South Canterbury
District Health Board
Enhancing the health & independence of the people of South Canterbury.

A Mechanism-Based Approach to Nausea & Vomiting in Palliative Care

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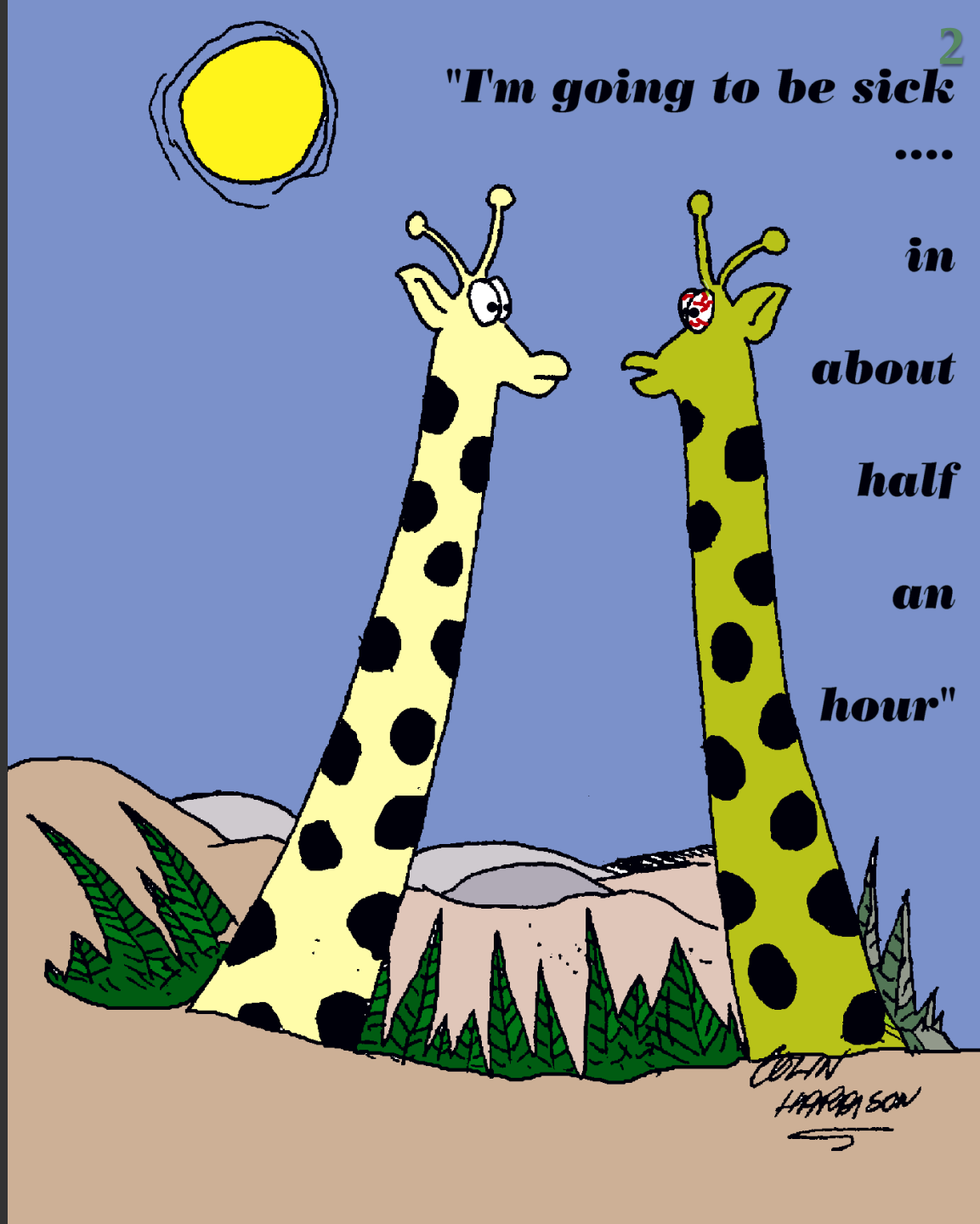
AGENDA

- Mechanism of Vomiting
- Neuroanatomy & Physiology
- Assessment
- Simple strategy
- Mechanism-based treatment
- Drug choices
- Q&A



Mechanism of Vomiting - 3 Phases

- Nausea – with clammy, sweating, salivation
  - ➔ Parasympathetic nervous system causes excessive salivation (to protect the tooth enamel from when acid contents of the stomach are vomited).
  - ➔ Sympathetic nervous system causes sweating as well as increase in heart rate
  - ➔ Motor system takes a deep breath (to prevent aspiration)
- Retching
  - ➔ Abdominal muscles undergo a few rounds of coordinated contractions together with the diaphragm and the muscles used in respiratory inspiration – nothing yet been expelled
- Expulsion [next slide]

Vomiting M

Soft palate rises to block nose & saliva protect teeth

Diaphragm tightens

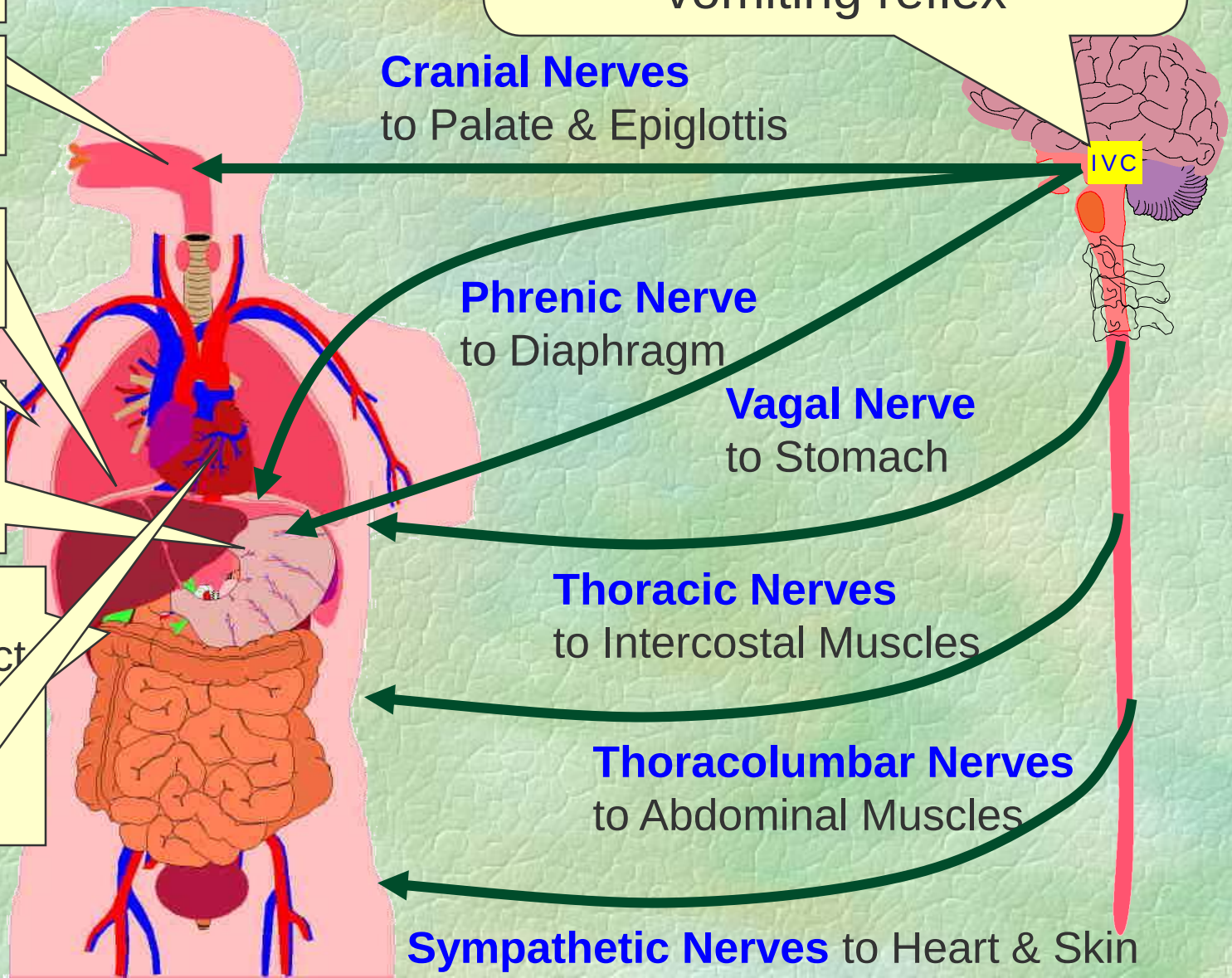
Chest wall tightens

GE sphincter & stomach relax

Abdominal muscles contract forcefully – retching, th… vom…

Sweating & Tachycardia

IVC, once sufficiently stimulated, initiates the vomiting reflex

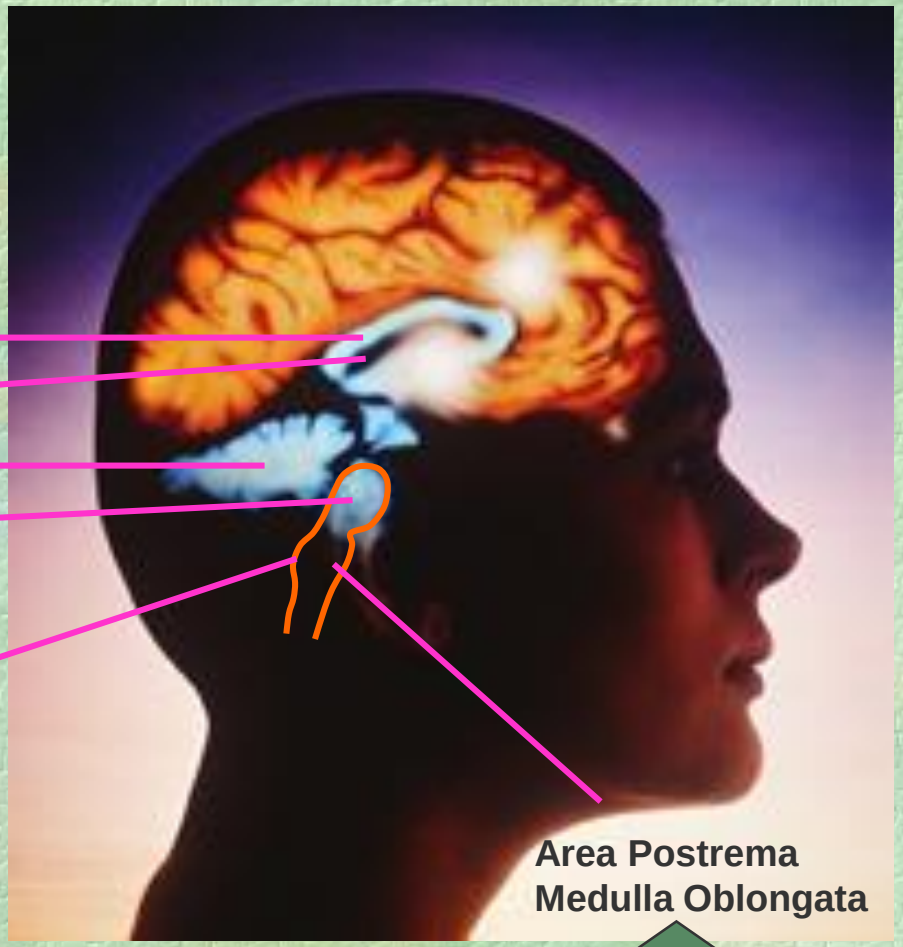


How is the vomitus expelled?

Two processes

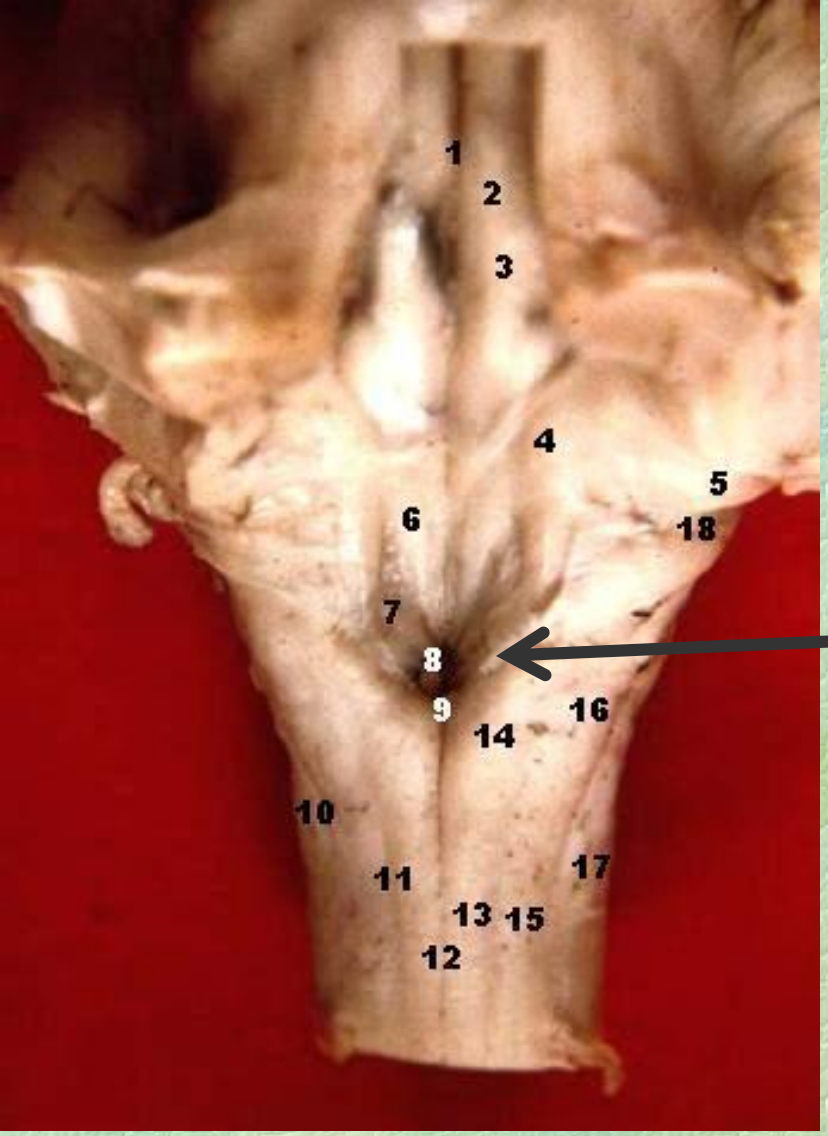
- Inspiration against a closed glottis
  - ➔ Lowers the pressure inside the thoracic cavity
- Contraction of the abdominal musculature.
  - ➔ Increases abdominal pressure, thus propelling the contents of the small intestine to move easily from a region of high pressure to a region of low pressure.
- Intestines undergo retro-peristalsis
  - ➔ Reverse peristalsis from mid-intestine and relax pyloric sphincter
  - ➔ As contents reach the lower oesophageal sphincter, it opens and pressure is suddenly released, propelling the gastric contents out through the relaxed oesophagus.

Neuroanatomy



Integrative Vomiting Centre (IVC)

Chemoreceptor Trigger Zone (CTZ)



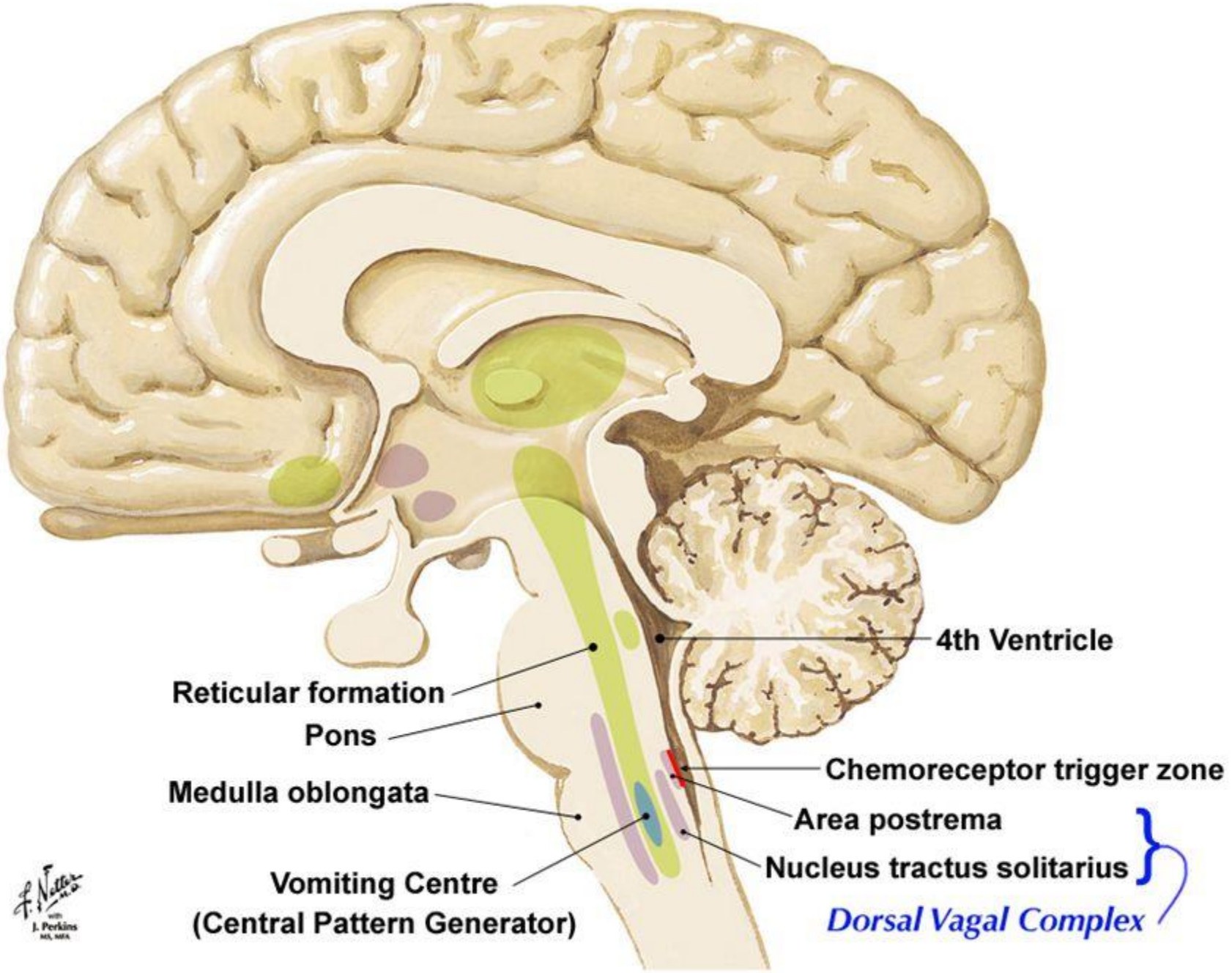
Caudal aspect of Medulla Oblongata

1. Sulcus medianus
2. Eminentia medialis
3. Colliculus facialis (Motor fibers of VII passing over Motor Nucleus of VI)
4. Area vestibularis
5. Area auditoria (Nucleus cochlearis dorsalis)
6. Trigonum nervi hypoglossi
7. Trigonum nervi vagi
8. **Area postrema (Chemoreceptor Trigger Zone)**
9. Obex
10. Sulcus posterolateralis
11. Sulcus intermedius posterior
12. Sulcus medianus
13. Fasciculus gracilis
14. Tuberculum gracile (Nucleus gracilis)
15. Fasciculus cuneatus
16. Tuberculum cuneatum (Nucleus cuneatus)
17. Funiculus lateralis medullae oblongatae
18. Apertura lateralis ventriculi quarti

Capillaries & Blood Brain Barrier (BBB)

Several disease states result in enhanced BBB permeability including hypertension, edema, inflammation, radiation exposure, ischemia & reperfusion (reoxygenation)

Specific changes at the BBB, such as opening of tight junctions, increased pinocytosis, decrease in membrane rigidity, changes in nutrient transport, and pore formation may enhance/reduce drug uptake

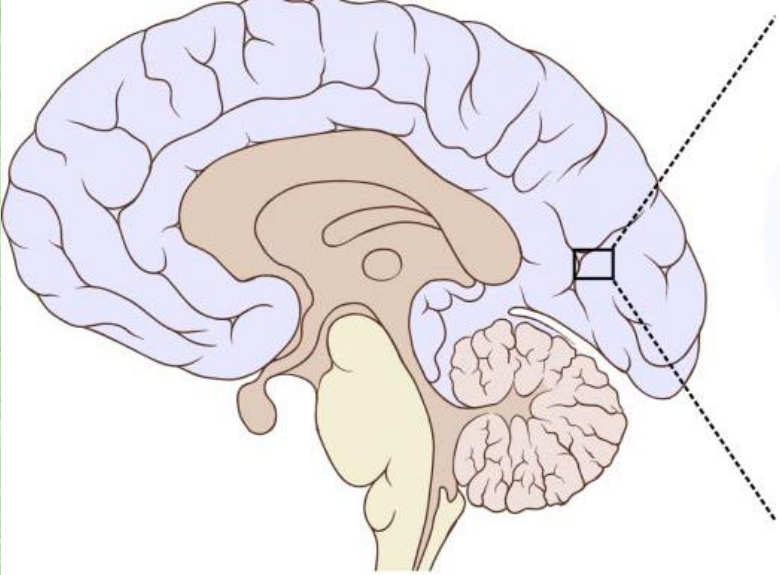

4th Ventricle
Reticular formation
Pons
Medulla oblongata
Vomiting Centre
(Central Pattern Generator)
Chemoreceptor trigger zone
Area postrema
Nucleus tractus solitarius
Dorsal Vagal Complex
F. Netter M.D.
with
J. Perkins
MS, MFA

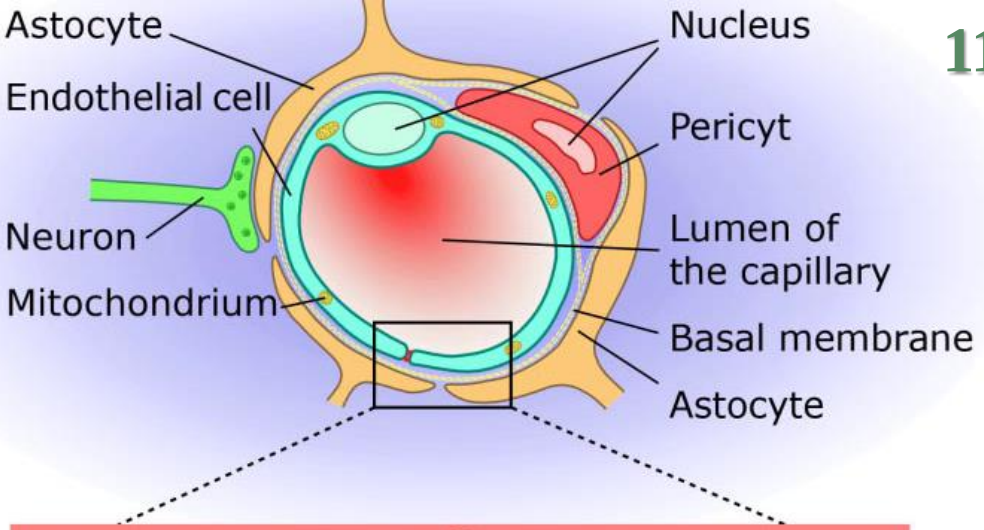
Blood Brain Barrier (BBB)

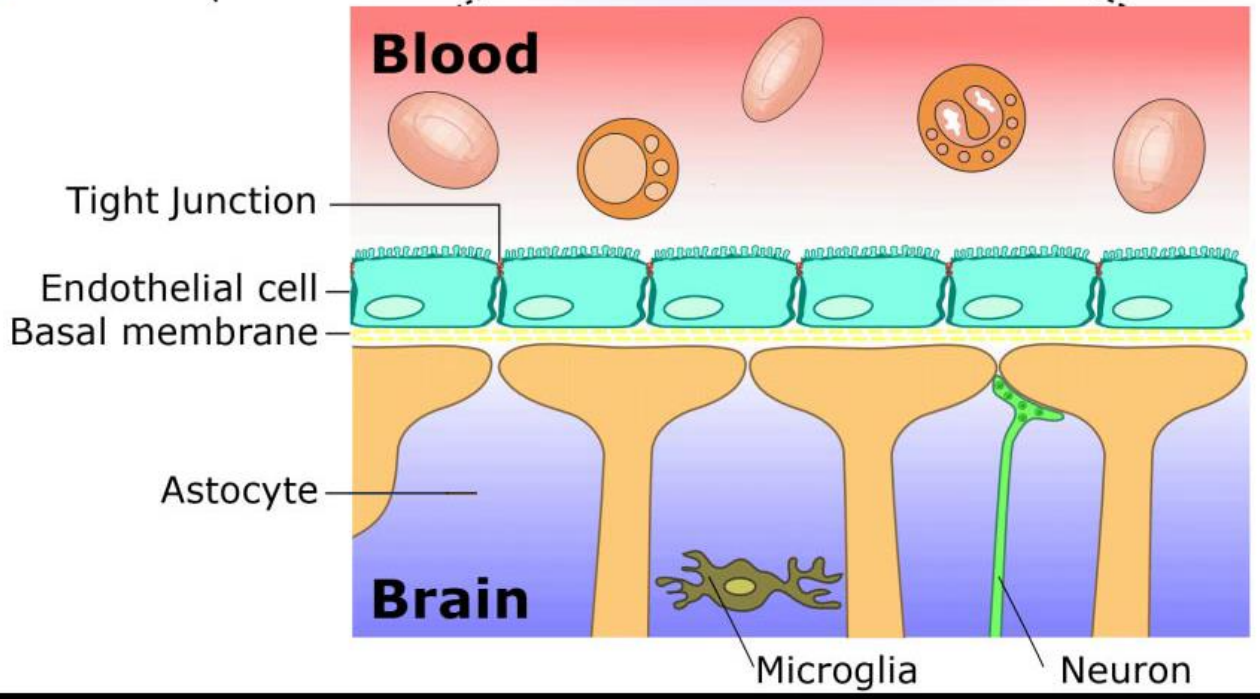
- BBB lets essential metabolites, such as oxygen and glucose, pass from the blood to the brain but blocks most molecules larger than about 500 daltons.

Arbitrary unit of mass, being 1/12 the mass of the nuclide of carbon-12, equivalent to 1.657 × 10−24

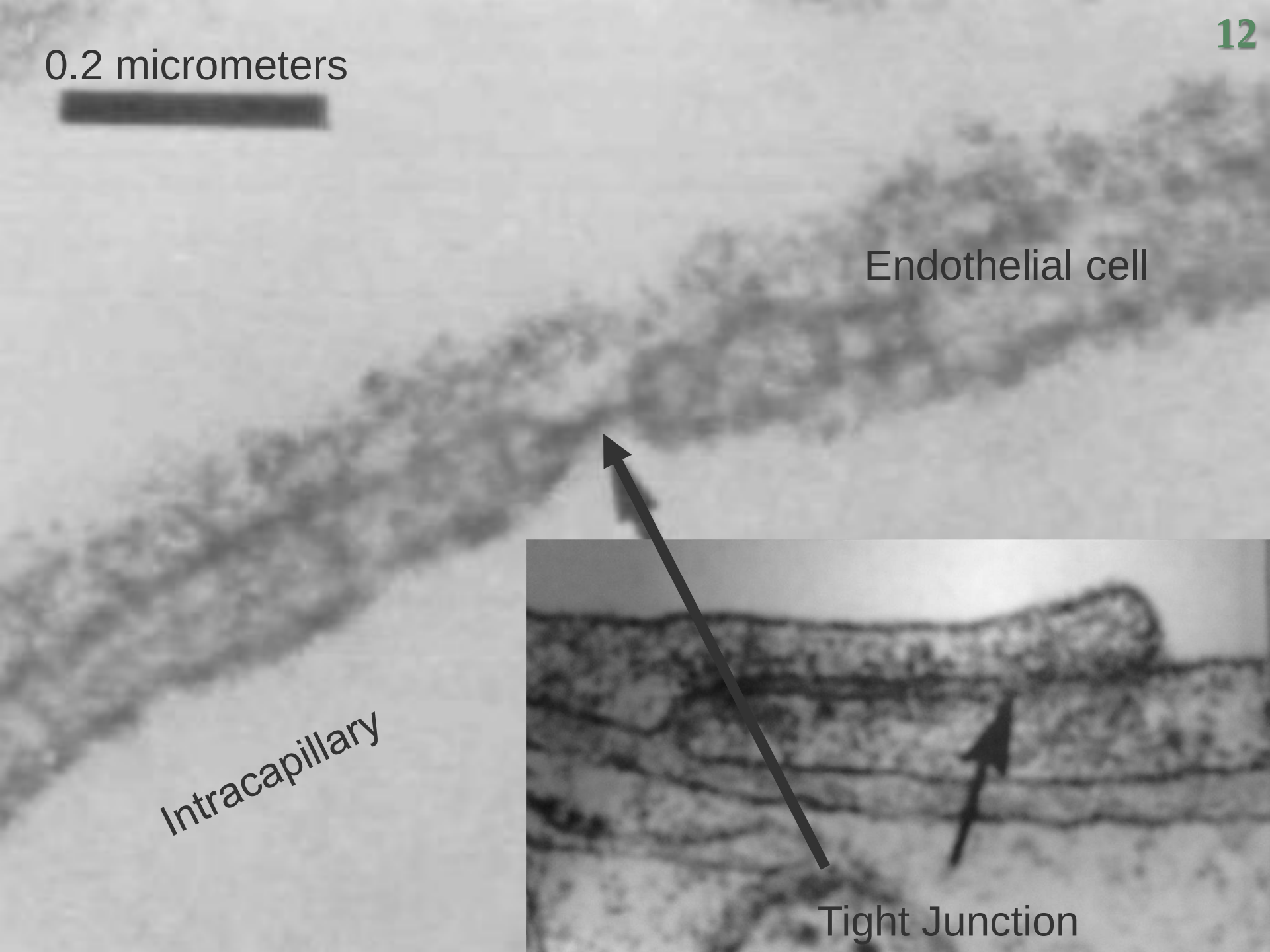
  - ➔ This is a low mass in biomolecular terms and means that everything from hormones & neurotransmitters to viruses and bacteria are refused access to the brain.
- A key aspect of the BBB are the thin, flat cells known as ***endothelial cells*** which form the walls of capillaries. In most parts of the body, the endothelial cells in the capillaries overlap at what are called junctions. These junctions are usually leaky enough to let a lot of different materials move through the wall of the blood vessel into the tissue and back again.
- However, in the brain endothelial cells meet each other at what are called ***tight junctions***. block the passage of most except for small molecules





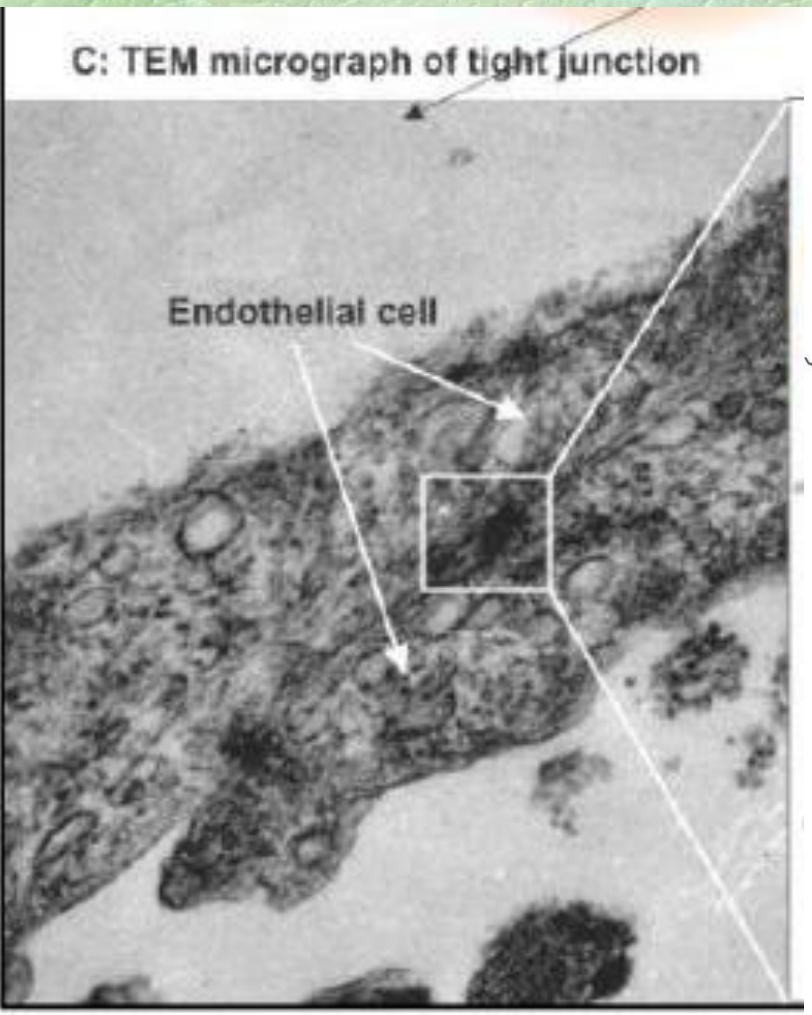


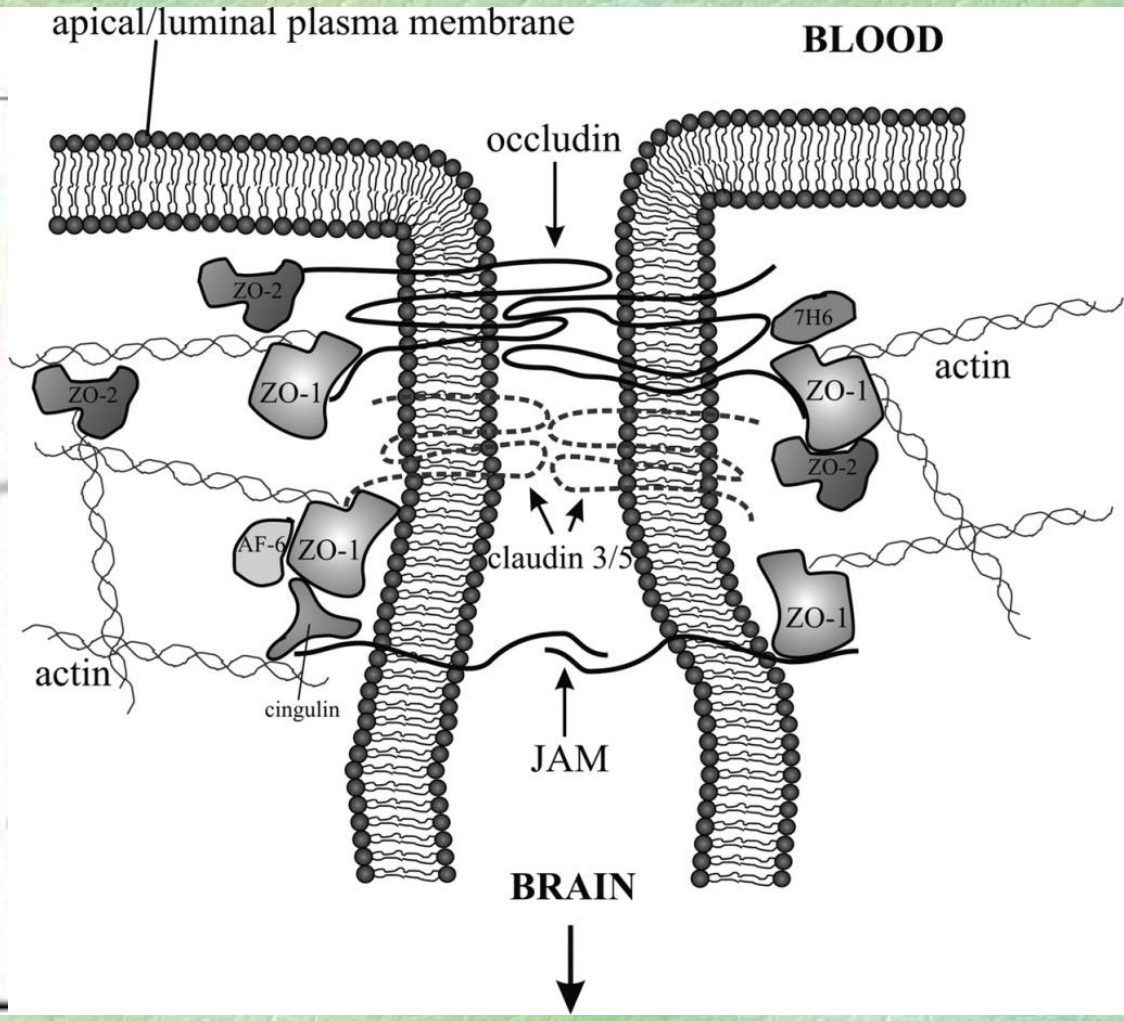
Also tanicytes


0.2 micrometers
Endothelial cell
Intracapillary
Tight Junction

Brain microvasculature

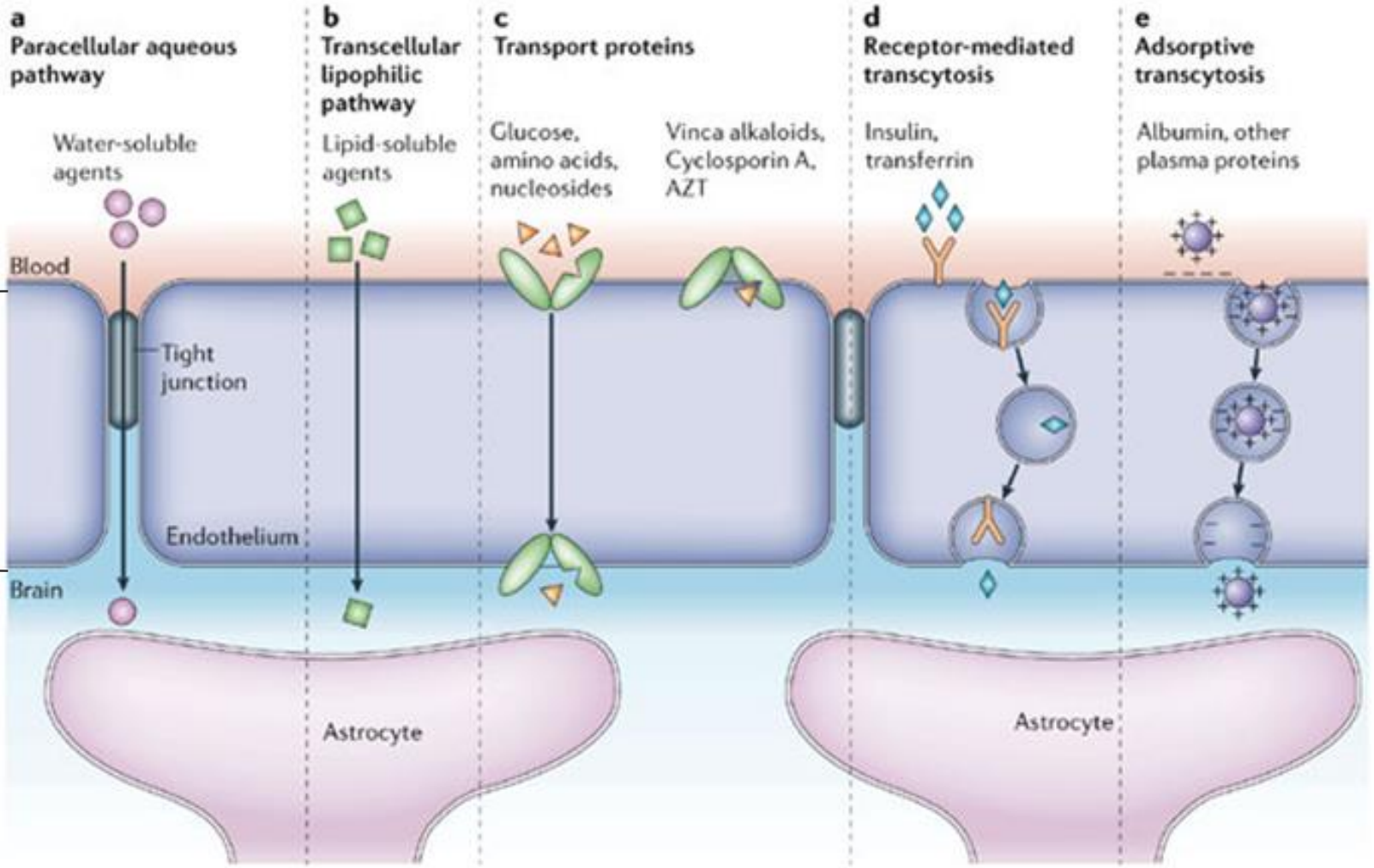
- Surface area of the brain microvasculature is ~ 100 cm2, with the capillary volume and endothelial cell volume constituting approximately 1% and 0.1% of the tissue volume, respectively
- Cerebral capillary endothelial cells - tight junctions
  - ➔ The tight junctions leads to high endothelial electrical resistance, in the range of 1500-2000 Ω× cm2 (pial vessels), as compared to 3-33 Ω× cm2 in other tissues
- The **adherens junction** is ~200 Å, while the **zonula occludens** (i.e. tight junction) is essentially occluded.
- 5-6 times more mitochondria per capillary cross-section in cerebral capillaries than skeletal muscle capillaries.





ZO = Zonula Occudens
JAM = Junctional Adhesion Molecules

Pathways across the blood–brain barrier



30% less

Abbott NJ *et al.* (2006) Astrocyte–endothelial interactions at the blood–brain barrier
Nat. Rev. Neuro. **7:** 41–53 doi:10.1038/nrn1824

BBB & Circumventricular Organs (Non-protected Areas)

The blood-brain barrier prevents toxic substances, large molecules, and neurotransmitters released in the blood from entering the brain. Four areas of the brain are ***not protected*** by the blood-brain barrier.

- **Area Postrema**

Not covered by the BBB because it senses toxins in the blood that the other parts of the brain are protected from. The area postrema triggers nausea and vomiting to prevent further ingestion of toxins.

- **Posterior Pituitary Gland**

Not covered by the BBB because the hormones it secretes (oxytocin, vasopressin) need to go into circulation and pass through the rest of the body.

- **Pineal Gland**

Not covered by the BBB and secretes the hormone melatonin, which controls circadian and seasonal rhythms, or sleep/wake cycles.

- **Median Eminence of the Hypothalamus**

The median eminence connects the hypothalamus to the pituitary gland. It is not covered by the BBB because hormones secreted by the pituitary gland collect in this region before being secreted into the bloodstream.

Area Postrema & CTZ

- The CTZ is located in the area postrema, one of the circumventricular regions. Unlike vasculature within the blood-brain diffusion barrier, the area postrema is highly vascularized with fenestrated endothelial cells , which lack tight junctions (zonae occludentes) between capillary endothelial cells.
- Do **not** contain tight junctions, which allows for free exchange of molecules between blood and brain.
- This unique breakdown in the BBB is partially compensated for by the presence of a tanycyte barrier (long basal process that projects from CVO to a distinct region of the hypothalamus)
- Thus large polar molecules, such as emetic toxins, can diffuse through to and reach the CTZ quite easily

Assessment

GENERAL R_X STRATEGIES …

Mechanism-Based Assessment

Based on:

• Why is one nauseated?	Etiology/Mechanisms
• Can I do something?	Specific interventions
• What does the patient want/not want?	Ethics, reality, choice ACP
• Can I give something?	Drug(s) related to receptor stimulus
• Can I minimize adverse?	Drug, dose, route

Cerebral
High CNS

Sights, Smells
Memories

Vestibular

Opioids
Cerebellar Tumor

Increased
Intracranial Press

Primary or
Met. Tumor

Nausea

Vomiting

Integrative Vomiting Centre (IVC)

NTS
CPG

(© S. Chu)

Chemoreceptor Trigger Zone

Toxic
- Ca Emetogenic
- Infection
- Radiation

Drugs
- Chemotherapy
- Opioids (mu, Δ)
- Digoxin, etc

Biochemical
- Uremia
- Hypercalcemia

GI Tract
Vagal

Distension
- Over-eating
- Gastric Stasis
- Extrinsic Press.

Obstruction
- High, mid, low
- Constipation

Chemical Irritants
- Blood, drugs

Mechanism-based Invest./Rx

Rule of thumb – Order only if can act on result

Lab Tests		Possible Active Rx	
	Ca++ Hypercalcemia		Fluid, Pamidronate, steroid
	Hgb GI bleed		Transfusion, ?surgery
	C&S UTI, infection		Antibiotics
	Creat. Renal failure		Nephrostomy, dialysis
	NH_3 Hepatic Enceph.		Lactulose (antibiotic/antifungal)
	Trop MI/ACS		Drugs/stents/monitor
Imaging			
	Xray Obstruction		?NGT/IV, ?surgery, ?PEG
	US Ascites, constip.		Paracentesis, laxatives
	CT/MRI Brain tumor		Steroid, RT/CT, ?surg.
EKG	MI		Rx CHF, arrhythmias, etc
LP	?infection/tumor		?Treat

Treatment

GENERAL R_X STRATEGIES …

General Treatment Strategy for N/V

- Strategic Steps
  - Stop vomiting to maintain oral route
  - Restrict intake
  - Settle nausea
  - Increase oral intake
- Ongoing Dietary Advice
  - Solids to sips until settled
  - Reduce volume intake
  - Cut out intolerant foods
  - Trial increase of volume

… cont'd

- Antiemetics Drugs
  - Drug choice
  - Individual titration
  - Varied routes
  - Combinations
- Common problem
  - Re-eat too soon
  - Over-eat too much
  - Intoler-eat what someone else thinks is good
  - [next slide re stopping end-stage/dying]

"He will die if he can't drink" "You can't let him starve"

10 talking points regarding naturally declining intake & dying:

1. What a patient can eat now will become less
2. What a patient can drink now will become less
3. Both eating and drinking will become zero
4. Cessation of eating and drinking is natural to the dying process, so also is 'fighting' against it
5. What is nutritionally of value at one stage is not at another
6. 'Aggressive' nutrition is best applied in early illness to maintain optimum level
7. 'Aggressive' nutrition in the advanced phase often contributes to difficult symptom control eg. TPN can cause problems, not improve situation
8. 'What one likes' becomes more important than 'what is of nutritional value'
9. 'What works' is not necessarily either 'what one likes' or 'what is nutritional'
10. The atmosphere surrounding eating is sometimes more important than the quantity or quality – includes social, visual, olfactory and physical factors

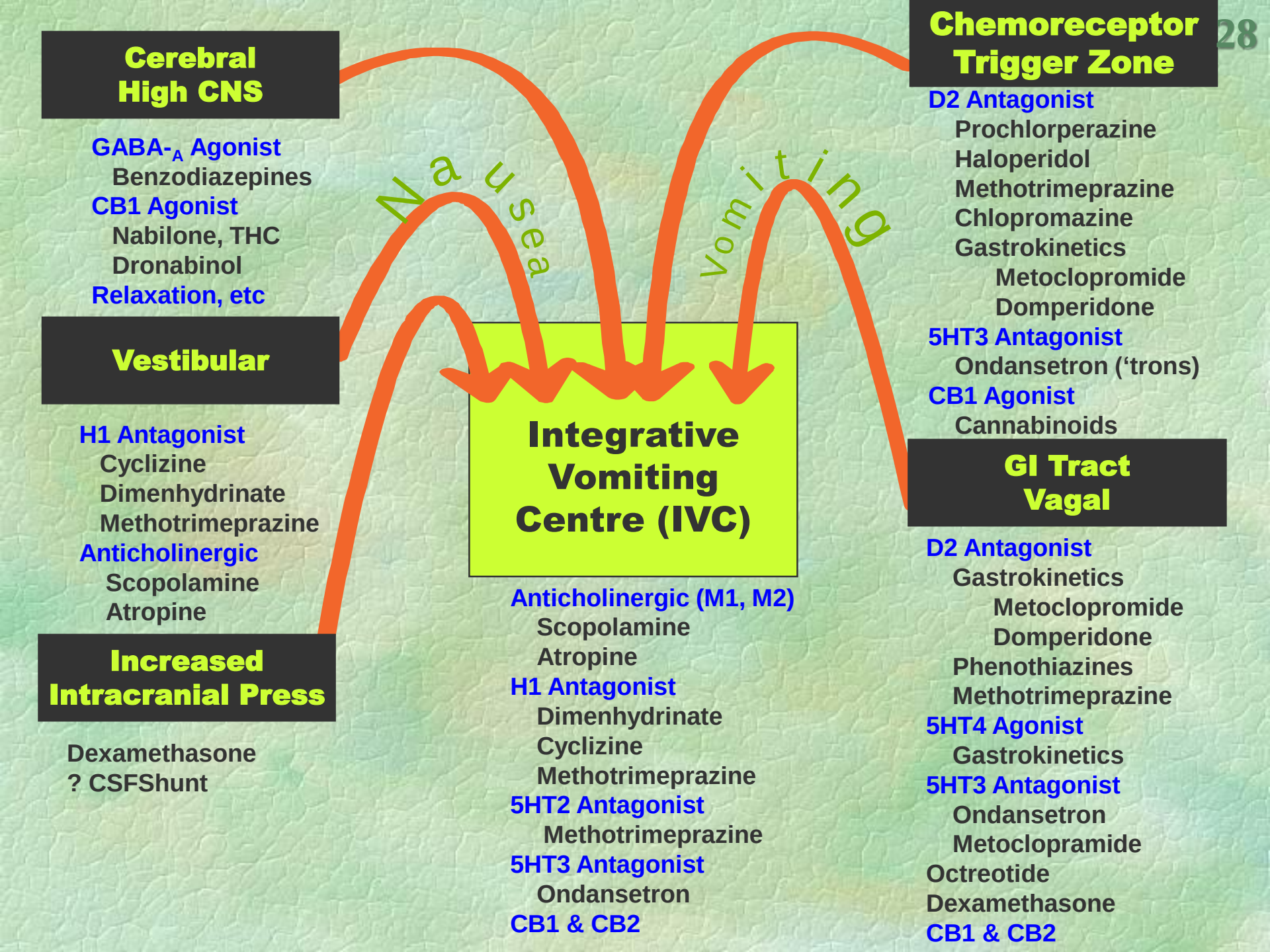
Drugs

MECHANISM-BASED APPROACH …

Drugs for Nausea

Not so much a specific class of antiemetics, but rather, drugs which exhibit such properties

- ✓ Neuroleptics
- ✓ Antihistamines
- ✓ Anticholinergics
- ✓ Anxiolytics
- ✓ Steroids
- ✓ Others


Cerebral
High CNS
GABA-A Agonist
Benzodiazepines
CB1 Agonist
Nabilone, THC
Dronabinol
Relaxation, etc
Vestibular
H1 Antagonist
Cyclizine
Dimenhydrinate
Methotrimeprazine
Anticholinergic
Scopolamine
Atropine
Increased
Intracranial Press
Dexamethasone
? CSFShunt
Nausea
vomiting
Integrative
Vomiting
Centre (IVC)
Anticholinergic (M1, M2)
Scopolamine
Atropine
H1 Antagonist
Dimenhydrinate
Cyclizine
Methotrimeprazine
5HT2 Antagonist
Methotrimeprazine
5HT3 Antagonist
Ondansetron
CB1 & CB2
Chemoreceptor
Trigger Zone
D2 Antagonist
Prochlorperazine
Haloperidol
Methotrimeprazine
Chlopromazine
Gastrokinetics
Metoclopromide
Domperidone
5HT3 Antagonist
Ondansetron (‘trons)
CB1 Agonist
Cannabinoids
GI Tract
Vagal
D2 Antagonist
Gastrokinetics
Metoclopromide
Domperidone
Phenothiazines
Methotrimeprazine
5HT4 Agonist
Gastrokinetics
5HT3 Antagonist
Ondansetron
Metoclopramide
Octreotide
Dexamethasone
CB1 & CB2

Antiemetic Possible Drug Choices

Mechanism-based

Category	Opioid Induced	Chemo Induced	Chemical toxin, etc	Motion Induced	High CNS	Vagal Stasis	Bowel Obstr.	Raised ICP
Prokinetic	1	1	1			1	?3	
Neuroleptic	2	3	2	3	2	2	2	2
Antihistamine	3	2	4	2				4
Anticholingeric				1			3	
Steroid		1	3			4	1	1
Octreotide							2	
5HT3 Antag	3	1	4			3	4	
Cannabinoid		4	5		3		6	5
Anxiolytic		2	3	4	1		5	3
NK-1 Antag.		2						

Common priority choices by M. Downing

Available Routes

Category		Oral	SC	IV	TD	SL/BC	Rectal
Prokinetic	Metoclopramide	✓	✓	✓	-	-	-
	Domeperidone	✓	-	-	-	-	✓
Neuroleptic	Haloperidol	✓	✓	✓			-
	Prochlorperazine	✓	-	-			✓
	Methotrimeprazine	✓	✓	✓			-
Antihistamine	Cyclizine	✓	✓	-	-	-	-
Anticholingeric	Scopolamine	-	✓	✓	✓	-	-
	Atropine	-	✓	✓	-	✓ (eye)	-
Steroid	Dexamethasone	✓	✓	✓	-	-	-
Octreotide	Octreotide	-	✓	-	-	-	-
5HT3 Antag	Ondansetron	✓	✓	✓	-	-	-
Cannabinoid	Marinol, Sativex (spray)	✓	-	-	-	✓	-
Anxiolytic	Midazolam, lorezepam	✓	✓	✓	-	✓	-
NK-1 Antag.	Aprepitant	✓	-	-	-	-	-

Vomiting Strategy by Intensity

Intensity	Drug Control Examples	Other Control
Level I *MILD*		
Mild Nausea or Occasional Vomit PO Meds are Retained	• ? Wait it out • Treat by mechanism base: Low doses: Eg. Prokinetic Eg. Neuroleptic (low dose) Eg. Antistamine, etc	Intake: Solids to Fluids until settled Analgesic: PO route
Level II *MODERATE*		
Moderate Nausea &/or Vomit 1-3x Daily Retains Partial PO Meds	• Don't wait it out • Mechanism based drugs and/or treatments • Slightly higher doses • May need combinatons	Intake: Clear fluids until settled Analgesic: PO/PR SC if unable PR Hold non-essential drugs Urgent: Review/ reassess possible active Rx measures

Intensity	Drug Control	Other Control
Level III *SEVERE*	**Examples**	
Severe Nausea &/or Vomit 3-6x Daily **Unable to Retain any PO Meds** **Urgency: high need to control**	**1. Haloperidol, Metoclopramide, Dexamethasone** **2. Cyclizine, Metoclopramide, Dexamethasone** **3. Methotrimeprazine (low dose), Metoclopramide, Dexamethasone** **4. Other eg. Ondansetron, ?octreotide, ?THC, ?olanzapine**	• **Intake: Sips of clear fluid only; IV hydration?** • **Analgesic: ISCI, CSCI or IV** • **Hold non-essential drugs** • **Urgent: Review/ reassess possible active Rx**
Level IV *EXTREME*		
Intractable Vomiting **Extreme distress & suffering** **Will die unless can be reversed**	• **Methotrimeprazine (high dose) for combined antiemetic, analgesic & sedative properties at high doses Eg. 75-300mg/24 hrs** • **+/- Dexamethasone** • ***Palliative Sedation*: Lorazepam/Midazolam** • **+/- Phenobarbital**	**Intake: Mouth care only ?consider NGT/PEG** **Analgesic: ISCI, CSCI or IV** **D/C All Oral meds ? Possible active Rx**

(Next time will review evidence in more detail)

VARIABLE & UNCLEAR NEWS …

Evidence & Limits

- Ondansetron
  - Main indication is chemotherapy, little evidence for general nausea (although 1998 Cancer: Tropisetron+Met+dex good), costly
- Octreotide
  - Some evidence diarrhoea (AIDS)✓; recent study no benefit in vomiting (obstruction) or ascites (Oncology 2012; used LAR; time to next tap p=0.17 but less discomfort p=0.01, bloating p=0.02, less SOB p=0.007
- Prokinetic
  - Better for low or partial obstruction; can try for high but usually not work
- Haloperidol
  - Variable evidence for neuroleptics; higher EPS than prochlorperazine
- Steroids & GI bowel – 'trend' to resolve; NNT 6; Cochrane 2000
- Times that nothing works well – consider pall sedation final option

Summary

- Complacency has no place in palliative care
- Assess to understand – multiple reasons
- Context of trajectory of illness & patient desire
- Nausea is often worse than vomiting
- Reduce intake to maintain oral route (ie. home)
- Use mechanism-based therapy
- Recurrence N/V is often too soon, too much

Questions & Discussion

Summary

- Used for pain, delirium, vomiting
- Prior doses for vomiting caused significant sedation and hypotension
- Clinically, low doses (2.5-12.5mg/24h by PO or SC) seem effective for nausea
- Recently identified sites of action including $5HT_2$ and D_2 receptor antagonism add scientific strength for it use

Thank you

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