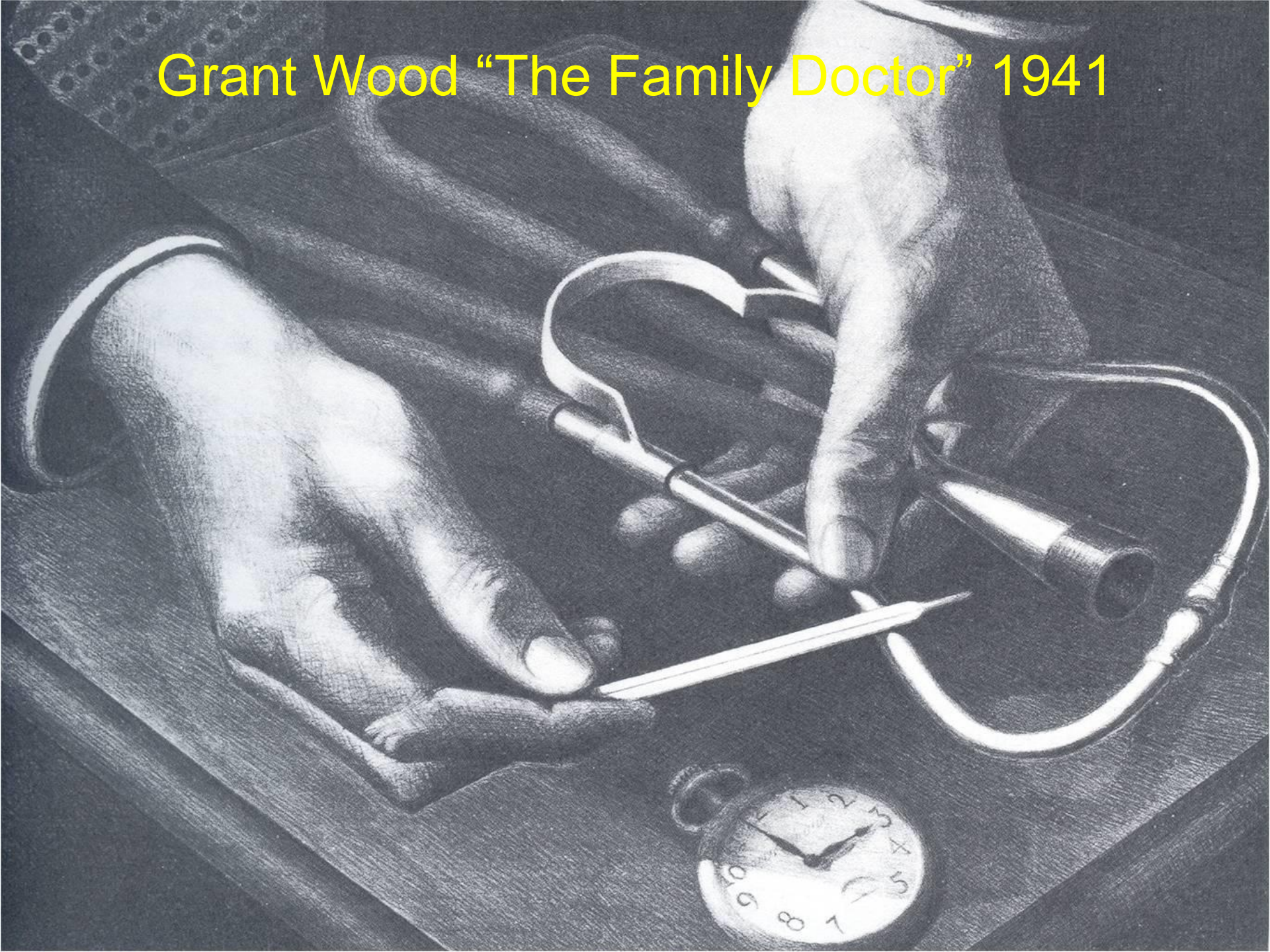


Grant Wood "The Family Doctor" 1941

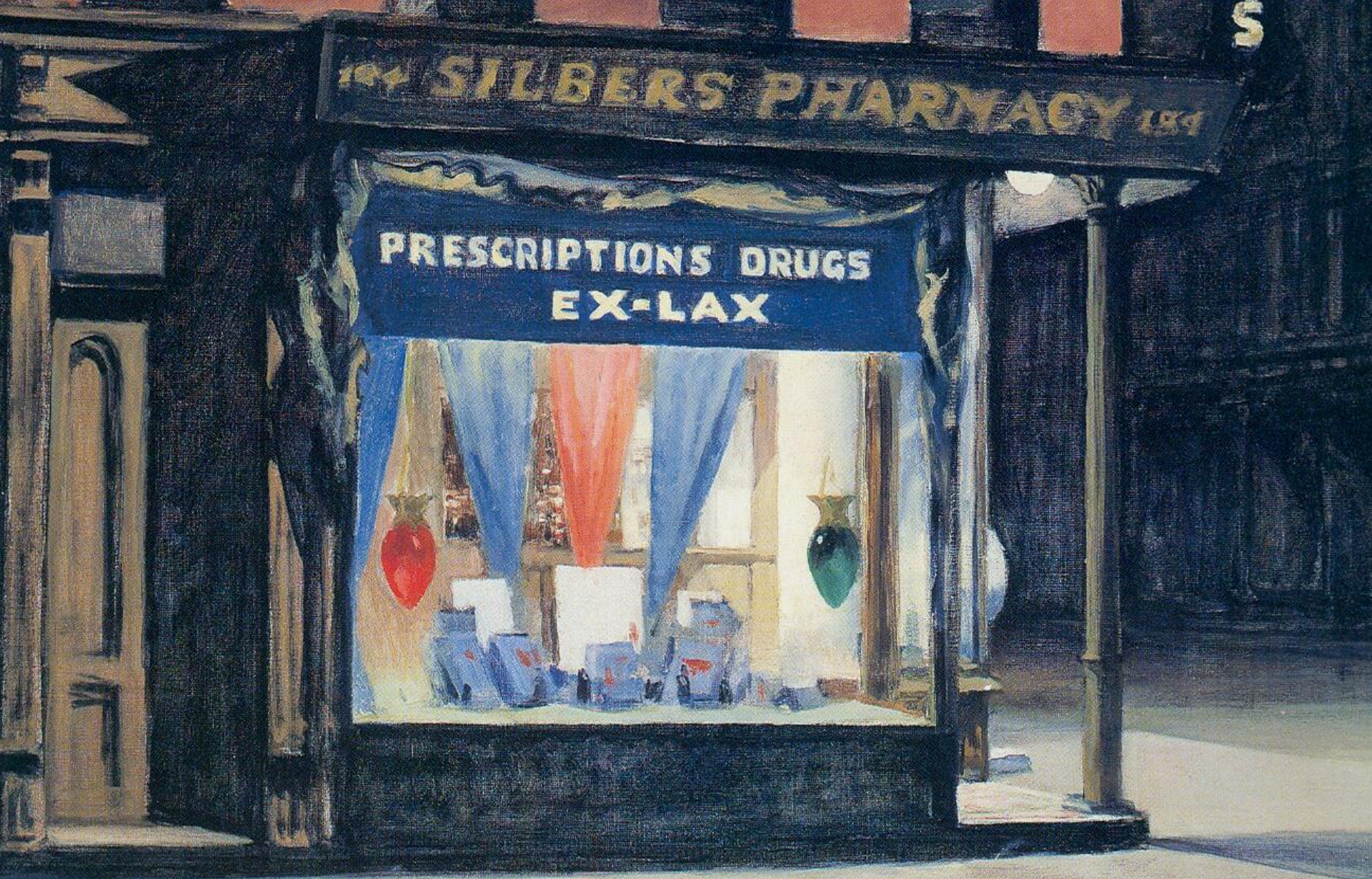


Chronic Constipation

New Treatment Options for Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation

Brian K. Cooley, M.D. FACG

Plano, Texas



Drug Store

Edward Hooper 1927 Museum of Fine Arts Boston

Definition of IBS

IBS is a functional bowel disorder with abdominal pain or discomfort associated with changes in bowel habits

Functional = absence of structural or biochemical abnormalities (eg. celiac disease, inflammatory bowel disease, GERD)

Main IBS subtypes

IBS-C: Constipation predominant

IBS-D: Diarrhea predominant

IBS-M: Mixed bowel pattern

IBS-U: Unclassified



Definition of CIC

CIC is a disorder of defecation characterized by infrequent bowel movements (less than 3/week), difficult passage of stool or both



Chronic = 3 or more months

Idiopathic = unknown cause, not related to medications, structural (colon cancer) or biochemical abnormalities (eg. hypothyroidism)

Difficult stool passage includes straining, incomplete evacuation, hard/lumpy stools, prolonged time between bowel movements, need for manual removal of stool

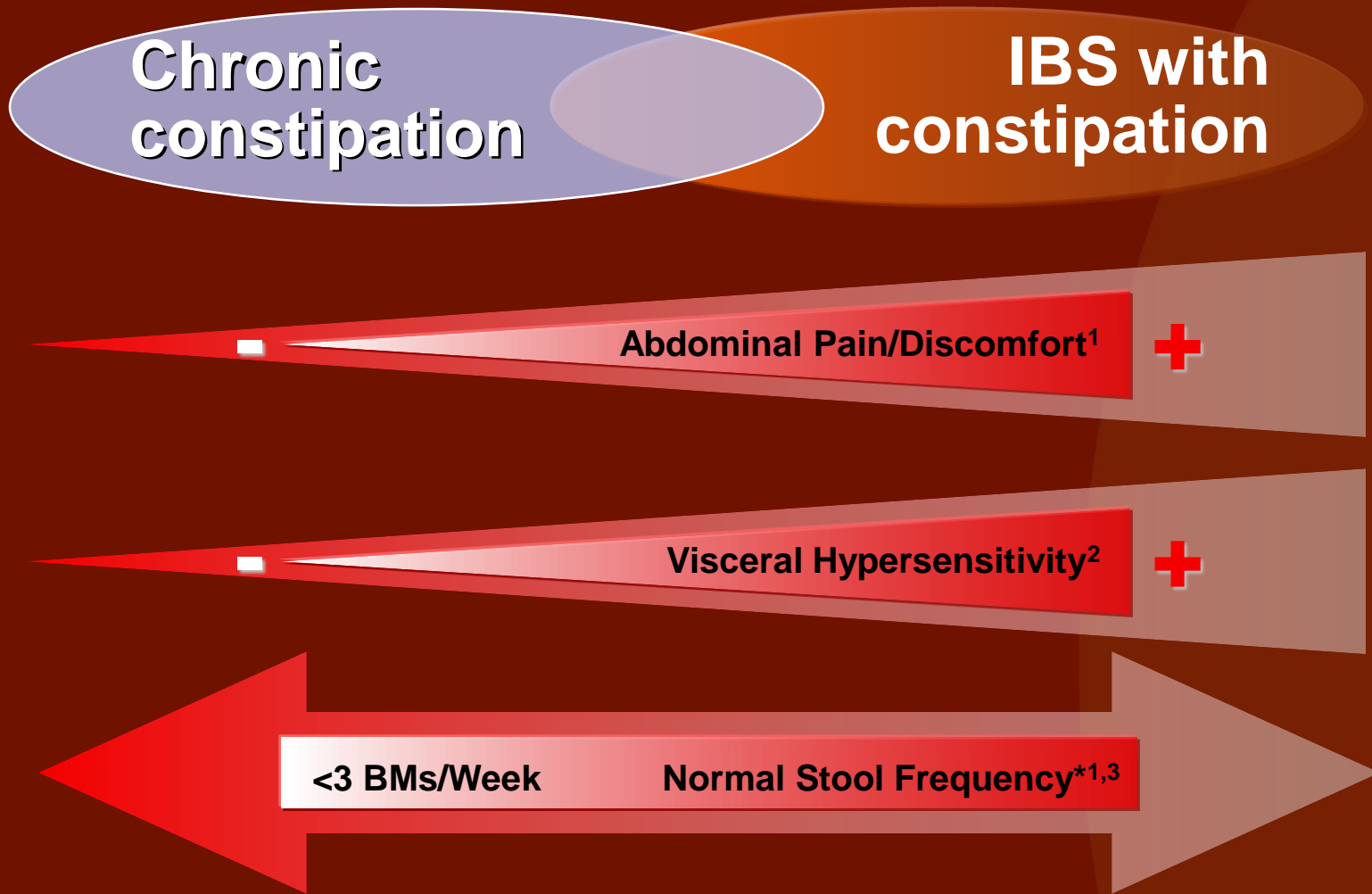
IBS Potential Risk Factors

- Age (25-55)
- Sex (60-70 percent of patients are women)
- Gastrointestinal infection and inflammation
- Food intolerance
- Psychiatric disorders
- History of sexual abuse

CIC Potential Risk Factors

- Age (more common in elderly)
- Sex (three times more women than men)
- Diet (low fiber and low caloric intake)
- Inactivity
- Multiple Medications
- Hemorrhoids and fissures

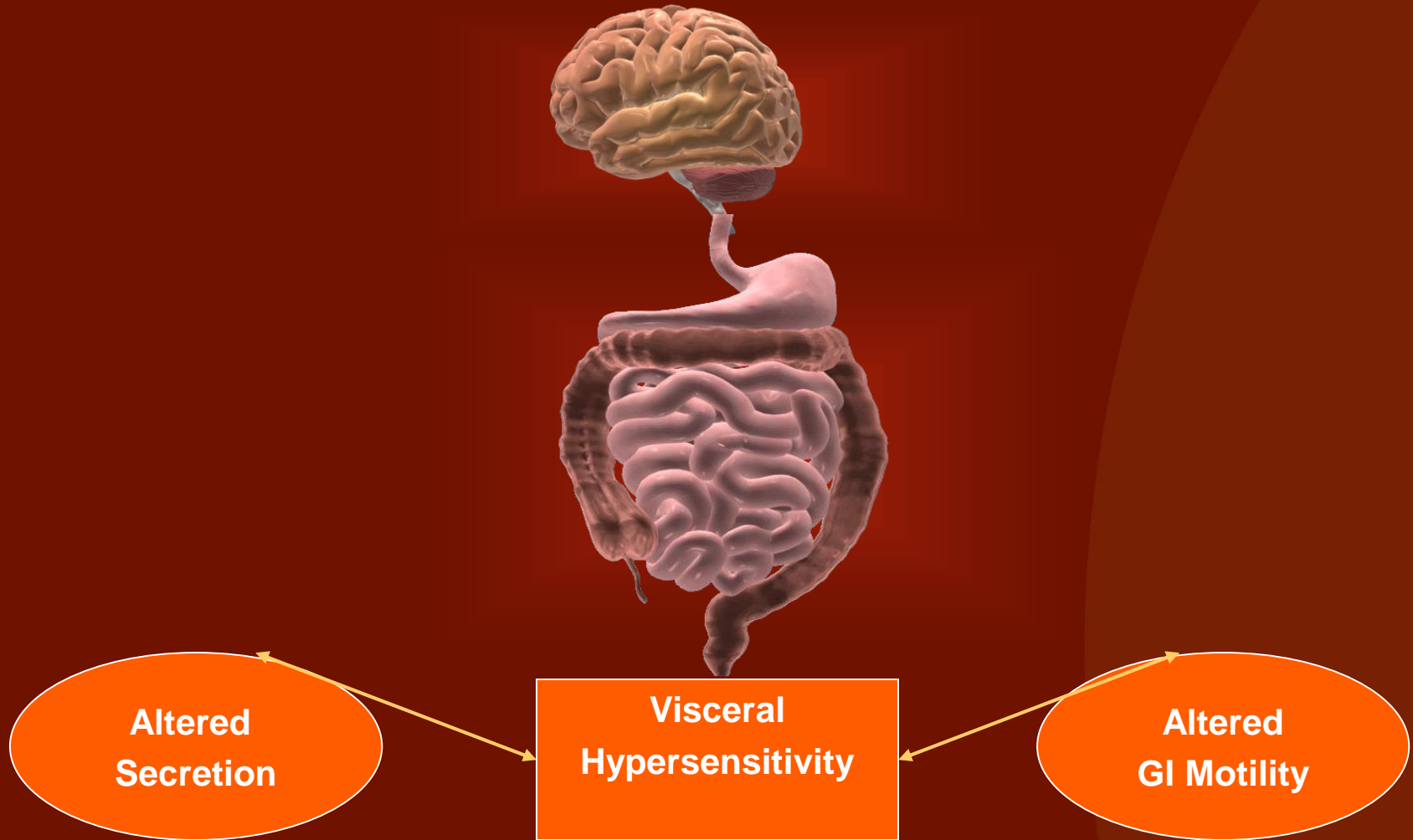
Differentiating Signs and Symptoms of Chronic Constipation (CC) and IBS-C



*3 BMs/day to 3 BMs/week is considered range of normal stool frequency

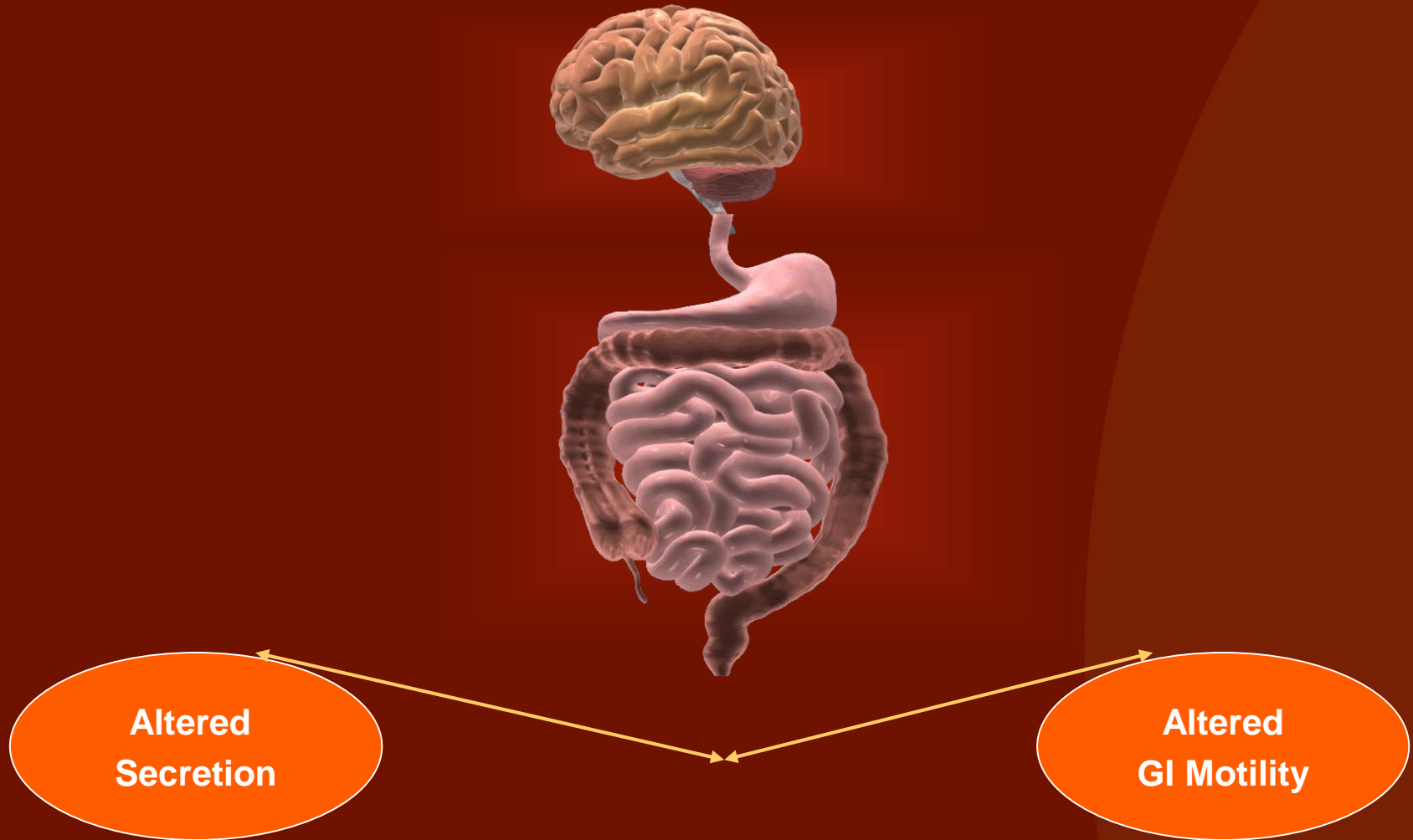
1. Brandt LJ, et al. *Am J Gastroenterol.* 2005;100(suppl 1):S5-S21. 2. Delvaux M. *Best Pract Res Clin Gastroenterol.* 2004;18:747-771. 3. Longstreth GF, et al. *Gastroenterology*, 2006;130:1480-1491.

Pathophysiology of IBS is Multifactorial



1. Ohman L, et al. *Dig Liver Dis* 2007;39:201-215.
2. Talley NJ, et al. *Lancet*. 2002;360:555-564.
3. Mayer EA, et al. *Aliment Pharmacol. Ther.* 2006;24:919-933.
4. Mayer EA, et al. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:G519-524.
5. Mulak A, et al. *Med Sci Monit*. 2004;10:RA55-62.
6. Delvaux M. *Best Pract Res Clin Gastroenterol*. 2004;18:747-771.

Pathophysiology of CIC is Multifactorial



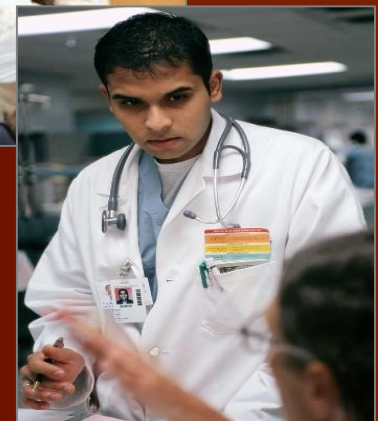
1. Ohman L, et al. *Dig Liver Dis* 2007;39:201-215.
2. Talley NJ, et al. *Lancet*. 2002;360:555-564.
3. Mayer EA, et al. *Aliment Pharmacol. Ther.* 2006;24:919-933.
4. Mayer EA, et al. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:G519-524.
5. Mulak A, et al. *Med Sci Monit*. 2004;10:RA55-62.
6. Delvaux M. *Best Pract Res Clin Gastroenterol*. 2004;18:747-771.

Prevalence and Impact of IBS-C and CIC

- US prevalence of IBS- C as many as 13 million
- US prevalence of CIC as many as 35 million
- IBS-C bothersome symptoms 135 days per year
- CIC bothersome symptoms 99 days per year
- IBS-C utilization of health care system 1.5 x more than age matched controls
- CIC utilization of health care system 1.4 x more than age matched controls

Increased Healthcare Utilization

- Increased healthcare utilization leads to higher costs of care for IBS-C and CIC patients
- Greater incidence of:
 - Outpatient visits
 - Surgeries
 - Prescription drugs
 - Radiology, lab tests



*Data based on survey of 2613 managed care plan members

Longstreth GF, et al. *Am J Gastroenterol.* 2003;98:600-607.

Associated Symptoms of IBS-C and CIC

- Patients may present with:
 - Migraine Headaches
 - Insomnia
 - Chronic Fatigue
 - Fibromyalgia
 - Depression, anxiety



Patient and Provider Frustration

- Chronicity and lack of effective treatment options often leads to frustration for both patient and physician.
- Patients can be very demanding and difficult to care for.
- This can lead to fragmented care and overutilization of the health care system

Medical “Profile” of Constipated Patient circa 1915

Classic Patient described as:

“generally a woman.”

“Lean cadaverous, flat chested.”

“Cold and clammy” hands.

Skin “bears many crops of pimples.”

Body odor “is apt to be distressingly noticeable.”

Medical “Profile” of Constipated Patient circa 1915

Her “abdominal muscles ...are flabby and flaccid and all the viscera which they should hold up are fallen in greater or less degree.”

She suffers “flatulence, and inveterate and incoercible constipation.”

Medical “Profile” of Constipated Patient circa 1915

She is “morose, querulous, and often suspicious,”

She exhibits “a complete absence of the joy of life.”

Berkeley 1915

“The Dreaded Colic”

George Cruikshank 1819

Philadelphia Museum of Art



IBS Typical Patient Profile

- Abdominal pain/discomfort associated with altered bowel habits¹
- Female²
- Age 25 to 54 years²
- Patients may also present with:
 - Headache^{3,4}
 - Poor sleep/fatigue^{3,4}
 - Fibromyalgia⁴
 - Depression, anxiety⁵



CIC Typical Patient Profile

- Age 65
- Female
- Many years of constipation
- Has tried multiple medications without lasting success
- Constipation causes more discomfort than pain



Approach to the Patient with IBS-C and CIC

- Physician patient relationship is very important
- Ask the patient to describe the symptoms including frequency and severity of discomfort
- Encourage the patient to describe their stools



Stool Form Correlates With Intestinal Transit Time

The Bristol Stool Form Scale

Slow Transit

Type 1



Separate hard lumps

Type 2



Sausage-like but lumpy

Type 3



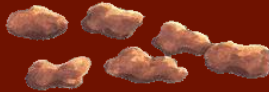
Sausage-like but with cracks in the surface

Type 4



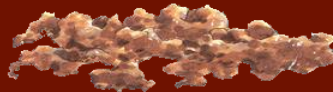
Smooth and soft

Type 5



Soft blobs with clear-cut edges

Type 6



Fluffy pieces with ragged edges, a mushy stool

Fast Transit

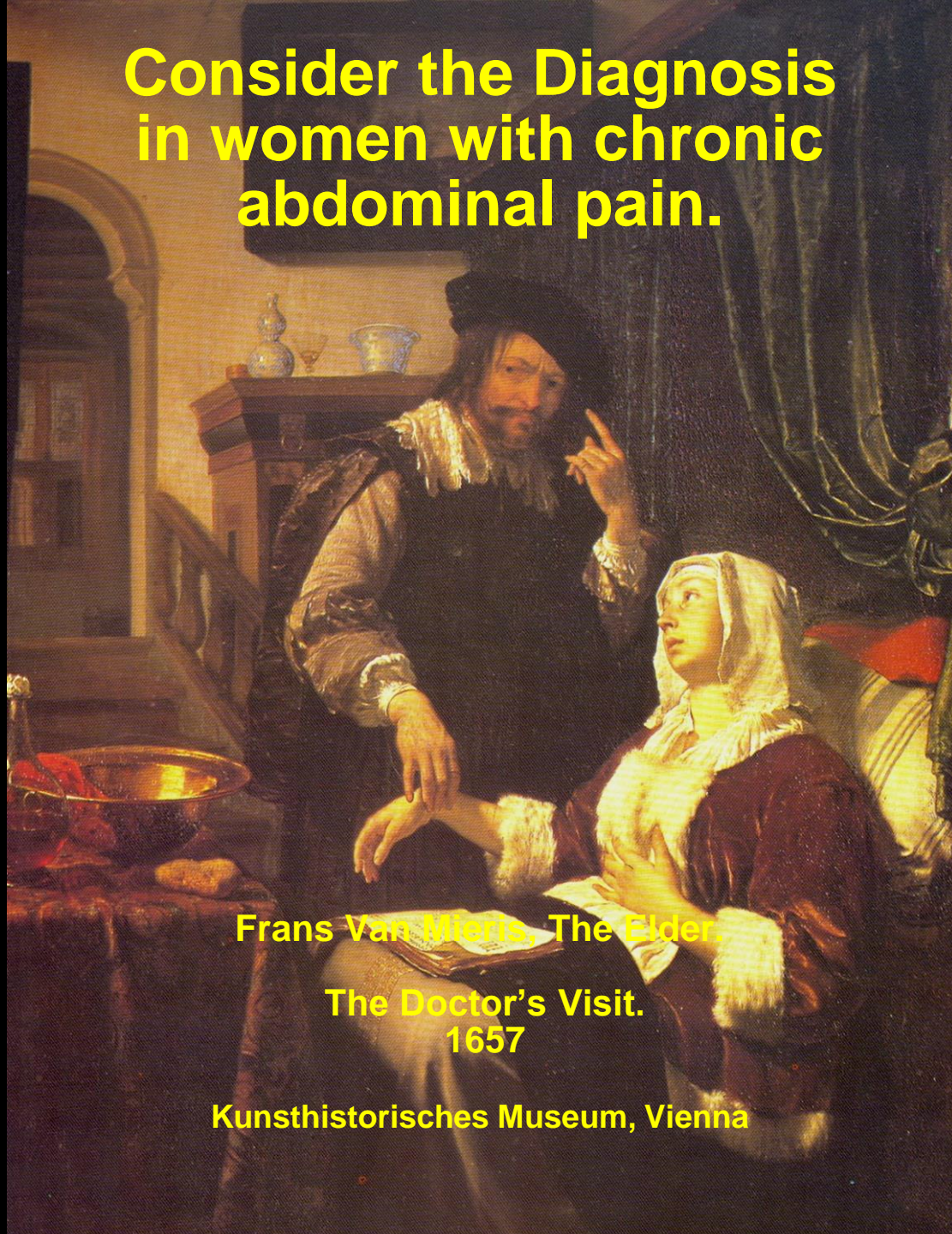
Type 7



Watery, no solid pieces



**Consider the Diagnosis
in women with chronic
abdominal pain.**



Frans Van Mieris, The Elder

**The Doctor's Visit.
1657**

Kunsthistorisches Museum, Vienna

Diagnosis of IBS-C and CIC

A Symptom-Based Approach

- Identify current symptom complex (abdominal pain, bloating, alteration in bowel habits)
- Look for Red Flags on history, physical, and lab tests
- Perform selected physical and diagnostic tests to rule out organic disease.
- Make a positive diagnosis
- Initiate a treatment plan based on symptoms
- Follow up office visit in 3-6 weeks

Red Flags

- **History**

- New onset of symptoms
- Onset after age 50
- Weight loss
- Anorexia
- Fever
- Rectal bleeding
- Family history of GI cancer, IBD, or celiac disease



- **Physical**

- Abnormal exam (malleable mass)
- Rectal exam
- Positive occult blood test



- **Initial Labs**

- ↓ HGB - ↑ Sed Rate
- ↑ WBC - Abnormal chemistry
- ↑ TSH - abnormal Celiac



Red Flags

Profile



**The Physical Exam
is
of Limited Value in
Diagnosing IBS!**

William Chandler

Dr. William Gleason

1785

Ohio Historic Society

Collaborative Relationship Results in Improved Treatment Outcomes

- Basic principles of effective clinician-patient collaboration:
 - Show empathy, acknowledge the pain
 - Listen actively
 - Reassure
 - Educate
 - Encourage the patient to participate by keeping a symptom diary
 - Negotiate and set reasonable treatment goals
 - Provide follow-up care



Treatments for IBS and CIC

Bulking Agents (eg, wheat bran, corn fiber, psyllium)

Often cause gas and bloating. Occasionally make constipation worse.

Antispasmodics (eg, hyoscyamine, dicyclomine)

Helpful for pain and spasm, but can worsen constipation and have anticholinergic side effects (dry mouth, decreased sweating)

Antidepressants (eg, TCAs, SSRIs)

Tricyclics work well to decrease visceral hypersensitivity but can worsen constipation. SSRIs have lots of GI side effects but are good for depressed patients

Serotonergic Agents (eg, Tegaserod and Cisapride)

Promotility drugs removed from market due to cardiovascular side effects

Osmotic Laxatives (MOM, MiraLax)

Effective and safe but can bloat and are often unpredictable

Stimulant Laxatives (Cascara, Dulcolax)

Effective short term but can lead to side effects like colonic atony long term.

IBS-C: Key Takeaways

- Wide range of symptoms with hallmarks being:
 - Abdominal pain/discomfort
 - Altered bowel habits
- Often undiagnosed
- Predominantly affects women age 25 to 54 years
- Decreases quality of life
- Fewer than one third of patients are satisfied with their remedies
- Clinician-patient collaboration is important in establishing diagnosis and treatment plan



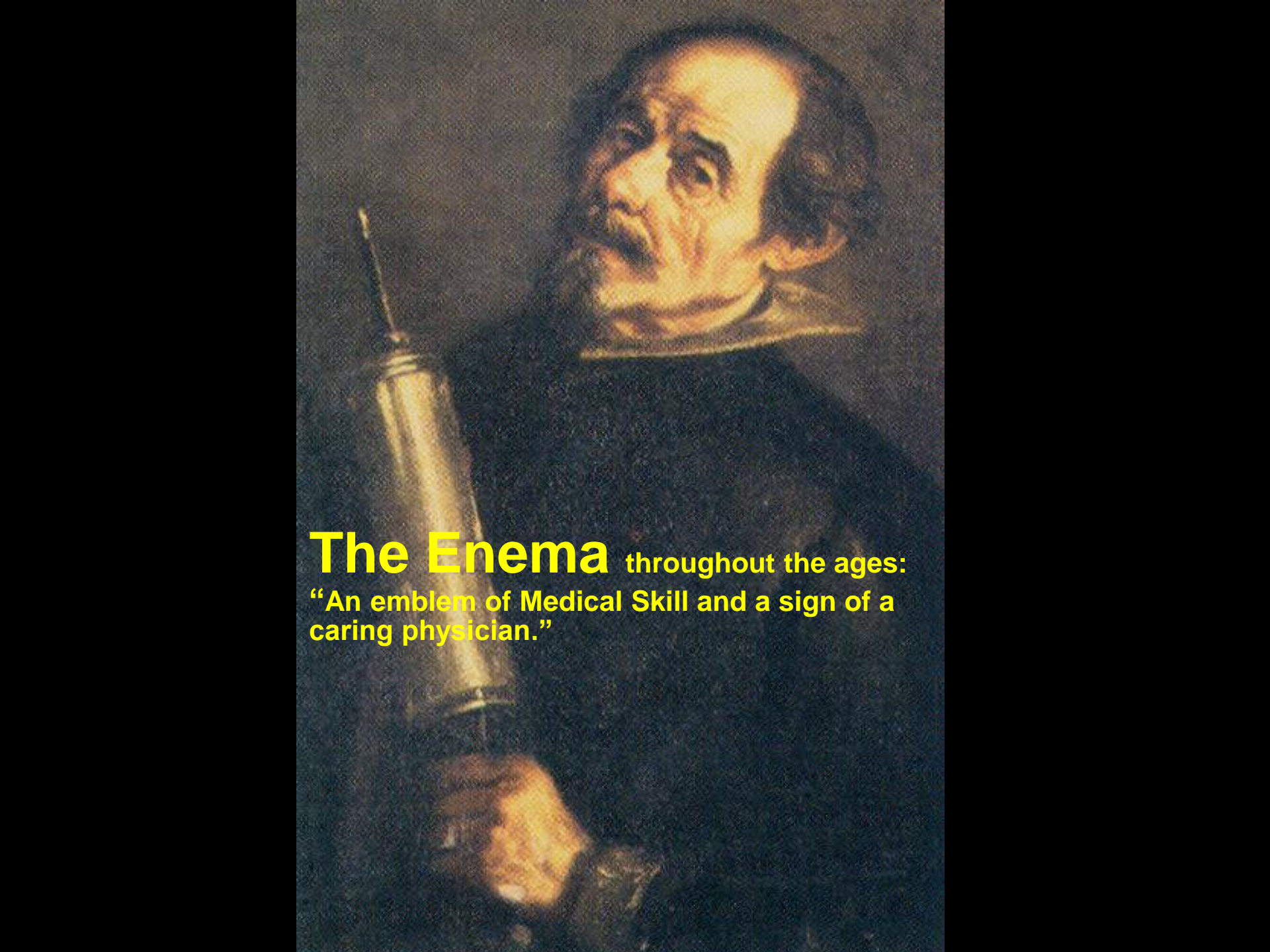
CIC: Key Takeaways

- Affects older patients most commonly
- Women affected more than men 2.2:1
- Major symptoms include infrequent or difficult to evacuate stools.
- Pain is not a primary symptom
- Quality of life may be diminished
- Most patients are unhappy with treatment outcome
- Good provider patient relationship important



Historical Perspective

- Constipation viewed as unhealthy
- “Autointoxication” theory of late 1800’s contributed to habitual use of laxatives
- Treatments of Constipation include:
 - Enemas
 - Laxatives
 - Mechanical and Electrical Devices
 - Physical Therapy and Exercise
 - Surgery

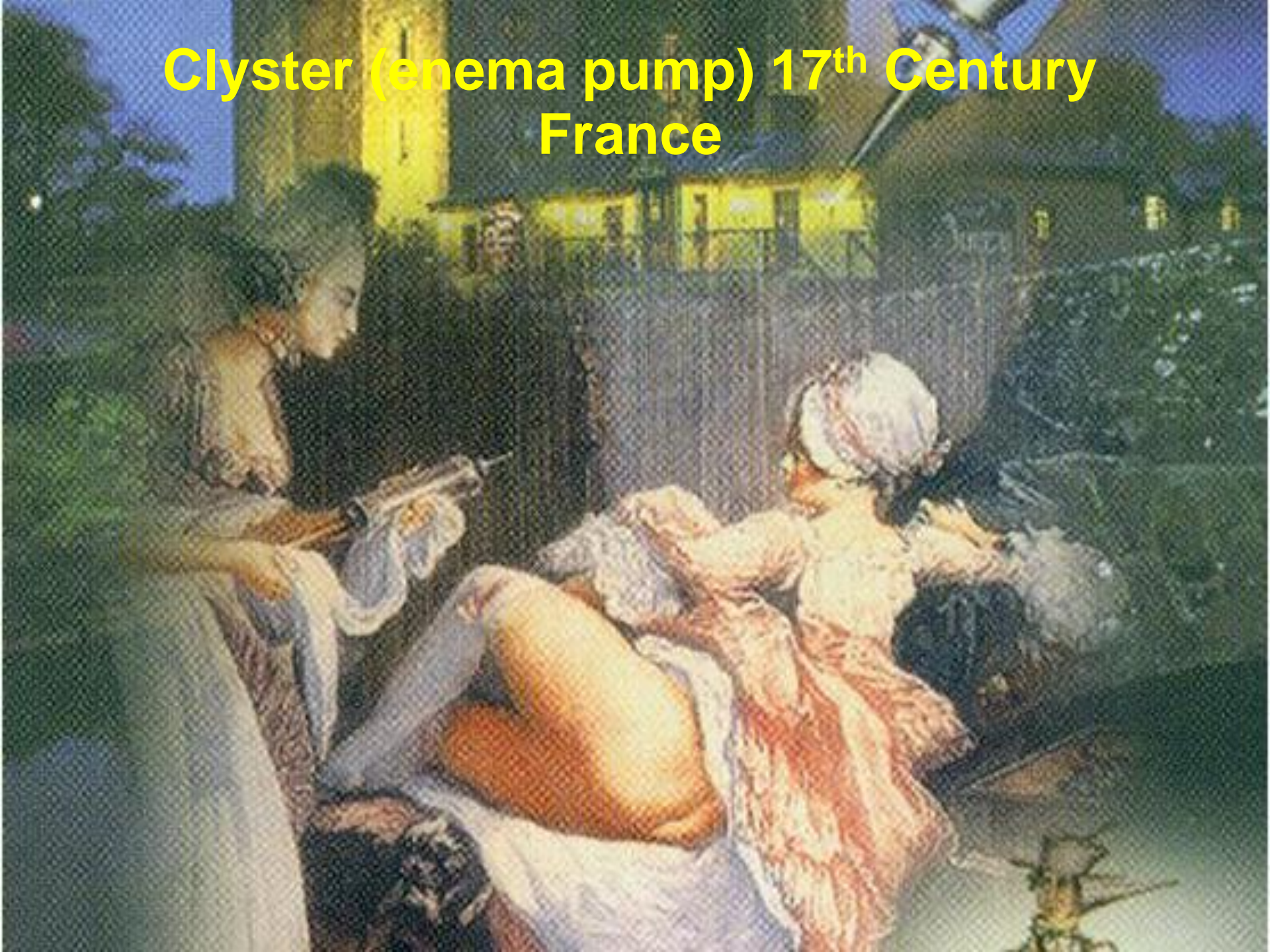
A painting of a man in a dark robe holding a large, ornate syringe. The man has a serious expression and is looking slightly to the left. The syringe is large and metallic, with a long needle. The background is dark and textured.

The Enema throughout the ages:
“An emblem of Medical Skill and a sign of a
caring physician.”

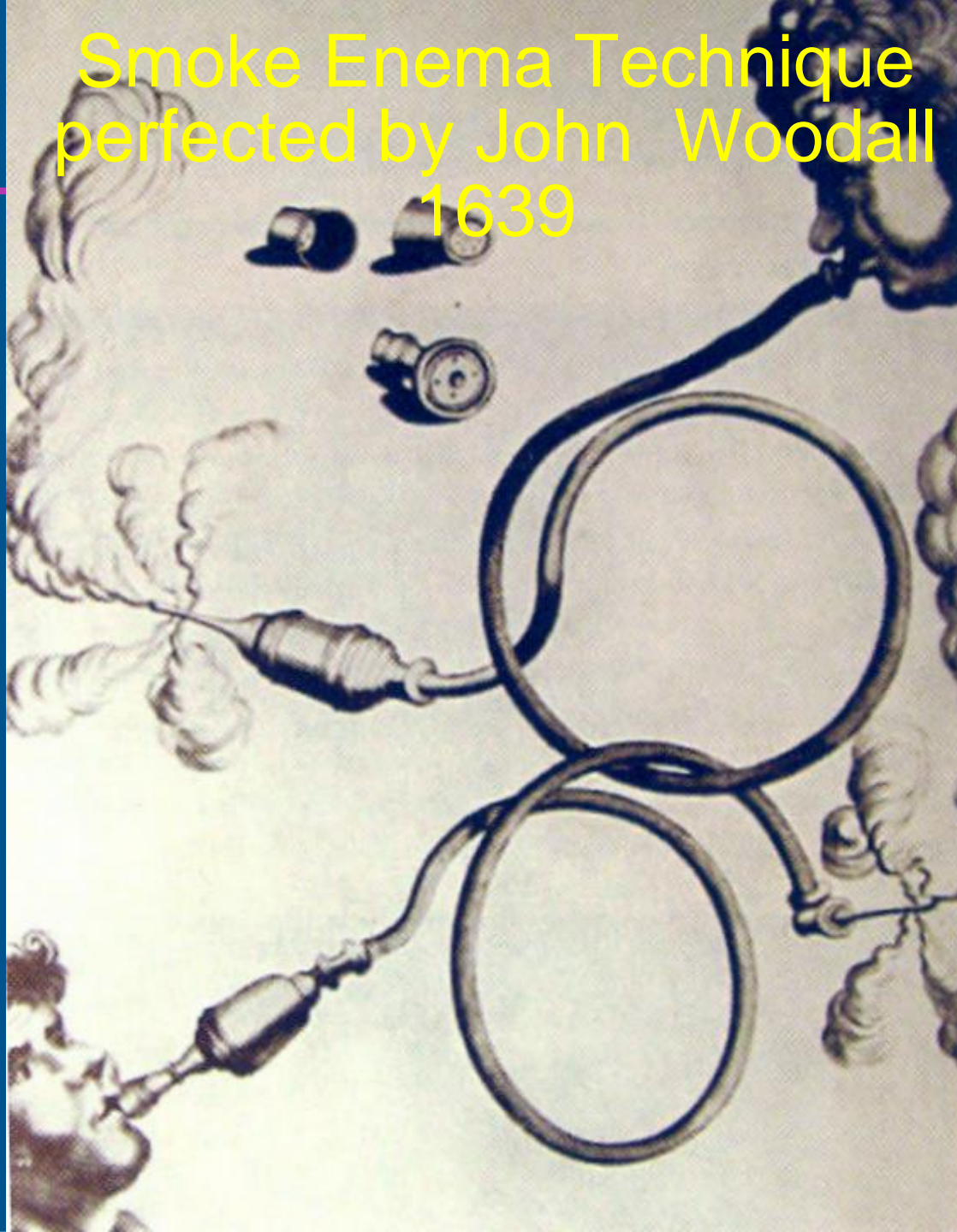
Galen 2nd Century instructing on the use of mild enemas for relief of constipation and stronger therapy for “flux, constant lustful desires and putrid ulcers”



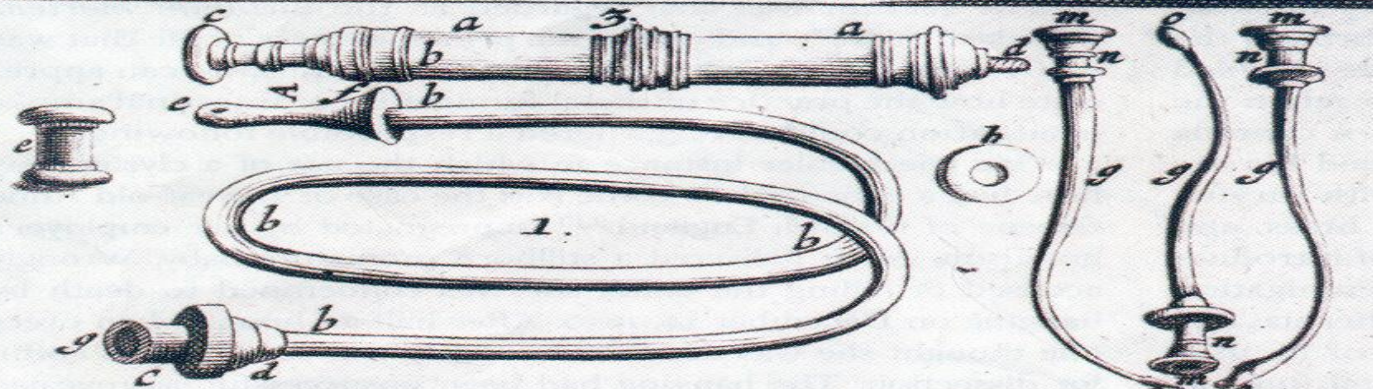
Clyster (enema pump) 17th Century France



Smoke Enema Technique perfected by John Woodall 1639

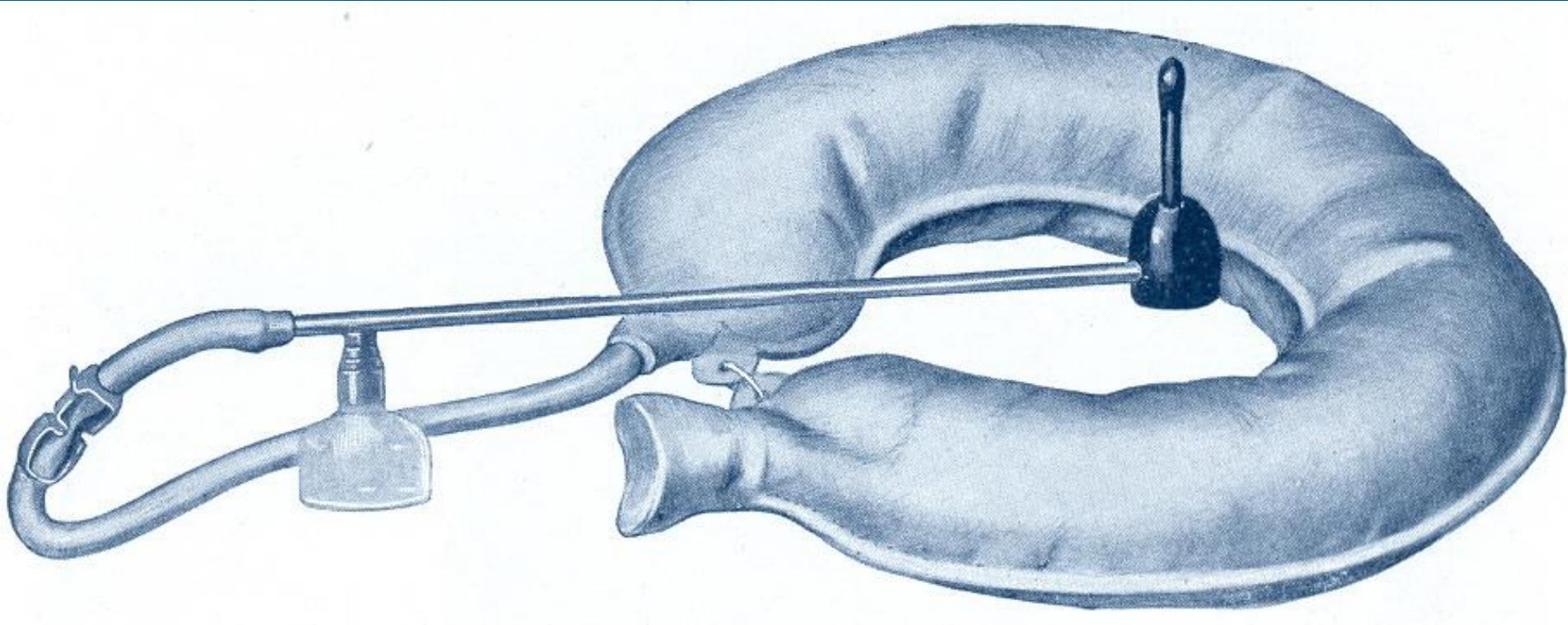


"Rectal Fumigation"

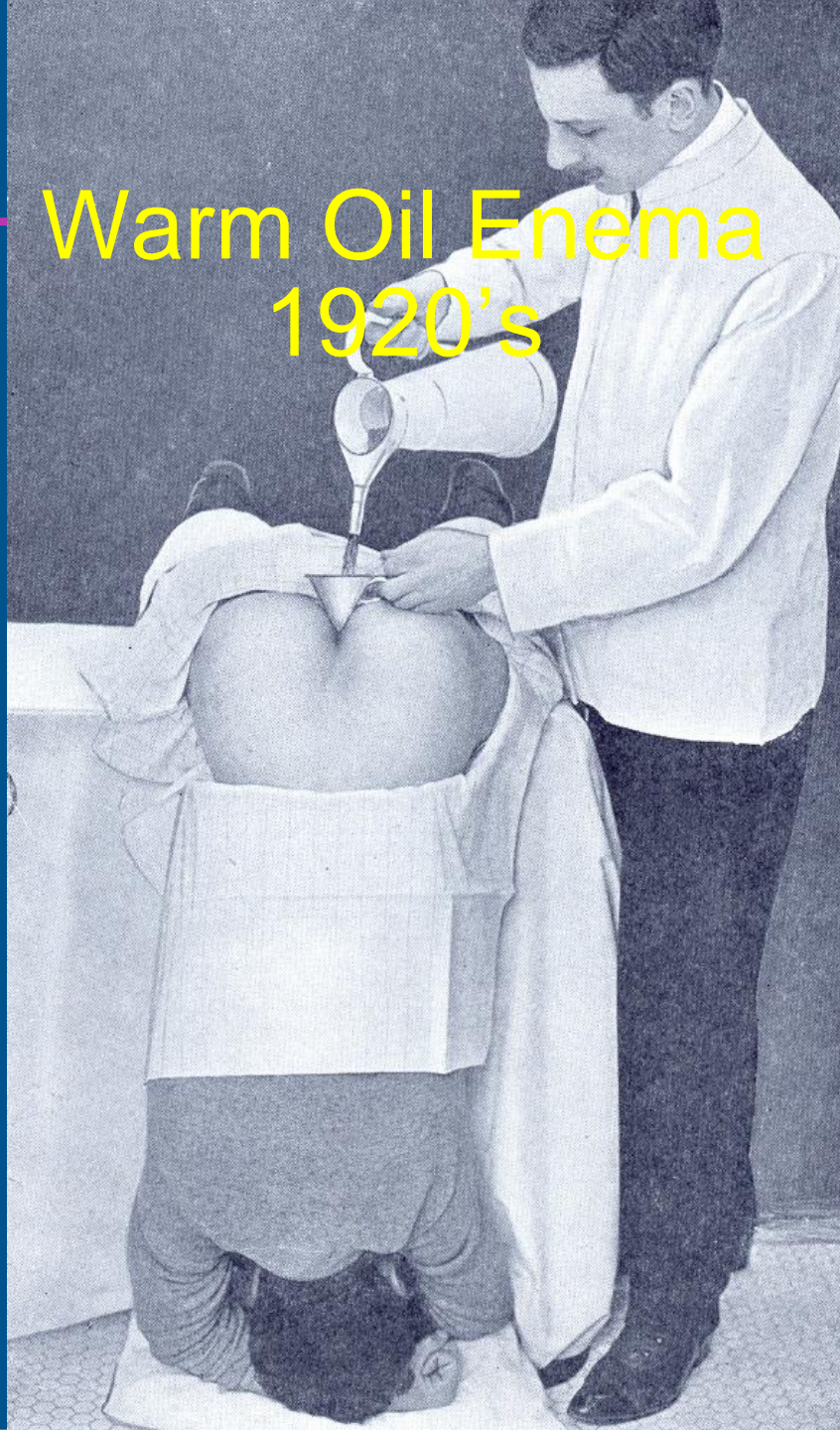


TAB. X. Append.

“Seat Enema” for Self administration 1920’



Warm Oil Enema 1920's



Laxatives and Purgatives



**SNAKE
OIL
LINIMENT**

THE
STRONGEST AND
BEST LINIMENT
KNOWN FOR PAIN
AND LAMENESS.

USED EXTERNAL
ONLY

FOR
RHEUMATISM
NEURALGIA
SCIATICA
LAME BACK
LUMBAGO
CONTRACTED
CORDS
TOOTHACHE
SPRAINS
SWELLINGS
ETC.



—FOR—
FROST BITES
CHILL BLAINS
BRUISES
SORE THROAT
BITES OF
ANIMALS
INSECTS AND
REPTILES.

GOOD FOR
MAN AND BEAST

IT GIVES
IMMEDIATE
RELIEF.

IS GOOD
FOR
EVERYTHING
A LINIMENT
OUGHT
TO BE
GOOD FOR

Manufactured by
CLARK STANLEY
Snake Oil Liniment
Company
Providence, R. I.

Clark Stanley's Snake Oil Liniment

Is for sale by all druggists. If your druggist fails to have it, tell him he can get it for you from any wholesale druggists or it will be sent to you to any part of the United States or Canada upon the receipt of fifty cents in stamps by addressing the

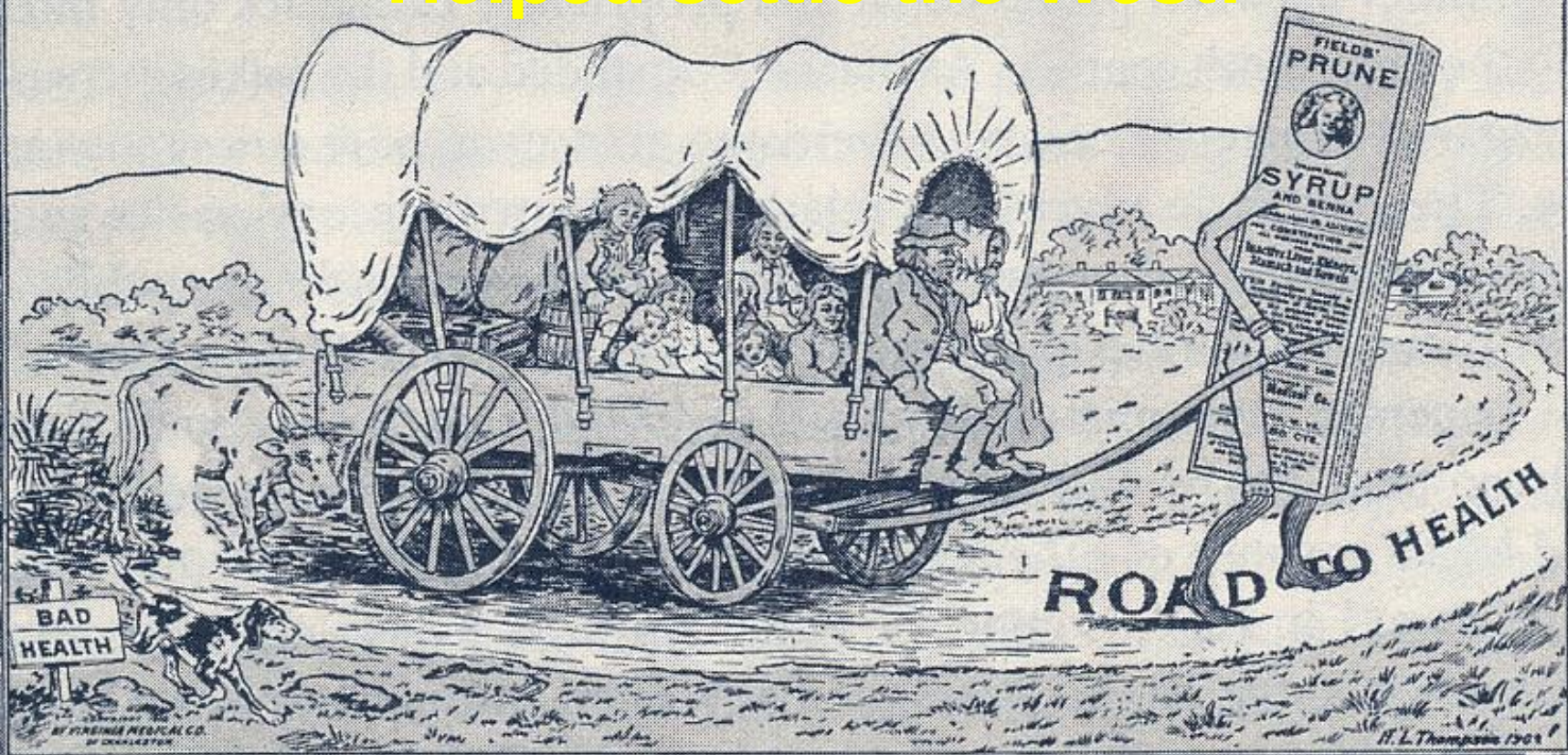
Clark Stanley Snake Oil Liniment Co.

PROVIDENCE, R. I.

Patent Medicines
were popular

FIELDS' PRUNE SYRUP

Helped settle the West!



Moves the Whole Family

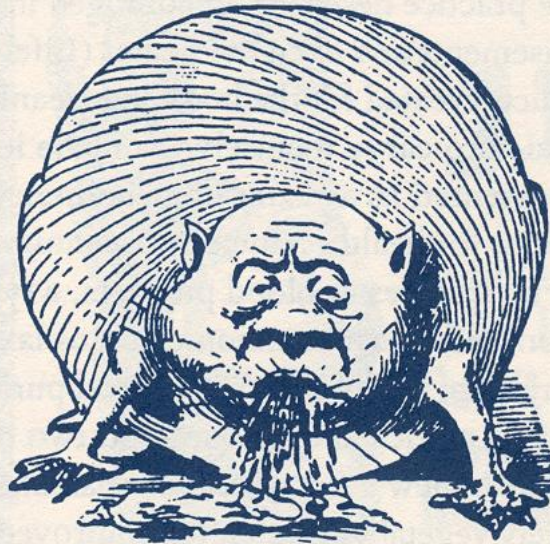
Nature's Gift



A good bowel
movement!

To Women

BOWEL BLOAT



A horrible, slimy monster that makes man's life a misery.

After eating: a bloated belly, belching of gas from the stomach, a foul, ill-smelling scurf on the tongue, dizziness, headache, a sour rising and spitting up of half-digested food, — it's Bowel Bloat.

When the bowels stop working they become filled with putrid, rotting matter, forming poisonous gases that go through the whole body. If you don't have a regular, natural movement of the bowels at least once a day your fate is bowel bloat, with all the nasty, disgusting symptoms that go with it.

There's only one way to set it right.

Clean yourself out gently but thoroughly and tone up your bowels with **CASCARETS**. Every form of bowel trouble is quickly and permanently

CURED BY
Cascarets
CANDY CATHARTIC
BEST FOR THE BOWELS
ALL DRUGGISTS

10c.
25c. 50c.

To any needy mortal suffering from bowel troubles and too poor to buy **CASCARETS** we will send a box free. Address Sterling Remedy Company, Chicago or New York, mentioning advertisement and paper.

LABORATOIRES de l'URODONAL

Produits
garantis et contrôlés.

Spécialités médicales
hautement scientifiques.

Laxatif physiologique

le seul faisant la rééducation
fonctionnelle de l'Intestin.

JUBOL

French Sponge Laxative
"promotes inner hygiene"

Évite l'Appendicite et l'Entérite,
Guérit les Hémorroïdes,
Empêche l'excès d'embonpoint et
Régularise l'harmonie des formes.

Le médecin moderne **ne purge plus** :
il jubolise l'intestin de son malade, car

Purger...

équivalait à passer
l'intestin au papier
de verre.

Le Juboliser

consistait à lui faire
un massage doux,
prolongé
et persuasif.

EN VENTE DANS TOUTES LES BONNES PHARMACIES DU MONDE ENTIER
et aux ÉTABLISSEMENTS CHATELAIN, 2 bis, Rue de Valenciennes, Paris (Métro : Gare de l'Est).

Prix : La boîte (n° 1 mois), 5 fr. ;
cure complète, 6 boîtes, n° 6 mois,
27 fr. Étranger, 5 fr. 50 et 30 fr.

Un Prospectus détaillé
accompagne chaque flacon.

**Soyez bon pour votre Intestin :
Jubolisez-le !**

Figure 4-2. Advertisement for the French product Jubol, which claimed to sponge and wipe the intestine, giving it a "sweet, prolonged and persuasive massage." "Be good to your intestine," the ad urges. "Jubolize it." [The William H. Helfand Collection, New York].

Persistency Plus Kruschen—That's All

How One Plucky Woman Lost 102 Pounds of Fat

Almost Unbelievable, Nevertheless True

Dear Friends:

You advertise Kruschen Salts for reducing, so I finally tried them and when I started I weighed 219 pounds and when I took them for a year and 3 weeks, I lost exactly 102 pounds.

I am 23 years old and I look at least 5 years younger now than I did when I was fat. I have a picture of myself before and after so if you want to see them let me know.

I am always telling my friends about the wonderful salts. I am always advertising them.

I took 2 bottles every month for 3 weeks and 3 weeks. I am now down to 117 pounds. I lost 102 pounds in 1 year and 3 weeks.

I am sure if you let me know I will send you a picture of myself before and after.

Yours truly,

Miss Nellie Simpson,
1903 Wayne St., Swanton, N.Y.
Oct. 1, 1931

The picture at the top is Miss Nellie Simpson before taking Kruschen. Her weight was 219 lbs. Contrast this with the charming picture on the left showing Miss Simpson after she reduced 102 lbs. with the Kruschen treatment and now weighs 117 pounds.



Laxatives Help you lose weight!

The Modern Safe Way—Right Way to Lose Fat

A fashionably slender figure as well as glorious, magnetic health can now be yours! Just take a half teaspoonful of Kruschen Salts in a glass of hot water every morning before breakfast.

You can hasten the reducing action of Kruschen by going lighter on potatoes, pastry and fatty meats.

Unlike other Salts, Kruschen doesn't reduce by rushing food thru your system. Rather it's an ideal blend of 6 separate mineral salts which help every gland, nerve and body organ to function properly.

Women everywhere are overjoyed with this marvelous reducing treatment. Pound by pound of surplus fat leaves and soon you possess that trim, bewitchingly slender figure you've always craved.

What splendid new strength, greater body activity, vivaciousness in every body movement! More alert thinking powers! Kruschen keeps the bowels, kidneys and liver in fine condition—it frees you from poisons and toxins and gives radiantly clear complexion—REAL beauty which only comes from within a perfect functioning system.



An 85c bottle of Kruschen (lasts 4 weeks) is sold by druggists the world over—so start this SAFE method to lose ugly fat TO-DAY!

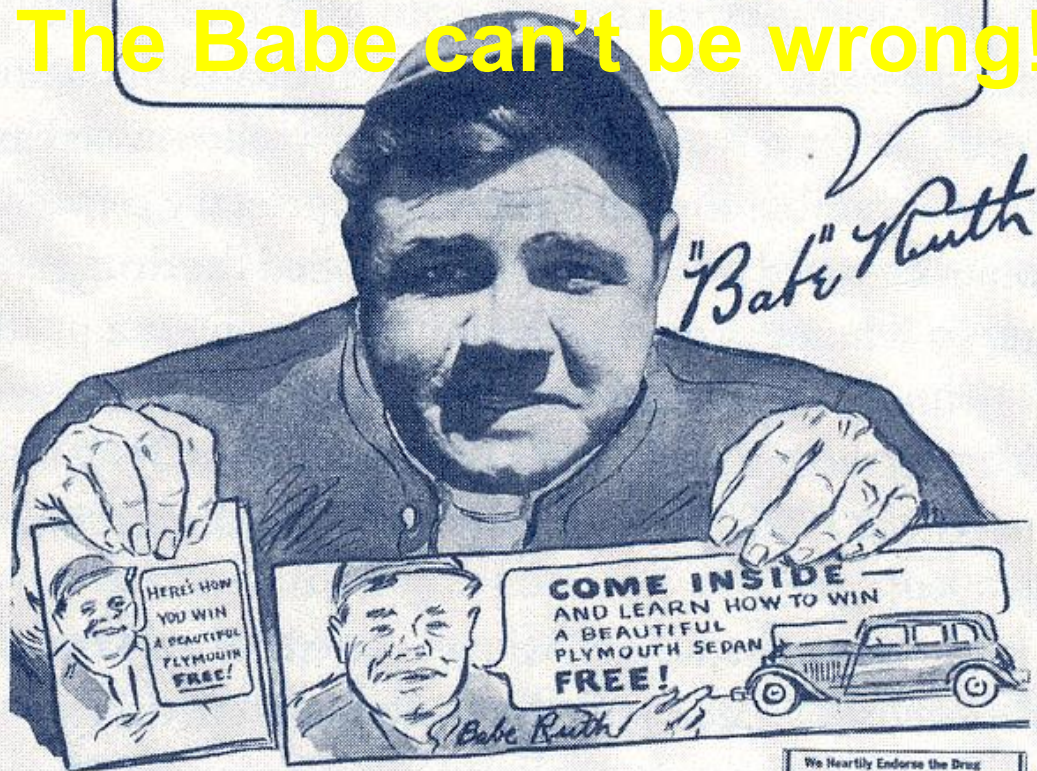
KRUSCHEN SALTS

"IT'S THE LITTLE DAILY DOSE THAT DOES IT"

They Can imitate the Advertising Copy, but they Can't imitate the Product
E. Griffith Hughes Inc.—Rochester N.Y.

**PUT ME TO WORK
IN YOUR STORE**

The Babe can't be wrong!



• Have you heard about the sensational new FEEN-A-MINT contest, sponsored by Babe Ruth to be introduced in the Hearst Comic Weekly on July 2nd?

First prize, a brand-new Plymouth Sedan. One hundred second prizes, baseballs autographed by Babe Ruth. And to everyone who enters, win or lose, a lifelike Babe Ruth mask, a complimentary package of FEEN-A-MINT, and a new scientific booklet.

Here's a set-up that's not only going to sell a lot of FEEN-A-MINT, but is also going to bring thousands of people into drug stores all over the country. What about your store? Where are the people in your neighborhood going to get their information?

Drop a line to Health Products Corporation and ask for these Babe Ruth window stickers and leaflets giving full details of the contest, to be given away to your customers.

We Heartily Endorse the Drug Institute of America Because:

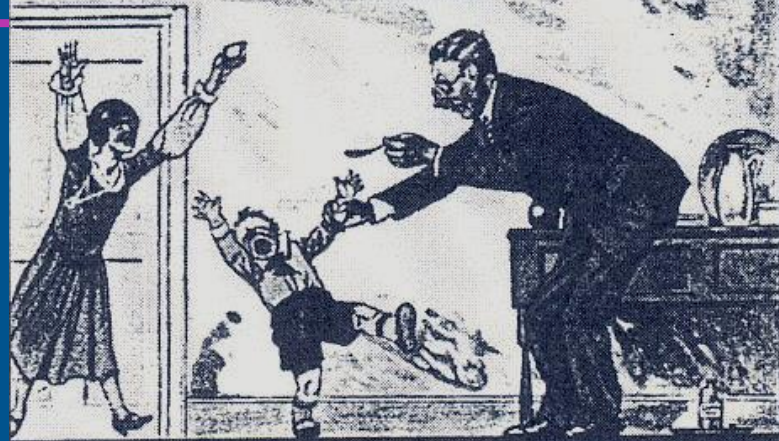
We stand now as we have always stood for the principles that are incorporated in the Institute's program. We, as manufacturers, will consider it a pleasure to cooperate with our customers and other branches of this important business group to make it a better and greater industry.

W. H. Berg
Pres., Health Products Corp., Jamaica, N. Y.

Feen-a-mint

White's Cod Liver Oil Concentrate Dillards Aspergum Feen-a-mint

Mamma knows best
“Good” Moms give
it to their children!



Feen-a-mint
The Chewing **LAXATIVE**
No Taste but the Mint-
Chew it like Gum

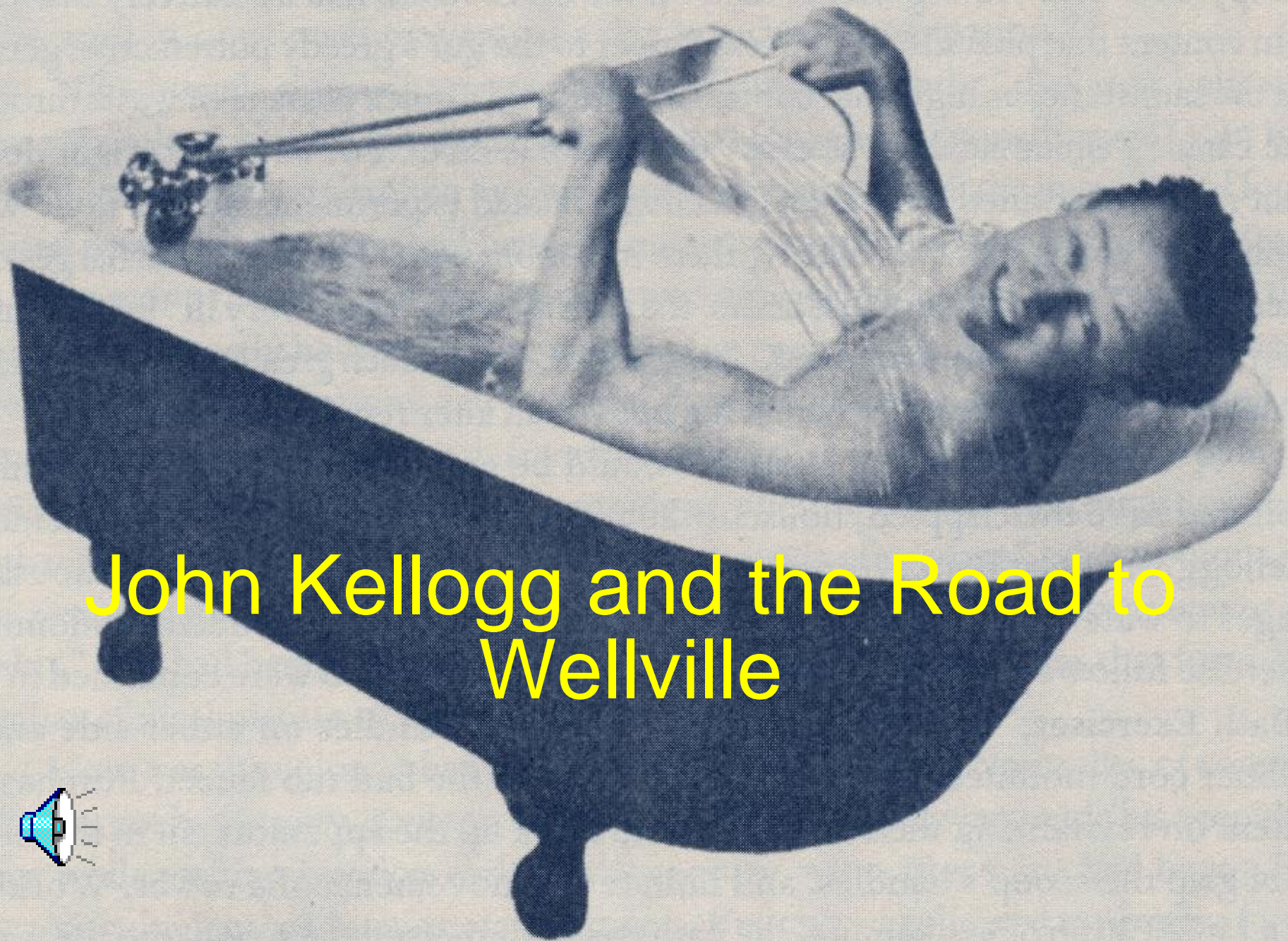
Physical Therapy and Exercise

The Battle Creek Sanitarium

The ideal place to rest; to accurately learn your exact physical condition, to have applied the physiological and dietetic methods necessary to eliminate the causes of your illness and to build up per-

HEALTH permanent health. Luxurious modern appointments, moderate rates, delicious health cuisine, 200 kinds of baths, electricity, swimming pools, **REST** indoor palm garden, tonic Michigan climate, 860 feet above sea level; 300 trained nurses, 30 physicians; accommodations for 1000 guests. Illustrated Catalogue free.

The Sanitarium, Box 75, Battle Creek, Mich.



John Kellogg and the Road to Wellville



Exercise Helps Prevent Constipation



Mechanical and Electrical Devices

The Better Way

Price \$3.75 Per Set in the U. S. Sold Only in Sets

DR. YOUNG'S IDEAL RECTAL DILATORS

(Reg. U. S. Pat. Office)
For the Auxiliary Treatment of
PILES AND CONSTIPATION
IN CONJUNCTION WITH DR. YOUNG'S PILEMENT FOR THE
RELIEF OF RECTAL IRRITATION AND ITCHING.

THE OBJECT of this treatment is to stretch or dilate the rectal muscles more than they have been accustomed to, and to a point where it causes some momentary pain or thrill. This quickly passes as the muscles relax and decrease with each treatment. The pain on inserting may be relieved by the free use of Dr. Young's Pilement, which also is recommended as a most satisfactory and convenient lubricant.

DIRECTIONS: Begin with a size that can be easily inserted. Lubricate with vaseline or with Dr. Young's Pilement and while in a squatting position—or while lying on the side with the knees drawn up, gently insert in the rectum as far as the flange or rim. Hold in place a minute and the rectal muscles will close and retain it. Sit or lie down and allow it to remain for half an hour

or an hour to get the best results. Ten minutes will accomplish much. When ready to use a larger size it is best to first use the next smaller size for a few minutes, inserting and withdrawing it several times. This is very beneficial and should not be overlooked. Try to use the Dilators each day; their regular use tends to tone and strengthen the muscles and the dilation method is sensible and practical. Keep your Dilators and make occasional use of them. You will find it well worth while. If used before retiring they will be found a promoter of more refreshing sleep by those who suffer from the conditions for which intended. Their use in the morning encourages natural bowel action, and at a time favored by nature.

TO CLEAN: Wash with hot or cold water and soap. Read important instructions in bottom of box.

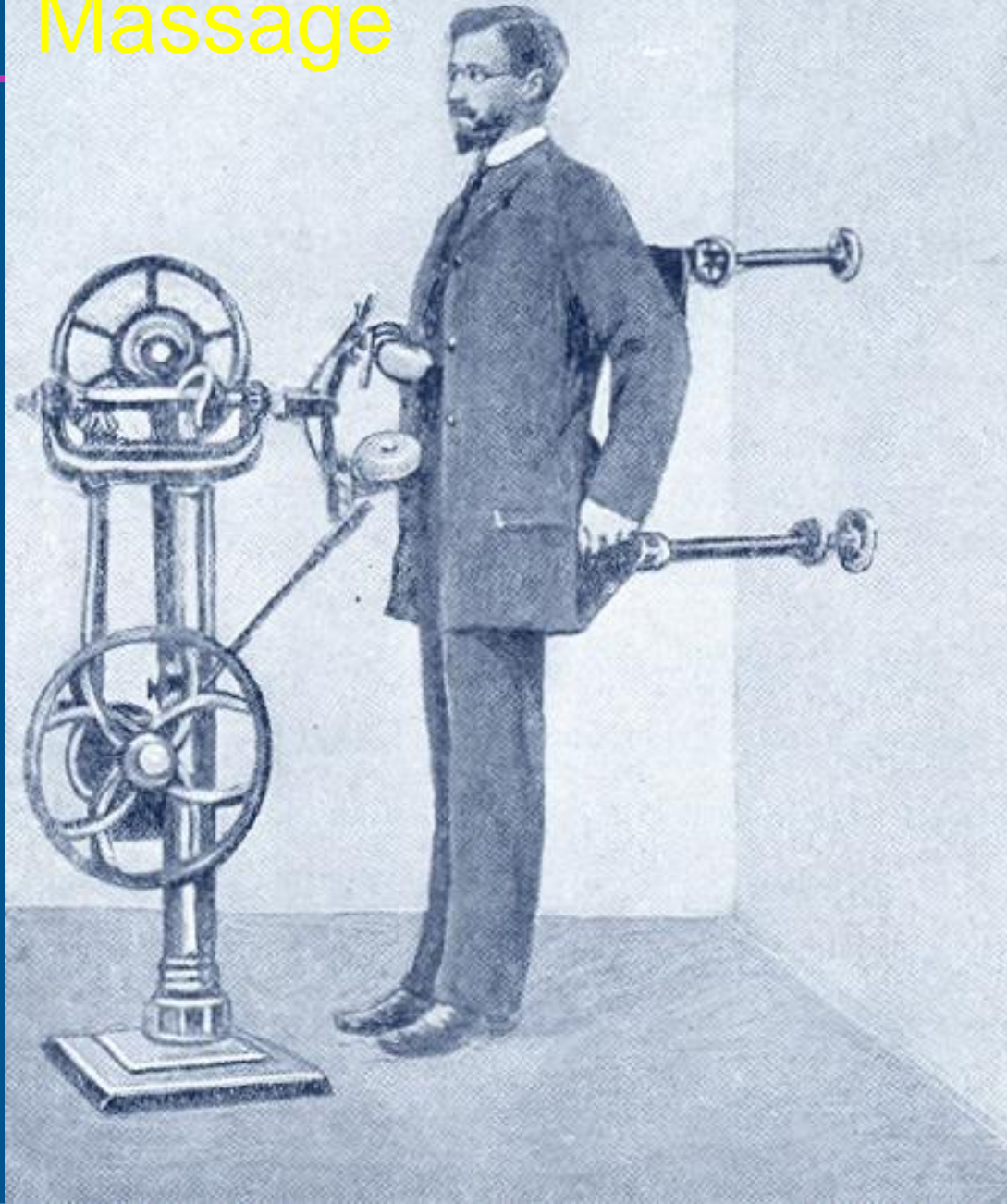
F. E. YOUNG & CO. Grand Crossing CHICAGO, U. S. A.



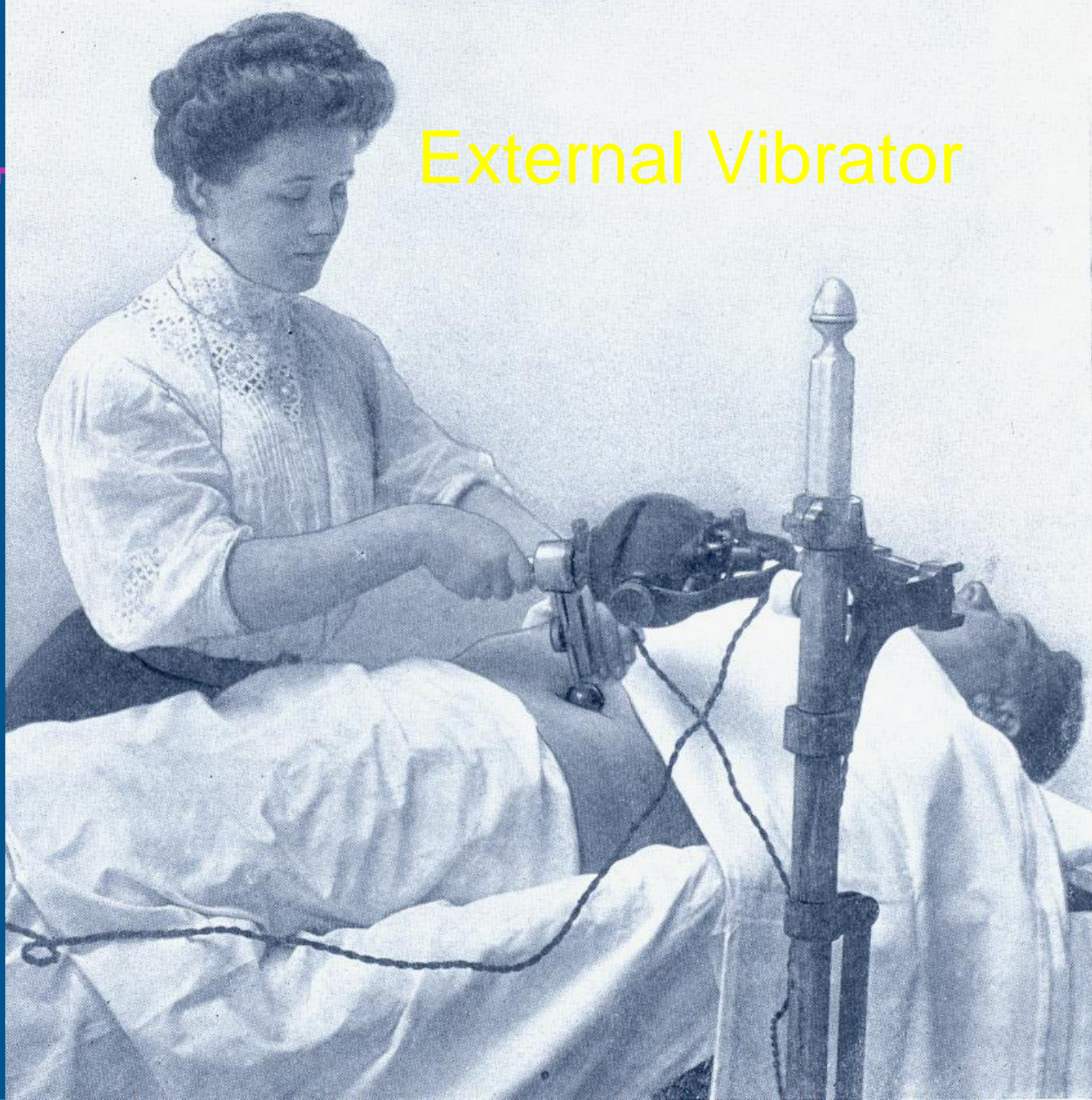
Mechanical Horse



Rotary Wheel Massage



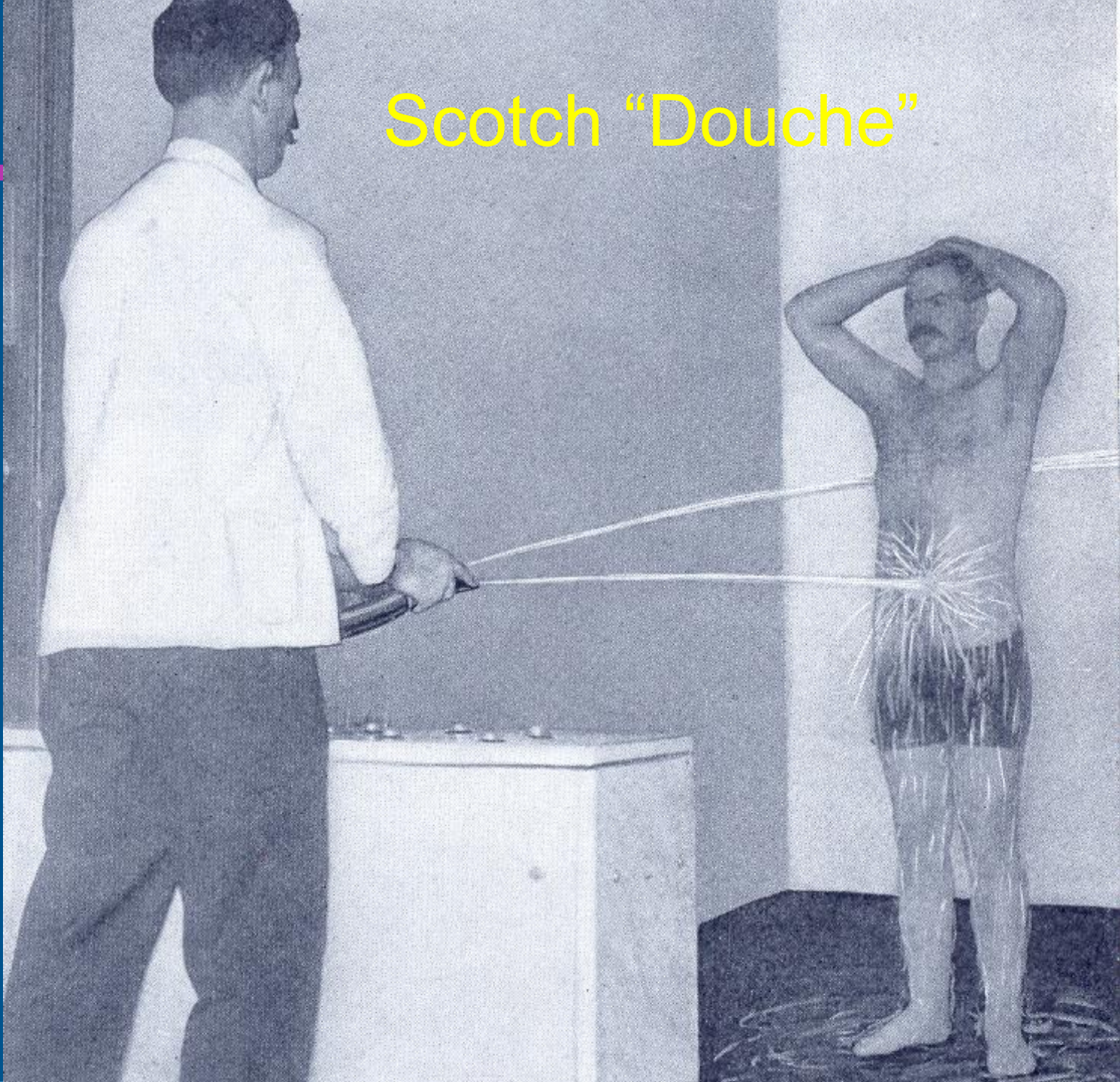
External Vibrator



Oxygen "Bath"



Scotch "Douche"



Electric Cabinet Featuring Galvanic, Faradic, High Frequency, and Sinusoidal Currents

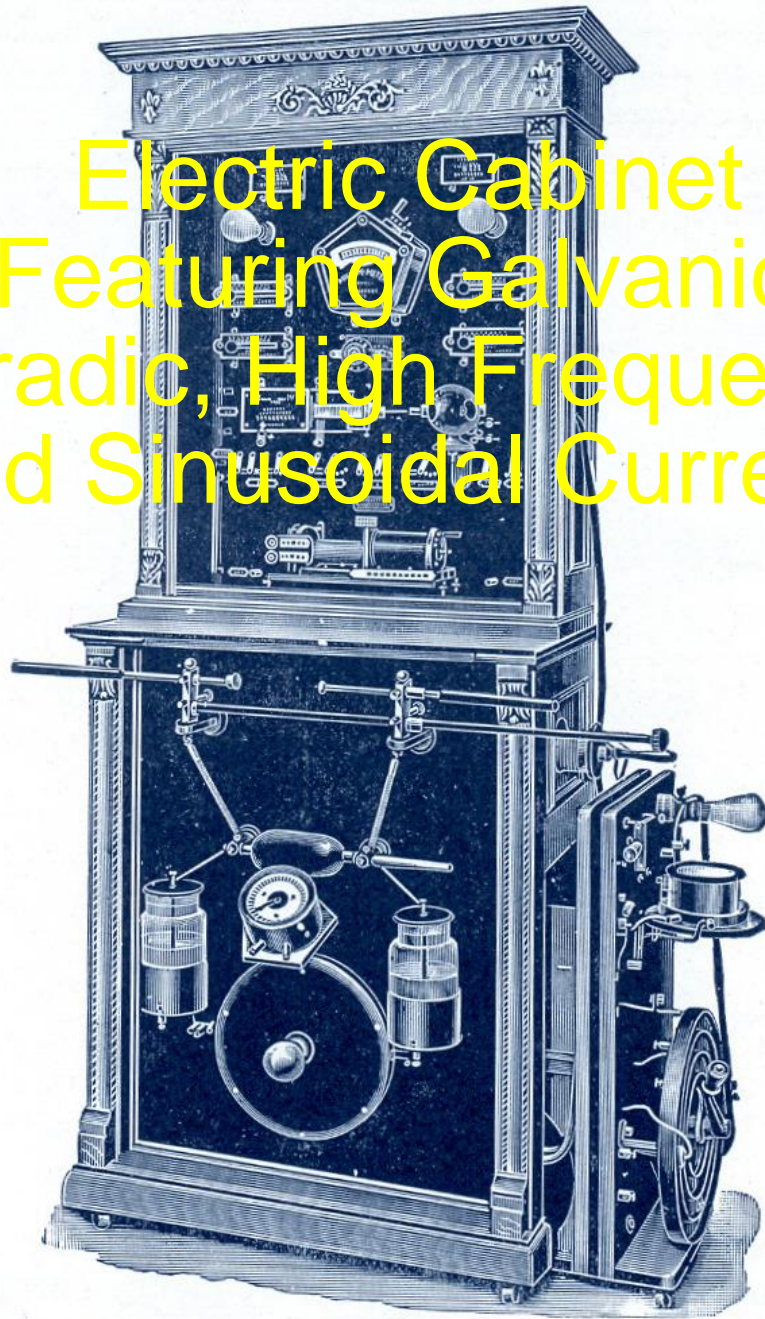
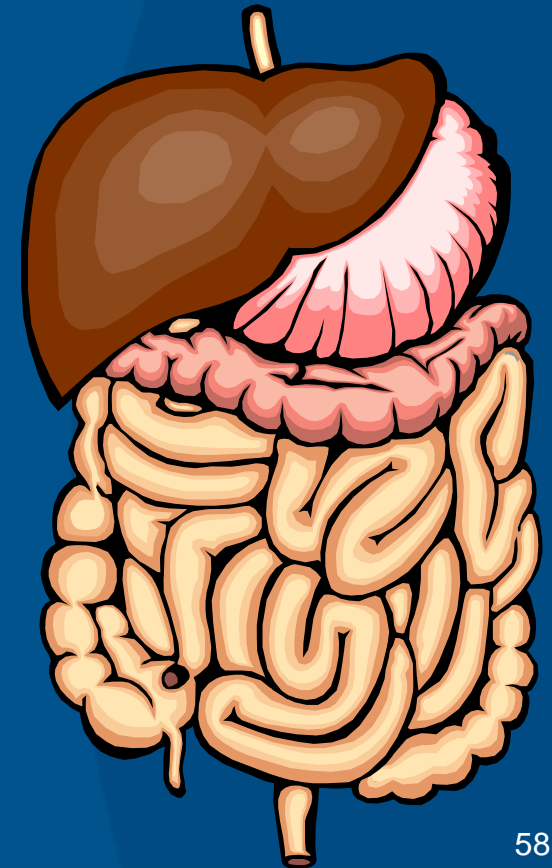


Fig. 835.—Author's electric cabinet combining the galvanic, faradic, high-frequency, and sinusoidal currents useful in different types of constipation.



Surgical Treatment of Constipation

- Lane's Kinked Colon theory
- Appendectomy
- Cecostomy with lavage
- Sigmoid Resection
- Sub total Colectomy



New Treatments for IBS-C and CIC

- Amitiza (Lubiprostone)
- Linzess (Linaclotide)
- Trulance (Plecanatide)

These drugs work by opening chloride channels in the gut which leads to increased intra-luminal fluid which causes increased motility.

Amitiza reduces pain in theory by tightening intracellular junctions

Linzess reduces pain through a direct effect of Cyclic GMP on intracellular nerves


Trulance does not have an IBS indication yet

AMITIZA® (lubiprostone): Approved for Treatment of CIC and IBS-C

- AMITIZA is indicated for the treatment of:
 - IBS-C in women ≥ 18 years old
 - Chronic idiopathic constipation (CIC) in adults
 - Opioid induced constipation (OIC) in adults with chronic non cancer pain

Dosing

IBS-C	CIC and OIC
8 mcg BID with food and water	24 mcg BID with food and water



AMITIZA® (lubiprostone) in IBS-C: Proposed Mechanism of Action

- The mechanism of action of AMITIZA in IBS-C is unknown
- Ex-vivo studies using ischemic porcine intestine suggest that activation of CIC-2 by lubiprostone has been shown to stimulate recovery of mucosal barrier function via the restoration of tight junction protein complexes¹
- The following illustrates the proposed mechanism of action of AMITIZA



Double Click for
Next Slide

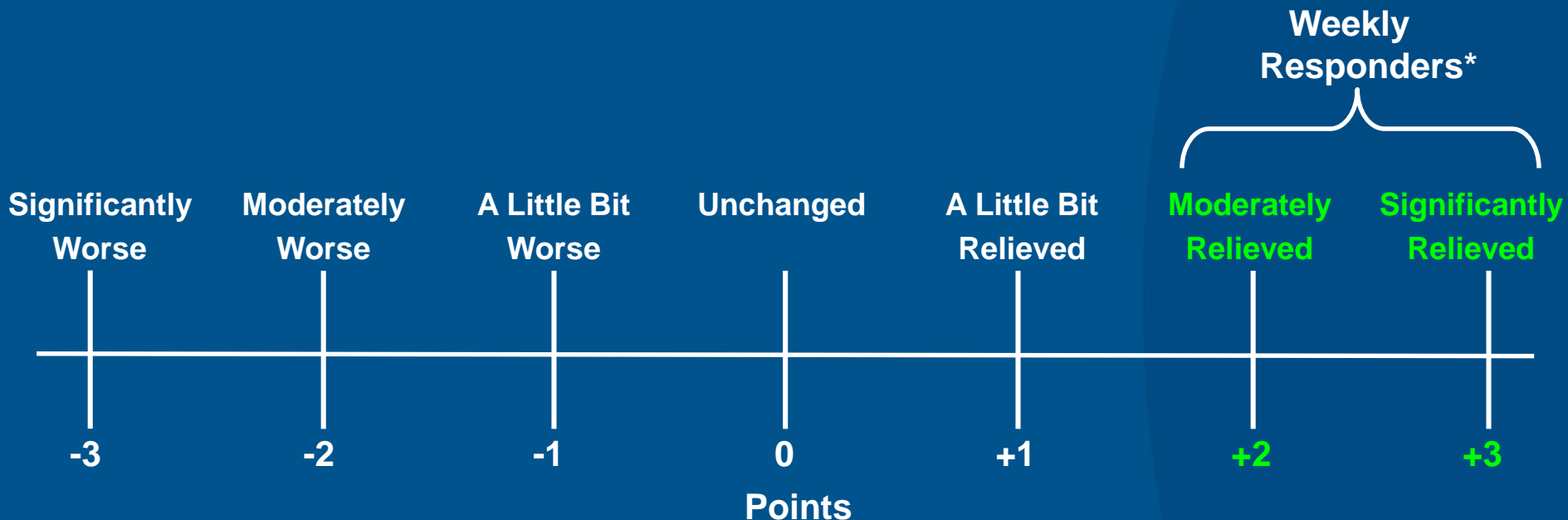


AMITIZA® (lubiprostone)

- An orally active, functional fatty acid with a unique mechanism of action
 - Selectively activates type-2 chloride channels (ClC-2)¹
 - Enhances intestinal fluid secretion without altering serum electrolyte levels²
 - Animal studies suggest that AMITIZA stimulates recovery of mucosal barrier function in ischemic porcine ileum and colon³
 - Approved for treatment of women ≥ 18 years old with IBS-C (8 mcg BID) and adults with chronic idiopathic constipation (24 mcg BID)⁴
 - Evaluated in >2200 patients in numerous clinical studies

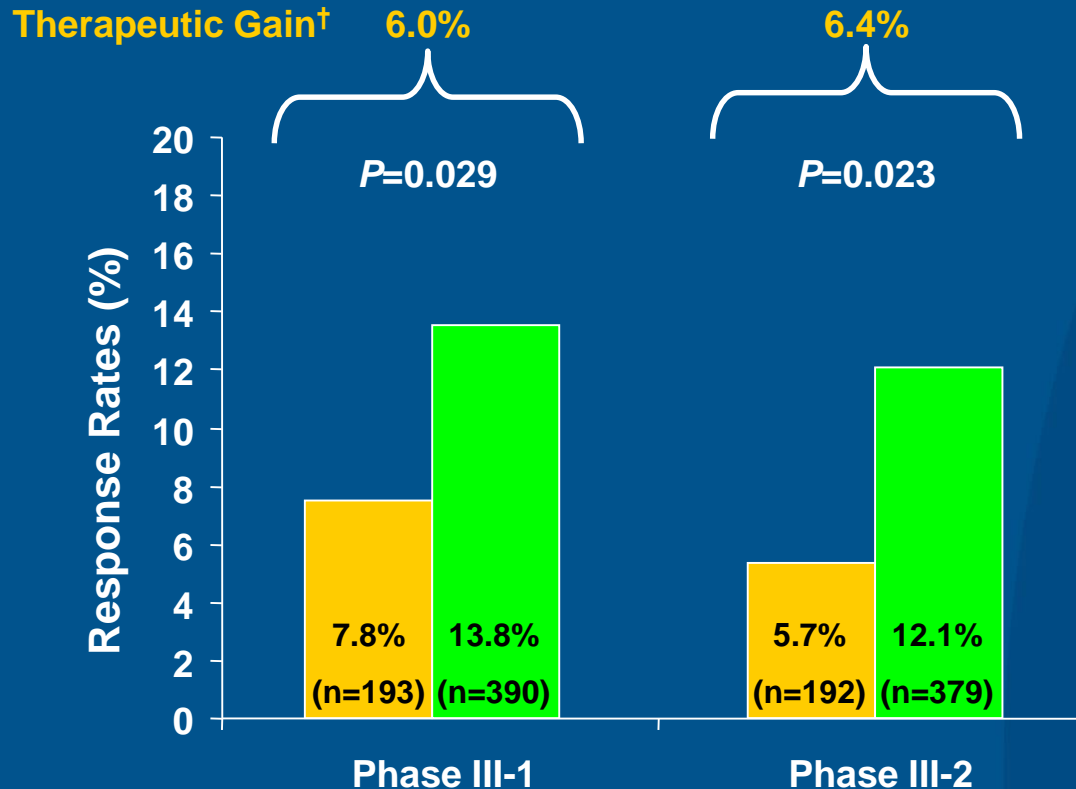
AMITIZA® (lubiprostone): Phase III IBS-C Studies Used Balanced 7-Point Symptom Relief Scale

- In 2 clinical studies, patients were asked weekly how they felt about their relief:
 - “How would you rate your relief of IBS-C symptoms (abdominal discomfort/pain, bowel habits, and other IBS-C symptoms) over the past week, compared to how you felt before you entered the study?”



*Significantly relieved and moderately relieved were considered to be responders

AMITIZA[®] (lubiprostone) IBS-C: Overall Responder* Rates



*Overall responders defined as subjects who were monthly responders for ≥ 2 out of any 3 months

†Therapeutic gain=treatment response rate minus placebo response rate

1. AMITIZA[®] [package insert]. Bethesda, MD: Sucampo Pharmaceuticals, Inc; 2008.
2. Sucampo Pharmaceuticals, Inc. Data on File.



AMITIZA[®] (lubiprostone): Incidence of AEs* Across All IBS-C Studies

Adverse Event	Placebo (%) n=435	AMITIZA (%) n=1011
Nausea	4	8
Diarrhea	4	7
Abdominal pain	5	5
Abdominal distension	2	3

*Treatment-related (possibly or probably related) adverse events reported by $\geq 1\%$ of subjects during double-blinded treatment (safety evaluable subjects) who took AMITIZA 8 mcg twice daily and that occurred more frequently with study drug than placebo

Pooled Safety Analysis from placebo-controlled 12-week trials=Phase II, Phase III-1, and Phase III-2 data

AMITIZA (lubiprostone) 24 mcg Twice Daily: Demonstrated Rapid Relief in Majority of CIC Patients¹⁻³



* $P \leq 0.0024$ vs placebo. † $P < 0.0001$ vs placebo

Please see Important Safety Information in this presentation

1. AMITIZA [package insert]. Bethesda, MD: Sucampo Pharma Americas, LLC; 2013.
2. Johanson, F, et al. *Am J Gastroenterol*. 2007;102(1):1-8.
3. Data on file. Sucampo Pharma Americas, LLC.

Treatment with AMITIZA (lubiprostone) 24 mcg Twice Daily vs Placebo: Symptom Improvement in Two 4-Week CIC Studies

- Symptoms* included¹⁻³:
 - Abdominal bloating
 - Abdominal discomfort
 - Stool consistency
 - Straining
 - Constipation severity
- In patients with CIC, the most common adverse reactions (incidence >4%) were nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence¹

* Secondary endpoint in phase 3 studies

Please see Important Safety Information in this presentation

1. AMITIZA [package insert]. Bethesda, MD: Sucampo Pharma Americas, LLC; 2013.

2. Banish CF, et al. *Dig Dis Sci*. 2010;55(4):1090-1097.

3. Johanson JF, et al. *Am J Gastroenterol*. 2008;103(1):170-177.

AMITIZA® (lubiprostone)

- An orally active, functional fatty acid with a unique mechanism of action
 - Selectively activates type-2 chloride channels (ClC-2)¹
 - Enhances intestinal fluid secretion without altering serum electrolyte levels²
 - Animal studies suggest that AMITIZA stimulates recovery of mucosal barrier function in ischemic porcine ileum and colon³
 - Approved for treatment of women ≥ 18 years old with IBS-C (8 mcg BID) and adults with chronic idiopathic constipation (24 mcg BID)⁴
 - Evaluated in >2200 patients in numerous clinical studies

AMITIZA[®] (lubiprostone): Important Safety Information

- AMITIZA[®] (lubiprostone) is indicated for the treatment of Chronic Idiopathic Constipation (24 mcg) in adults and for Irritable Bowel Syndrome with Constipation (8 mcg) in women ≥ 18 years old
- AMITIZA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be thoroughly evaluated by the treating physician to confirm the absence of such an obstruction prior to initiating AMITIZA treatment.

Please see Takeda representative for full prescribing information.

AMITIZA[®] (lubiprostone): Important Safety Information

- The safety of AMITIZA in pregnancy has not been evaluated in humans. AMITIZA should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Women who could become pregnant should be capable of complying with effective contraceptive measures.

Please see Takeda representative for full prescribing information.

AMITIZA[®] (lubiprostone): Important Safety Information

- Patients taking AMITIZA may experience nausea. If this occurs, concomitant administration of food with AMITIZA may reduce symptoms of nausea. Patients who experience severe nausea should inform their physician.
- AMITIZA should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment and inform their physician if the diarrhea becomes severe.
- Patients taking AMITIZA may experience dyspnea within an hour of first dose. This symptom generally resolves within three hours, but may recur with repeat dosing. Patients who experience dyspnea should inform their physician.

Please see Takeda representative for full prescribing information.

AMITIZA[®] [package insert]. Bethesda, MD: Sucampo Pharmaceuticals, Inc; 2008.

AMITIZA[®] (lubiprostone): Important Safety Information

- In clinical trials of AMITIZA (24 mcg) in patients with Chronic Idiopathic Constipation, the most common adverse reactions (incidence >4%) were nausea (29%), diarrhea (12%), headache (11%), abdominal pain (8%), abdominal distention (6%), and flatulence (6%).
- In clinical trials of AMITIZA (8 mcg) in patients with Irritable Bowel Syndrome with Constipation, the most common adverse reactions (incidence >4%) were nausea (8%), diarrhea (7%), and abdominal pain (5%).

Please see Takeda representative for full prescribing information.

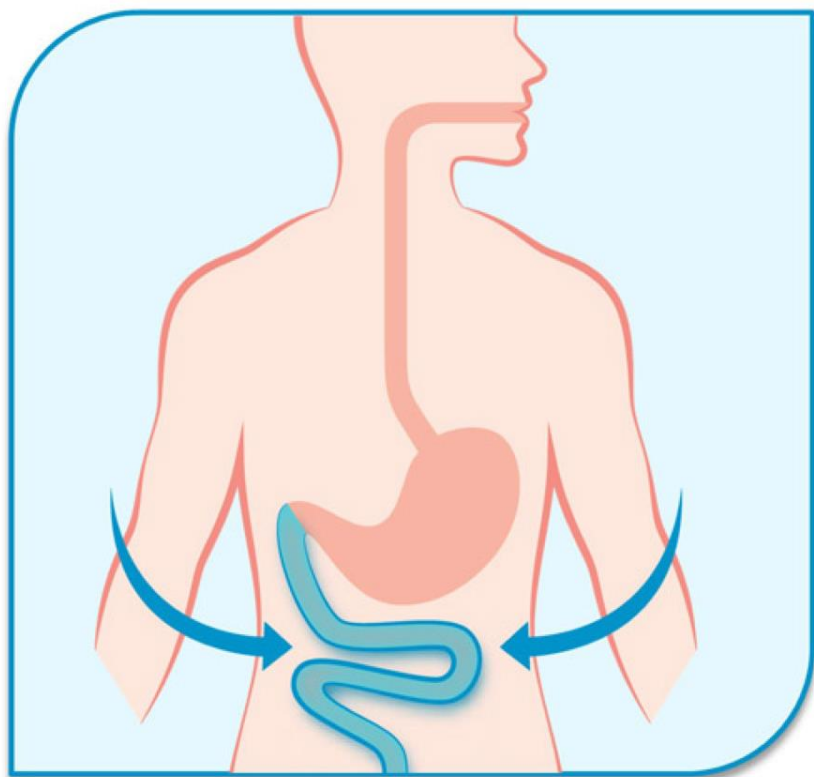
AMITIZA[®] [package insert]. Bethesda, MD: Sucampo Pharmaceuticals, Inc; 2008.

Linzess [®]
(linaclotide) capsules
290 mcg for IBS-C • 145 mcg for CIC

A Clinical Review

Please see Important Safety Information section in this presentation and full Prescribing Information provided to you at this presentation and at LINZESShcp.com.

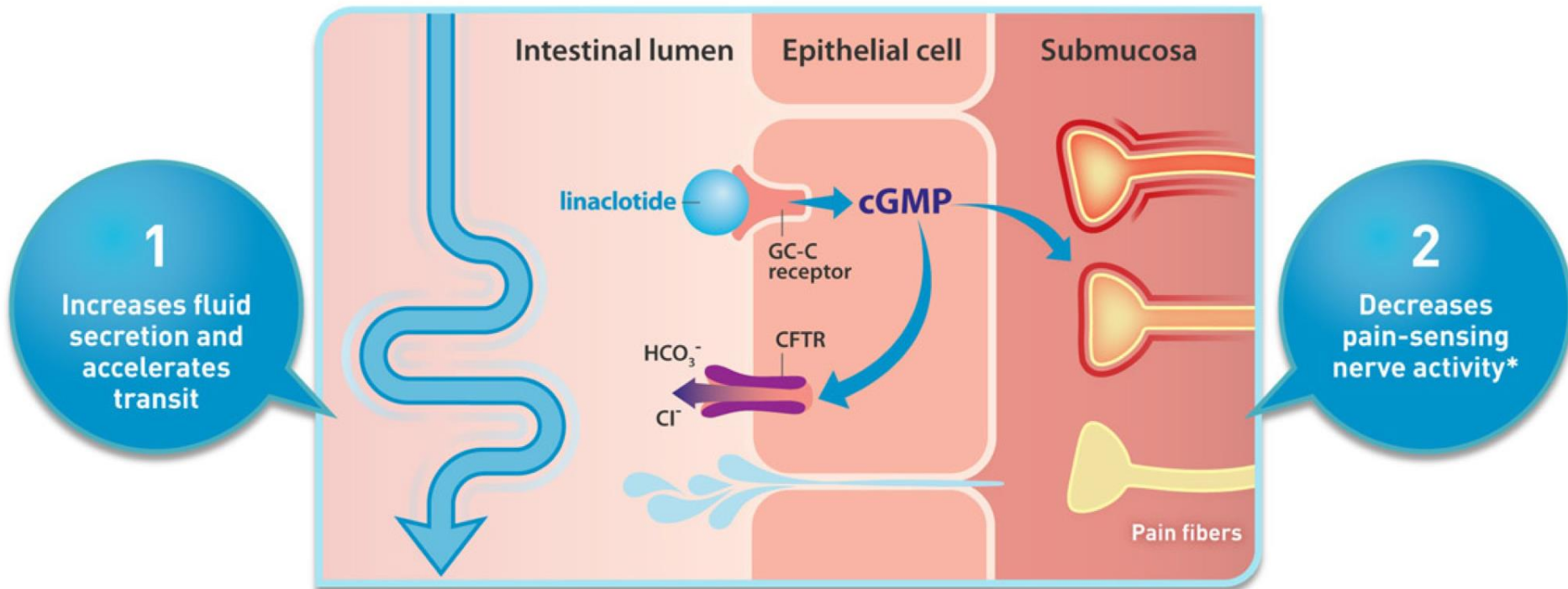
LINZESS Acts Locally and is Minimally Absorbed



**LINZESS acts locally
in the intestines**

- LINZESS is a guanylate cyclase-C (GC-C) agonist
- LINZESS selectively binds with high affinity to the GC-C receptor, which is located almost exclusively in the intestines
- LINZESS is minimally absorbed with low systemic availability
 - LINZESS is expected to be minimally distributed to tissues
 - While no drug-drug interaction studies have been conducted, no systemic drug-drug interactions are anticipated
- LINZESS is metabolized within the GI tract

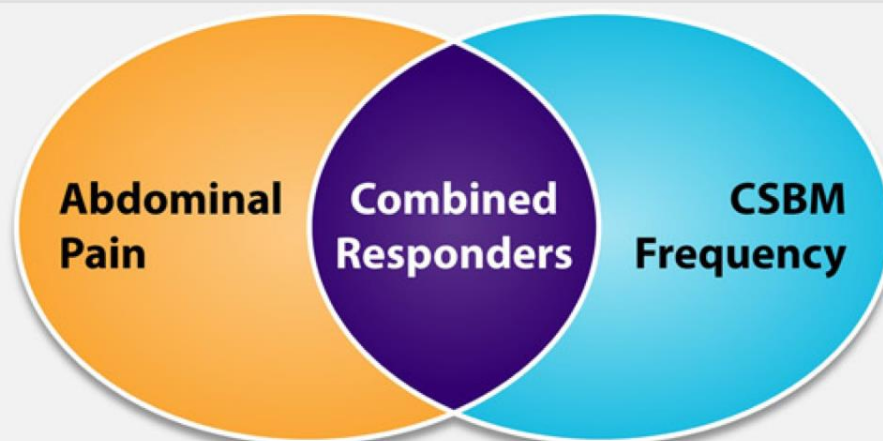
LINZESS is Thought to Work in Two Ways, Based on Nonclinical Studies



***Clinical relevance of the effect on pain fibers in nonclinical studies has not been established.**

IBS-C: Responder Criteria

Trials Evaluated Abdominal Pain Responders, CSBM Responders, and Combined Responders



In the Same Week

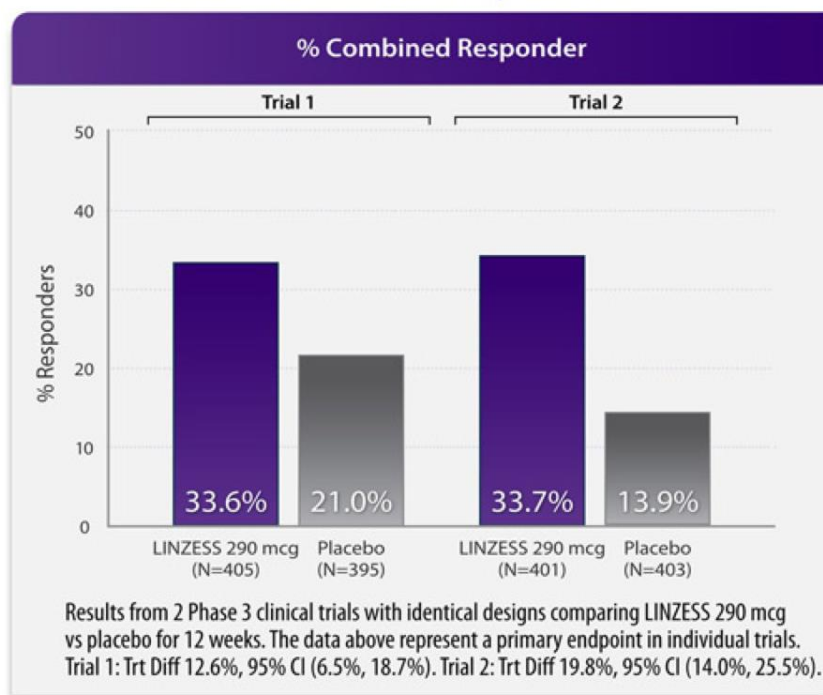
Combined Responders demonstrated significant improvement on 2 measures

Measure	Area of Improvement	Threshold for Weekly Response	Combined Responder
At least 6 of 12 weeks	Abdominal Pain Responder	≥30% reduction over baseline	✓
	CSBM Responder	Increase of ≥1 over baseline	

IBS-C: Significant Responder Rates vs Placebo in Abdominal Pain and in CSBMs Combined

Responder Rates: at least 6 out of 12 Weeks

**34% of LINZESS-treated Patients
were Combined Responders**



- In IBS-C clinical trials, the most common adverse reactions in LINZESS-treated patients were diarrhea, abdominal pain, flatulence, headache, viral gastroenteritis, and abdominal distension

Summary of Additional IBS-C Efficacy

Time to Maximum Effect: *CSBM*

Max **CSBM effect** occurred and was maintained until end of study; Abdominal pain effect separated from placebo



1

WK

Time to Maximum Effect: *Abdominal Pain*

Max **abdominal pain effect** occurred and was maintained until end of study



6 – 9

WK

Bowel Movement Frequency

LINZESS increased **CSBM frequency** by more than 2 CSBMs, ~1.5 more than placebo



12

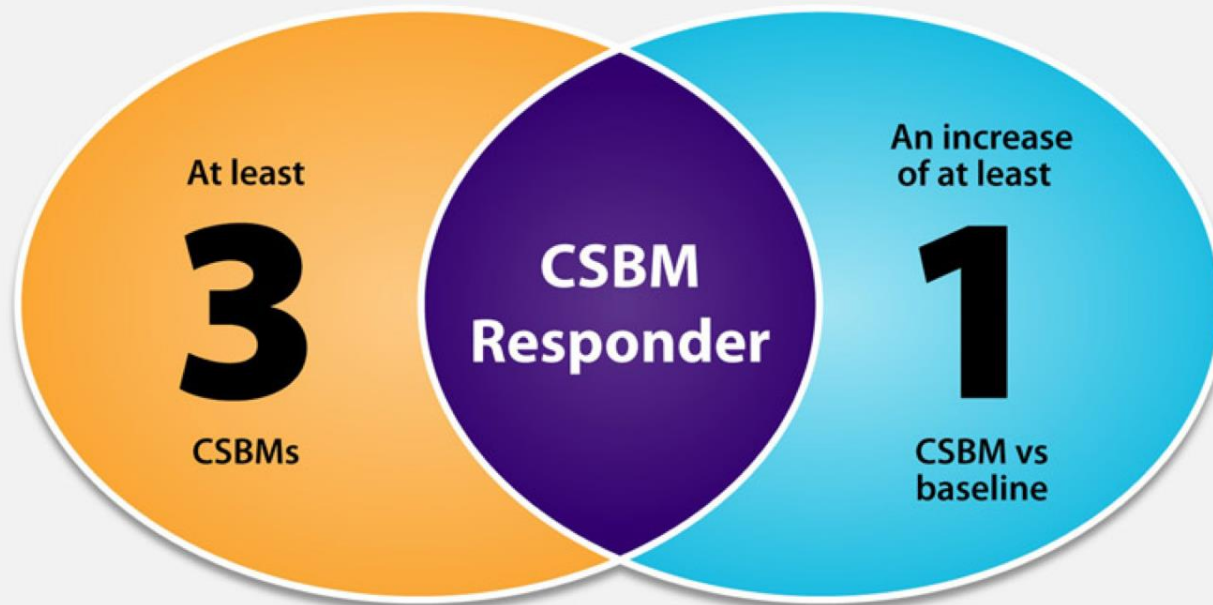
WK

0 2 4 6 8 10 12 14 16

Study Week

CIC: Primary Endpoint

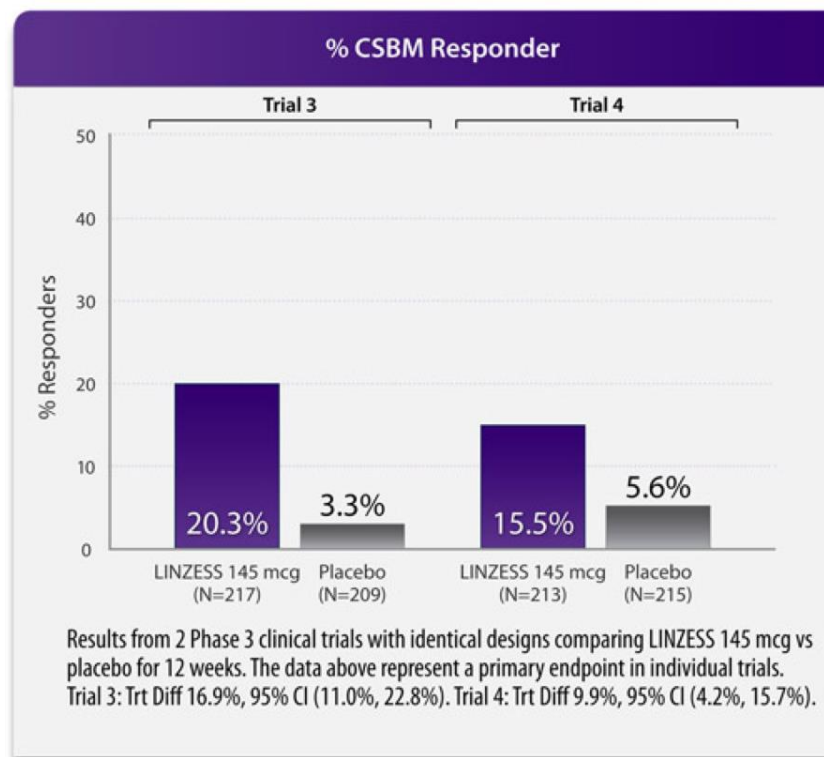
Trials Evaluated CSBM Responders Based on 2 Criteria



In the Same Week for ≥ 9 of 12 Weeks

CIC: CSBM Responders

More Than Twice as Many CSBM Responders with LINZESS vs Placebo



- In CIC clinical trials, the most common adverse reactions in LINZESS-treated patients were diarrhea, abdominal pain, flatulence, upper respiratory tract infection, sinusitis, and abdominal distension

Summary of Additional CIC Efficacy

Time to Max. Effect

Max **CSBM** effect occurred and maintained until end of study

1
WK

Bowel Movement Frequency

LINZESS increased **CSBM frequency** by more than 2 CSBMs, ~1.5 more than placebo

LINZESS increased **SBM frequency** by more than 3 SBMs, ~2 more than placebo

Stool Consistency

LINZESS improved **stool consistency** versus placebo

12
WK

Study Week

Most Common Adverse Reactions in IBS-C and CIC Trials

Adverse Reactions Reported in $\geq 2\%$ of LINZESS-treated Patients and at an Incidence Greater Than in the Placebo Group

IBS-C		
Adverse Reactions	LINZESS 290 mcg N=807 %	Placebo N=798 %
Gastrointestinal		
Diarrhea	20	3
Abdominal pain*	7	5
Flatulence	4	2
Abdominal distention	2	1
Infections and Infestations		
Viral gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3
Severe diarrhea	2%	<1%
Discontinuation due to diarrhea	5%	<1%

CIC		
Adverse Reactions	LINZESS 145 mcg N=430 %	Placebo N=423 %
Gastrointestinal		
Diarrhea	16	5
Abdominal pain*	7	6
Flatulence	6	5
Abdominal distention	3	2
Infections and Infestations		
Upper respiratory tract infection	5	4
Sinusitis	3	2
Severe diarrhea	2%	<1%
Discontinuation due to diarrhea	5%	<1%

* "Abdominal pain" term includes: abdominal pain, upper abdominal pain, and lower abdominal pain.

.....
Trulance™
(plecanatide)

MOA

CLINICAL
RESULTS

SAFETY

DOSING &
PACKAGING

SAVINGS
& SUPPORT

RESOURCES



FOR ADULTS WITH
CHRONIC IDIOPATHIC CONSTIPATION (CIC)

**Going shouldn't mean
going to extremes**

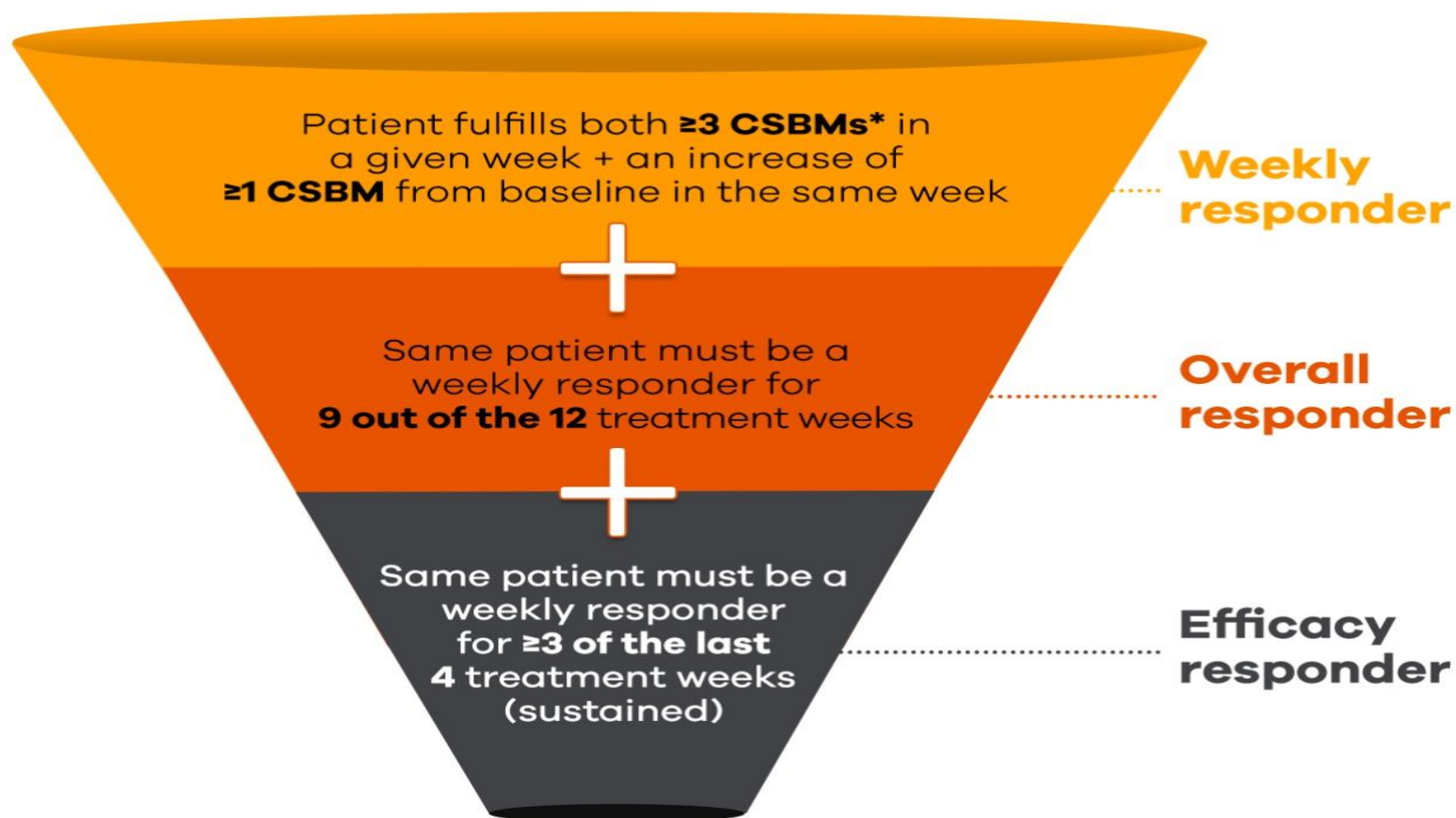
STUDY DESIGN

PRIMARY ENDPOINT

FREQUENCY OF SBMs

STOOL CONSISTENCY

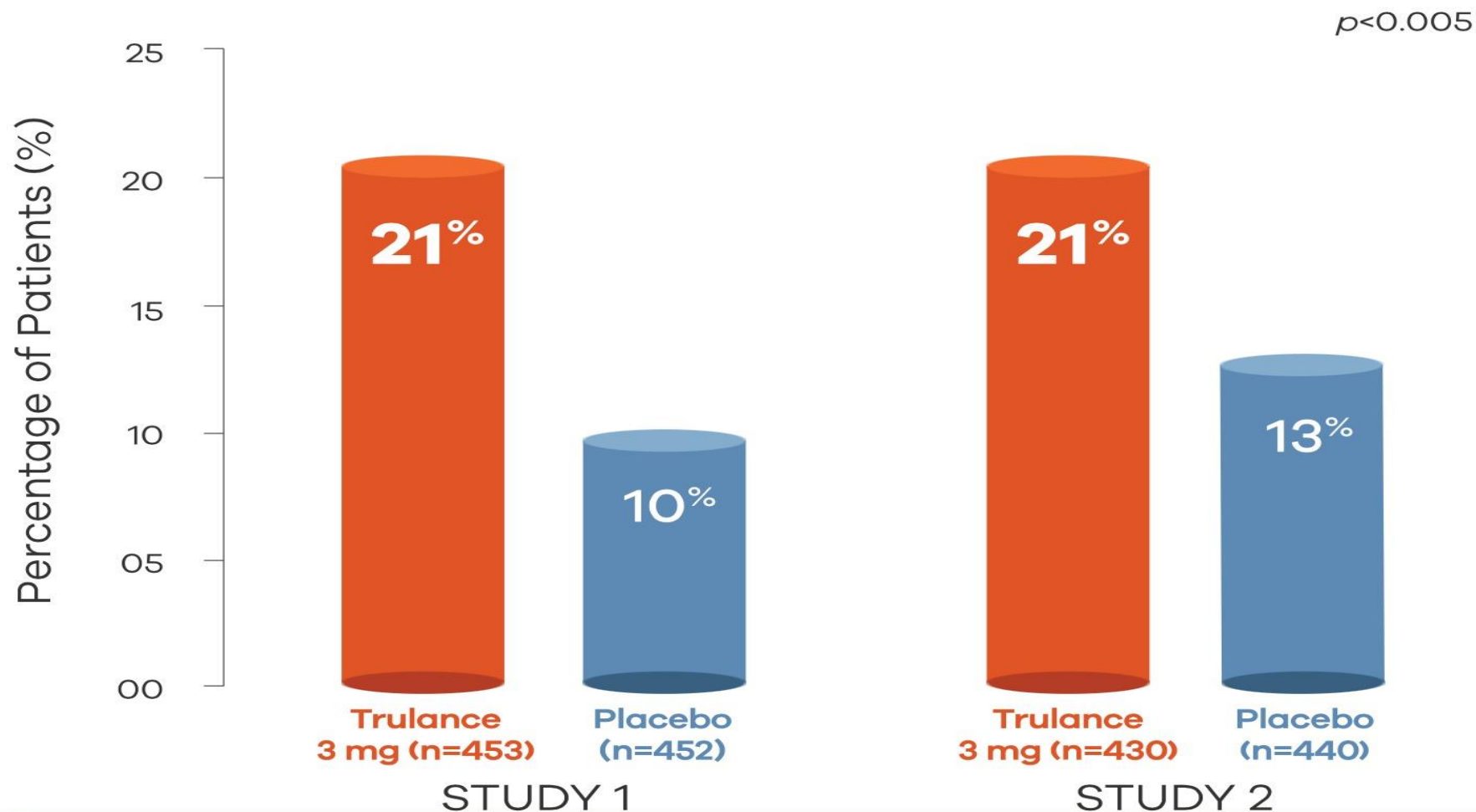
Trulance met the most stringent primary endpoint in CIC



Trulance was evaluated in the largest Phase 3 CIC clinical trials to date, involving more than 2600 patients¹⁻⁴

The percentage of efficacy responders (CSBM)* to Trulance was significantly greater than placebo¹

Primary endpoint: Efficacy responders over the 12-week treatment period vs placebo¹



Only Trulance met the most stringent criteria, evaluated in the largest Phase 3 CIC clinical trials to date¹⁻⁴

Established safety and tolerability

Trulance has well-established safety and tolerability, involving more than 1700 patients across 2 placebo-controlled, Phase 3 studies^{1,2}

Most Common Adverse Events (AEs) in Trulance Studies¹

AE	Trulance 3 mg (n=863) %	Placebo (n=870) %
Diarrhea	5	1

No additional AEs were reported in at least 2% of Trulance-treated patients, and at an incidence greater than placebo.

4% discontinuation rate for Trulance vs 2% on placebo¹

- 2% discontinuation rate due to diarrhea vs 0.5% for placebo

No drug-drug interactions occur with Trulance¹

- Trulance therapy is minimally absorbed with negligible systemic availability

- Severe diarrhea was reported in 0.6% of patients receiving 3 mg of Trulance vs 0.3% of placebo-treated

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

Trulance™ is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice administration of a single oral dose of plecanatide caused deaths due to dehydration. Use of Trulance should be avoided in patients 6 years to less than 18 years of age. The safety and efficacy of Trulance have not been established in pediatric patients less than 18 years of age.

Contraindications

- Trulance is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- Trulance is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

Warnings and Precautions

Risk of Serious Dehydration in Pediatric Patients

- Trulance is contraindicated in patients less than 6 years of age. The safety and effectiveness of Trulance in patients less than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid secretion as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than older patients to develop severe diarrhea and its potentially serious consequences.
- Use of Trulance should be avoided in patients 6 years to less than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in young mice and the lack of clinical safety and efficacy data in pediatric patients, use of Trulance should be avoided in patients 6 years to less than 18 years of age.

Diarrhea

- Diarrhea was the most common adverse reaction in the two placebo-controlled clinical trials. Severe diarrhea was reported in 0.6% of patients.
- If severe diarrhea occurs, the health care provider should suspend dosing and rehydrate the patient.

Adverse Reactions

- In the two combined CIC clinical trials, the most common adverse reaction in Trulance-treated patients (incidence $\geq 2\%$ and greater than in the placebo group) was diarrhea (5% vs 1% placebo).

Indication

- Trulance (plecanatide) 3 mg tablets is indicated in adults for the treatment of chronic idiopathic constipation (CIC).

Please also see the [full Prescribing Information](#), including [Box Warning](#), for additional risk information.

References: **1.** Trulance [package insert]. New York, NY: Synergy Pharmaceuticals Inc., 2017. **2.** Data on file. Synergy Pharmaceuticals Inc., 2017.

Medications for opioid induced constipation

- Relistor (methylnaltrexone bromide) this narcotic antagonist is now available in both parenteral and enteral forms (SC and PO)
- Movantic (naloxegol) another narcotic antagonist available only in tablet form
- Amitiza (lubiprostone) a chloride channel activator approved for OIC

Efficacy of OIC Medications

- Relistor injection 12 mg daily 59 percent responders vs 38 percent for placebo
- Relistor tablets 450 mg daily 52 percent responders vs 38 percent for placebo
- Movantick 25 mg tablets 44 percent response rate vs 29 percent for placebo
- Amitiza 24 mcg bid 27 percent responders vs 19 percent for placebo

Side Effects of OIC Medications

- Amitiza side effect similar to what was seen in CIC and IBS-C (nausea, abdominal pain, diarrhea, etc)
- Relistor and Movantik side effects include
 - Opioid withdrawal
 - Severe abdominal pain and diarrhea
 - Gastrointestinal perforation

Summary IBS-C and CIC

- Common Conditions
- More women affected than men
- Often Under diagnosed and patients often self medicate
- Presents a Significant Economic Burden
- Abdominal discomfort and altered bowel habits are hallmark symptoms of IBS, but CIC patients c/o difficult defecation
- Often associated with other symptoms (headache, depression, fatigue, etc)
- Physicians should look for Red Flags (weight loss, bleeding, etc)
- Organic conditions should be ruled out by selective testing
- In the past, treatment options have been limited and patient satisfaction has been low.
- A positive therapeutic relationship between the physician and patient is important
- Newer treatments are available



The Secret of Natural Beauty

WHEN your skin becomes sallow, rough, blotchy or disfigured with pimples — it is nature's way of telling you that there is something wrong with your system.

Use EX-LAX regularly to cleanse your system — and you'll do more toward helping nature give you a clear, healthy complexion and bright sparkling eyes, than by using the best cosmetics you can buy. The best cold creams or soaps can not rub blemishes away.



Gastroenterologist's search for "Inner Hygiene"

