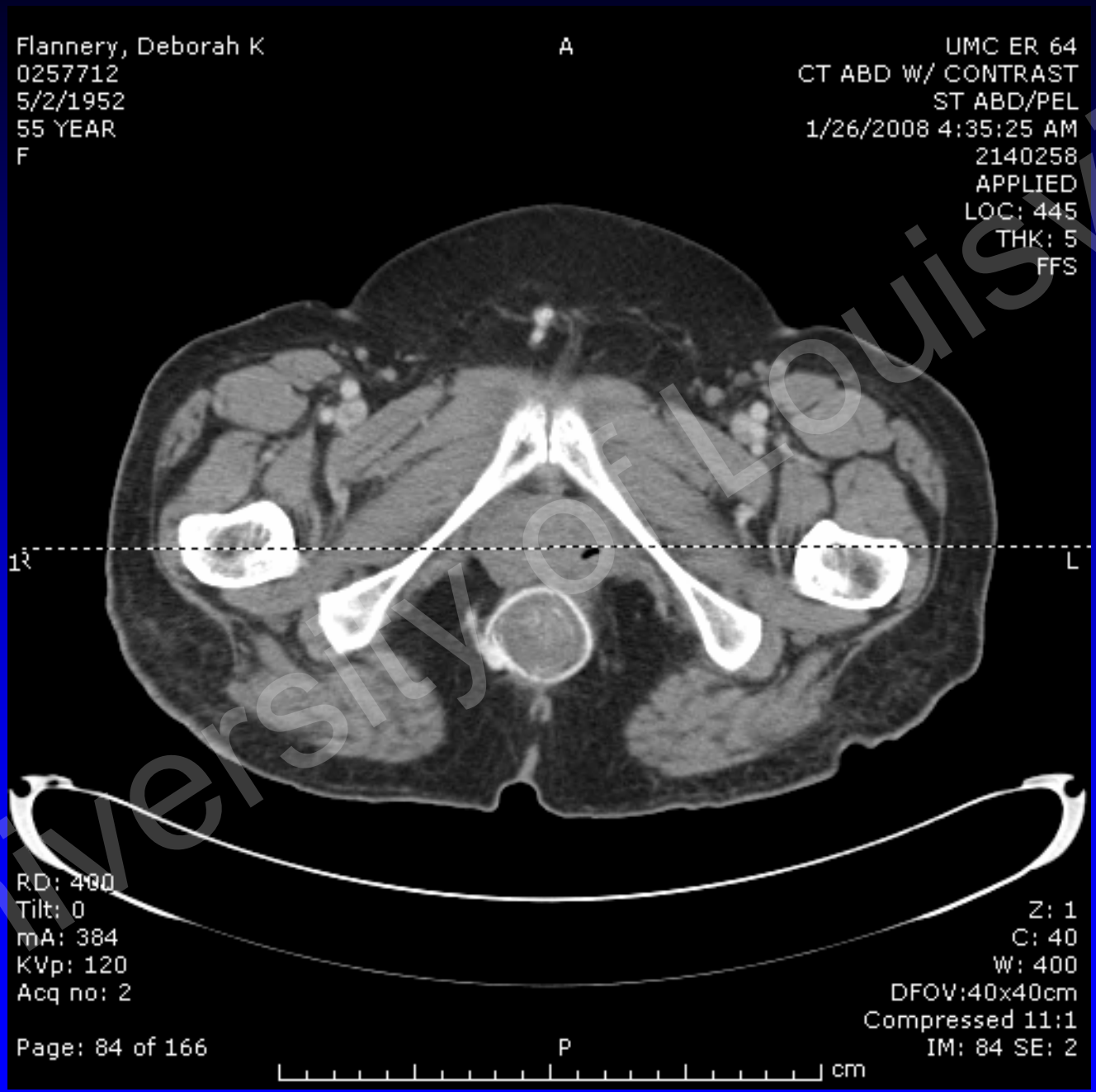




Norton et al. Br J Surg 1999;89:1159-63. 100 patients with fecal incontinence.

Predictor of Poor Outcome with Biofeedback

- Severe fecal incontinence
- Unable to follow instructions
- Pudendal neuropathy
- Underlying neurological problems



Constipation

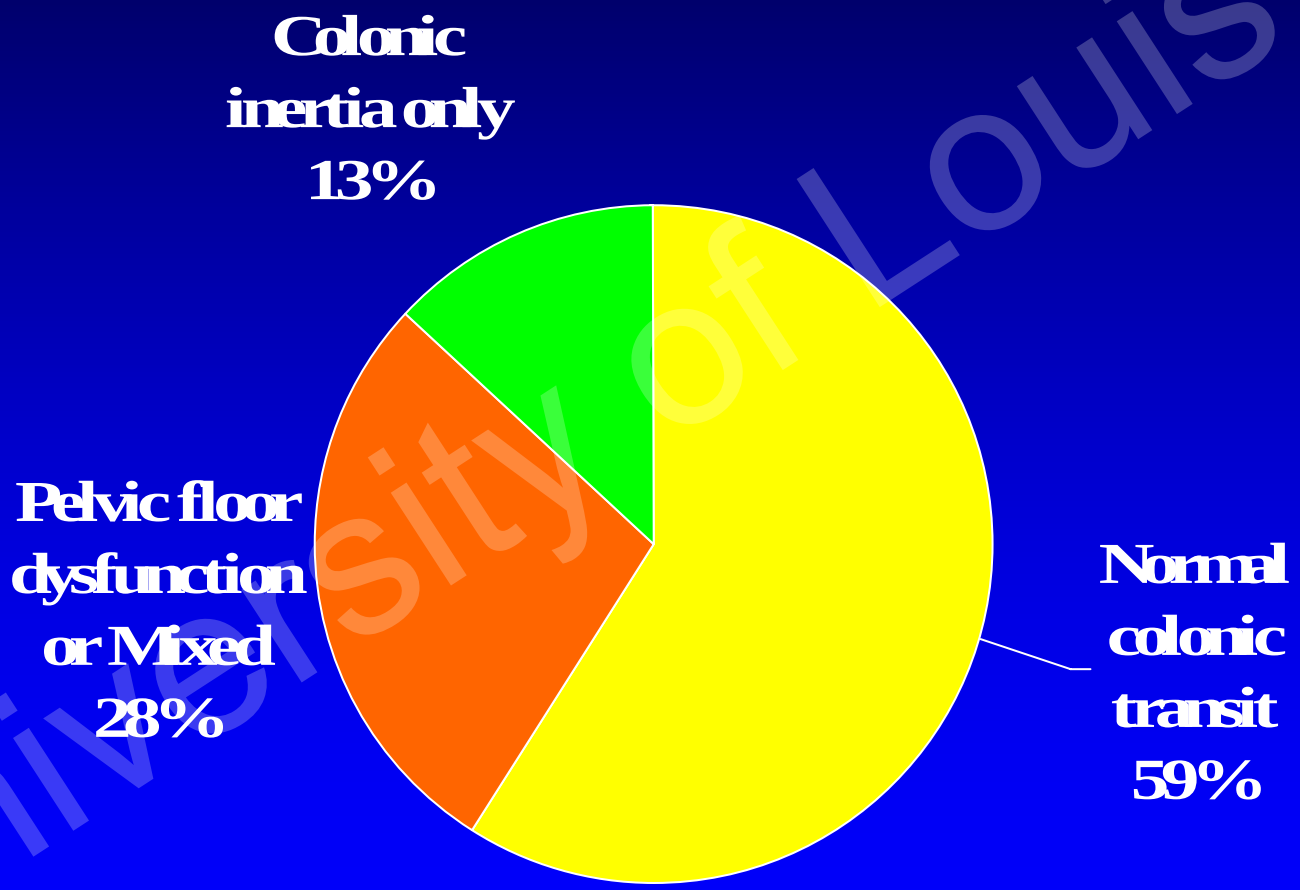
Normal Bowel Habits Vary Widely

- Normal stool frequency
  - 2 BM's/day to 2 BM's/week
- Stool weight
  - 20-250 g/day
- Stool consistency
  - Formed to semi-formed

Classification of Constipation

- Normal transit
- Colonic inertia
  - Diffuse
  - Left-sided
- Obstructive defecation

Evaluation of Constipation at Tertiary Referral Center



Nyam et al. Dis Colon Rectum 1997;40:273-279. (N=1,000)

Causes of Colonic Inertia

- Metabolic
  - hypothyroidism, hypercalcium, hyperparathryoidism
- Neurologic
  - Autonomic neuropathy, diabetes, paraneoplastic syndrome, intestinal pseudo-obstruction, CIDP, amyloidosis, multiple sclerosis
- Collagen vascular disease
  - scleroderma, lupus
- Idiopathic

Medications Causing Colonic Inertia

- Anticholinergics
- Anticonvulsants
- Antidepressants and psychotherapeutic drugs
- Antiparkinson drugs
- Calcium channel blockers
- Opiates
- Cation-containing agents
  - sucralfate, iron supplements, bismuth

Current ACG Recommendations for Treatment of Chronic Constipation

Grade A	Polyethylene glycol, lactulose, tegaserod
Grade B	Bran or psyllium bulking agents, osmotic laxatives based on magnesium hydroxide, stool softeners, OTC stimulant laxatives with senna or bisacodyl
Grade C	Herbal supplements (aloe, mineral oil), combination of grade B therapies, biofeedback

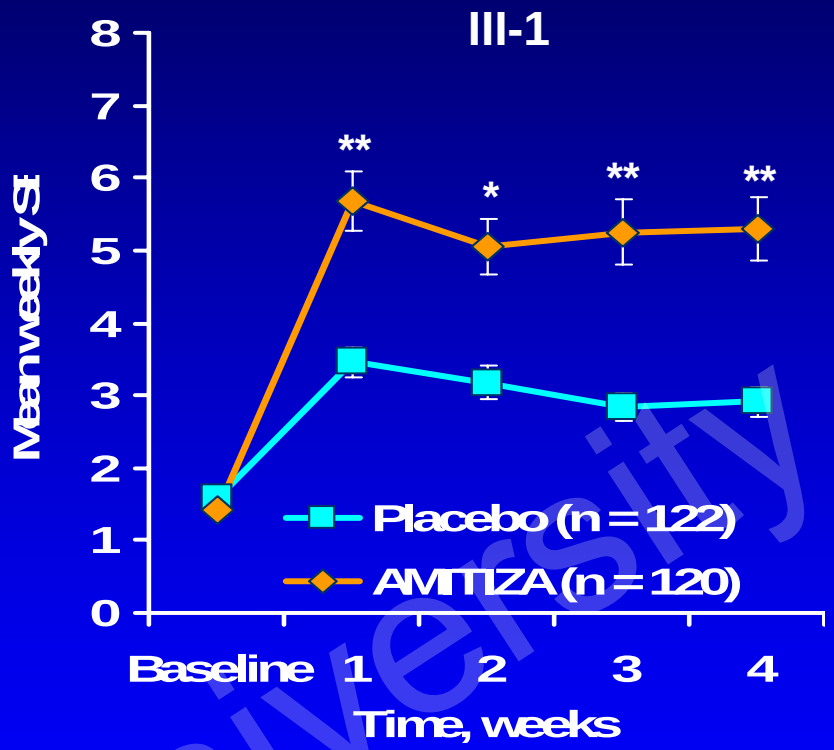
ACG = American College of Gastroenterology; OTC = Over-the-counter.

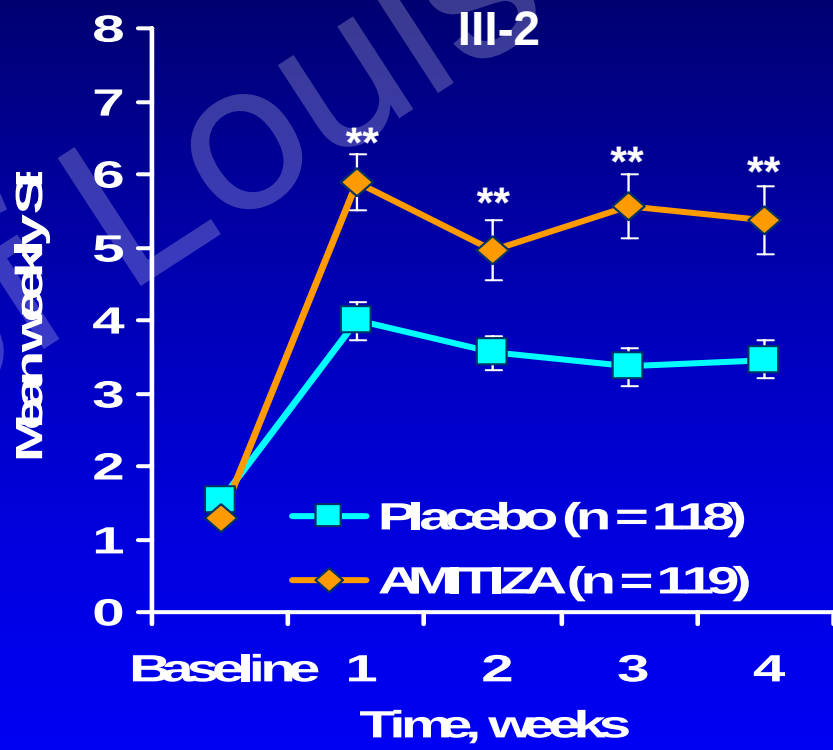
American College of Gastroenterology Chronic Constipation Task Force. *Am J Gastroenterol*. 2005;100(suppl 1):S1-S4.

OTC Therapy for Constipation

- Fiber (bran, psyllium, methylcellulose)
- Stool softener (docusate sodium)
- Hyperosmolar agents (sorbitol, lactulose)
- Suppository (glycerol, bisacodyl)
- Saline laxative (magnesium)
- Stimulants (bisacodyl, anthraquinones)
- Lubricant (mineral oil)
- Enemas (mineral oil, tap water, phosphate, SMOG)

AMITIZA™ (lubiprostone) Increased Weekly Spontaneous Bowel Movements





AMITIZA significantly increased SBM over baseline and placebo by week 1

SBM = Spontaneous bowel movements.
*P < .01, **P < .001, AMITIZA 48 mcg versus placebo.

Safety Profile of Lubiprostone in All Phase II and III Trials

Adversed events	Patients, n (%)	
	Placebo (n = 316)	AMITIZA™ 48 mcg (n = 1,113)
Nausea	16 (5.1)	346 (31.1)
Diarrhea	3 (0.9)	147 (13.2)
Headache	21 (6.6)	147 (13.2)
Abdominal distension	9 (2.8)	79 (7.1)
Abdominal pain	7 (2.2)	75 (6.7)
Flatulence	6 (1.9)	68 (6.1)
Vomiting	3 (0.9)	51 (4.6)
Dizziness	4 (1.3)	46 (4.1)

AMITIZA™ (lubiprostone)-Induced Nausea

- Nausea rates ranged from 27.1% in long-term safety studies to 31.1% in all trials combined
  - Incidence decreased when AMITIZA was administered with food
  - Incidence was lower in male and elderly populations
  - Long-term exposure to AMITIZA did not elevate the risk for nausea
- Across all studies, nausea incidence for individuals ≥ 65 years of age was 18.6%

Obstructive Defecation

Symptoms Suggestive of Obstructive Defecation

- Chronic, protracted straining
- Prolong, painful defecation
- Need for manual disimpaction
- Need for certain body position
- Bulging sensation against vaginal wall
- Urinary and fecal incontinence

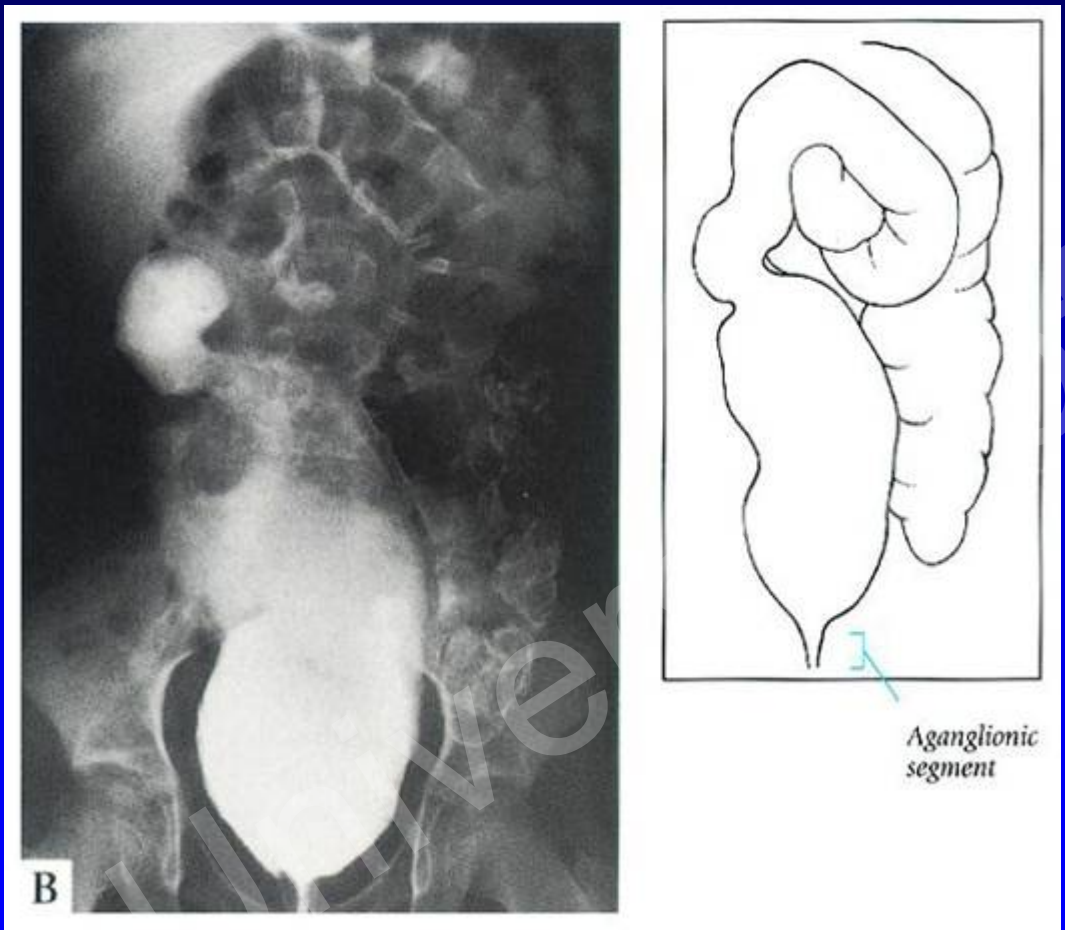
Causes of Obstructive Defecation

- Anismus (paradoxical pelvic muscle contraction)
- Pelvic floor dysfunction (descending perineum syndrome)
  - rectocele, enterocele, cystocele
- Impaired rectal sensation
- Megarectum
- Hirschprung's disease
- Rectal prolapse
- Intussusception

Neurologic Causes of Obstructive Defecation

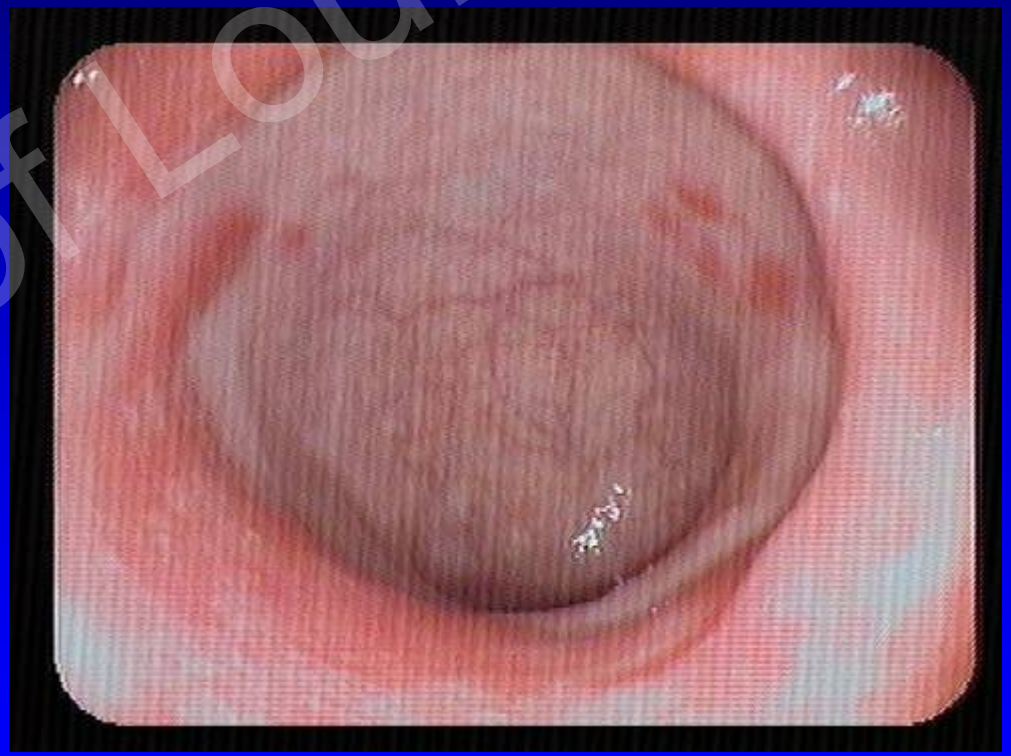
- Impaired rectal sensation
  - Diabetes
  - Multiple sclerosis
  - Spinal cord injury
  - Caudal equina syndrome
- Impaired sphincter relaxation
  - Hirschprung's disease

Hirschsprung's Disease



Solitary Rectal Ulcer from Rectal Prolapse

Before surgical repair



After

Causes of Anismus

- Behavioral
  - Pain during defecation
  - Surgery, injury, fissures, hemorrhoids
  - Excessive straining of pelvic floor
- Childhood factors
- Sexual and emotional abuse
- Idiopathic

Biofeedback for Anismus

- Visual reinforcement
  - EMG & anorectal manometry: reduce puborectalis muscle activity while straining
- Bowel management program
- Pelvic floor relaxation
- Physical exercise
- Psychotherapy or stress therapy

Summary

- Fecal incontinence and constipation are common
- Clinical history is key
- Beware of coexisting conditions
- Anorectal manometry is very helpful to identify functional defect and to direct therapy