Measuring CFTR Dysfunction in Chronic Pancreatitis

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A parent complained to a gastroenterologist about their child's strange eating habits.

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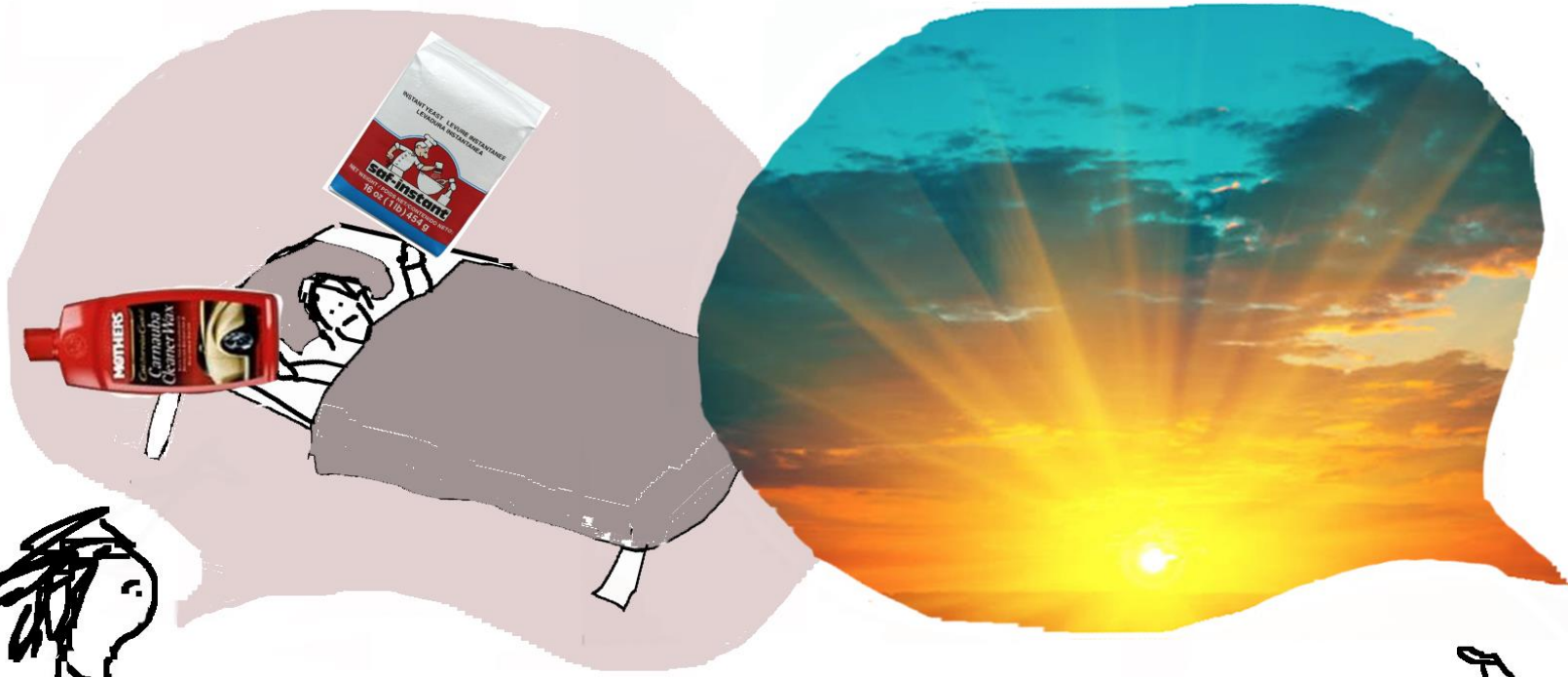
–"All day long they lie in bed and eat yeast and car wax. What will happen to them?"



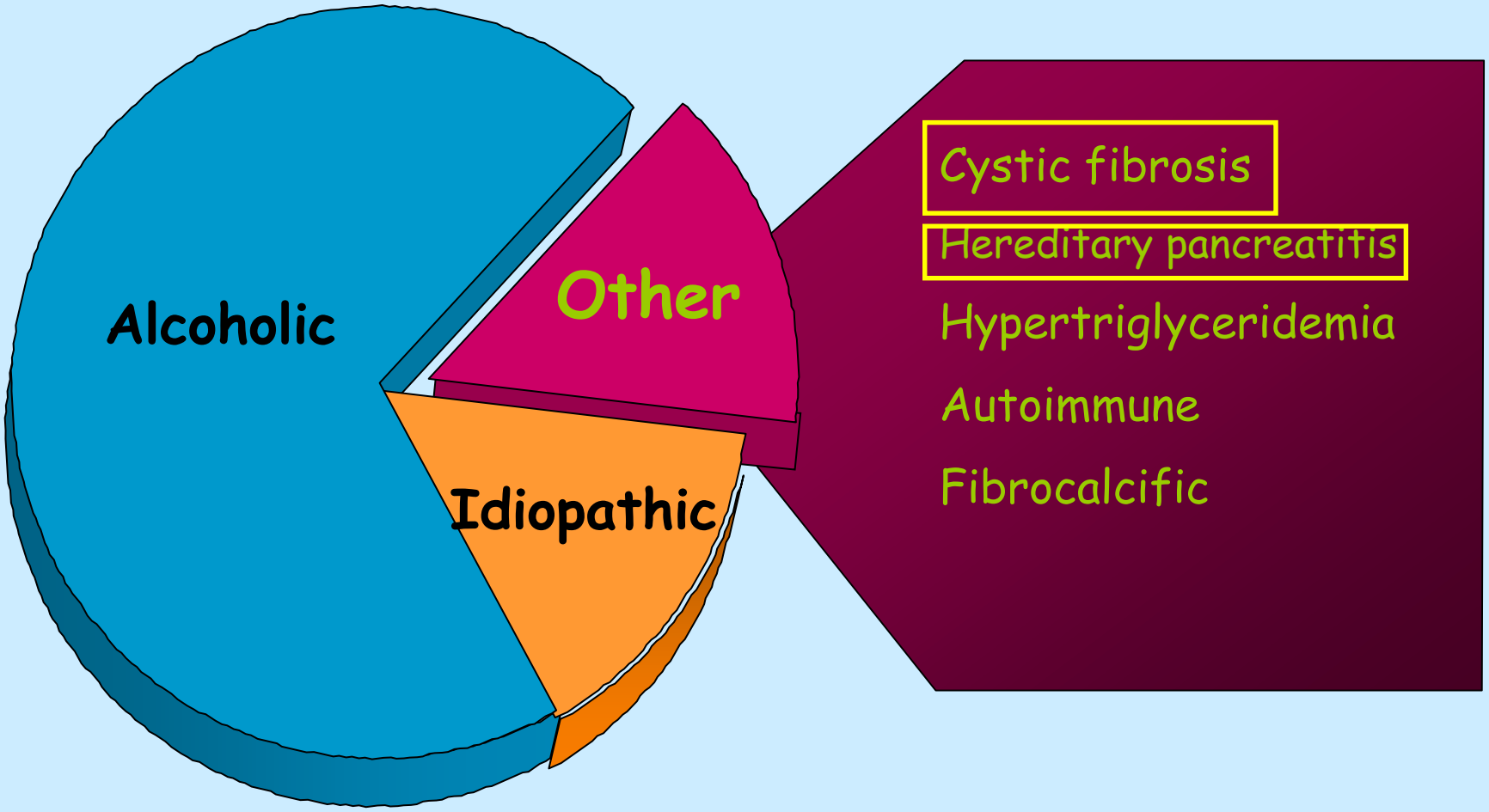
A parent complained to a gastroenterologist about their child's strange eating habits.

–"All day long they lie in bed and eat yeast and car wax. What will happen to them?"

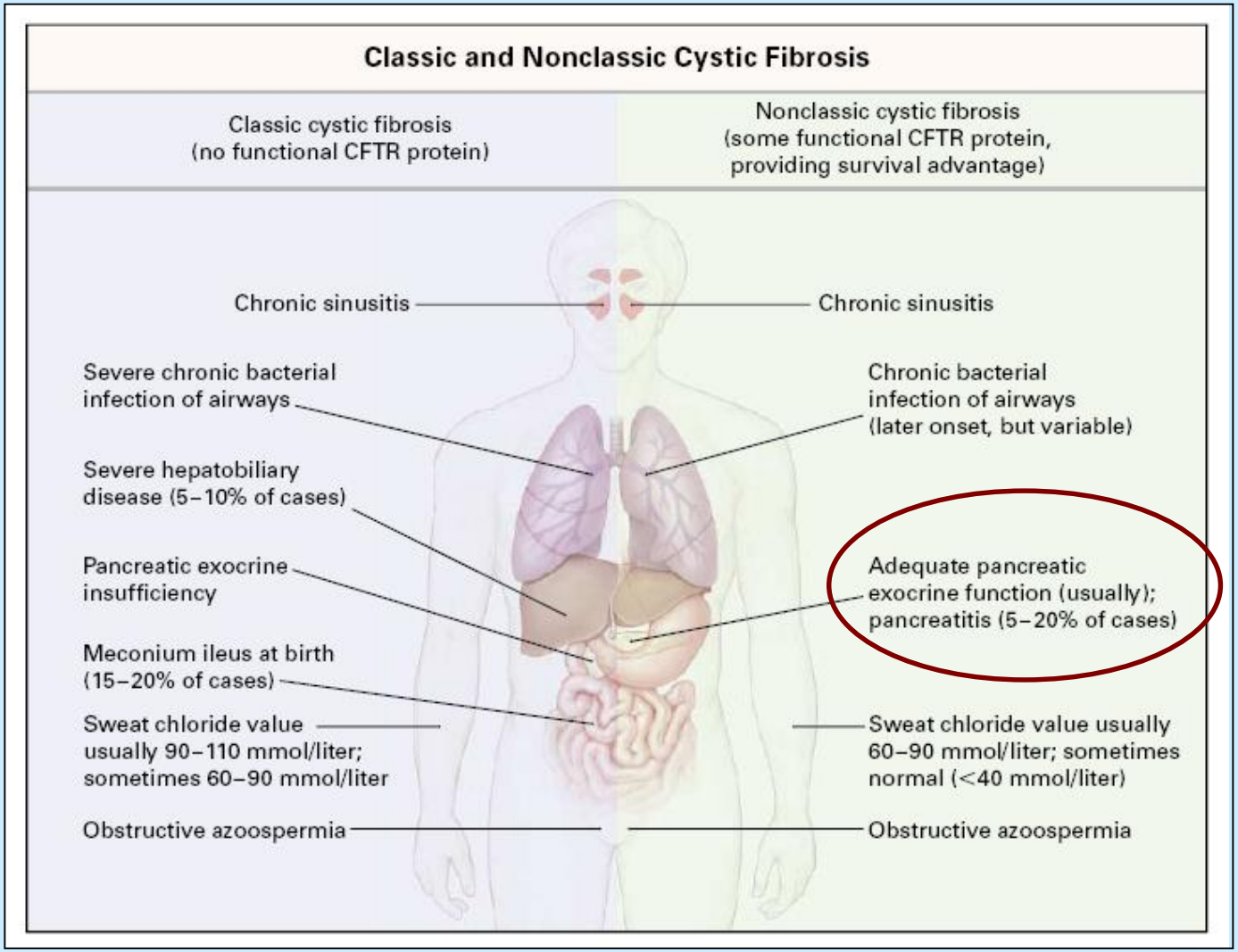
–"Eventually..." said the gastroenterologist, "...they will rise and shine."

YAEL WILSCHANSKI MFA 2019

Etiologies of recurrent/chronic pancreatitis

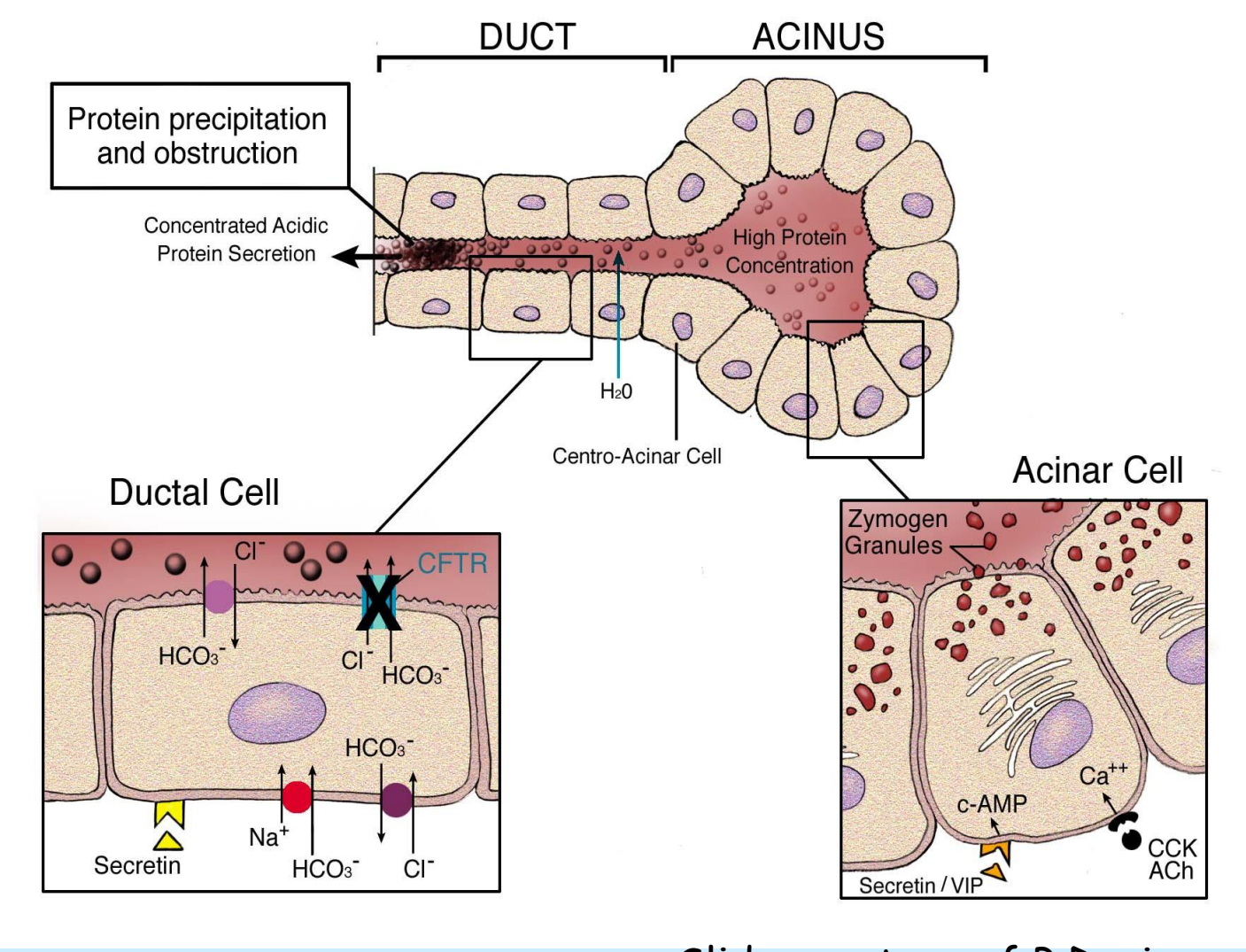


CLASSIC AND NONCLASSIC CF



Knowles and Durie, NEJM 2002

PATHOGENESIS OF PANCREATIC DISEASE IN CF



Slide courtesy of P Durie

Exocrine Pancreatic Status

- Pancreatic Insufficiency 85%
- Pancreatic Sufficiency 15%

Non classic CF patients
(atypical presentation of CF)

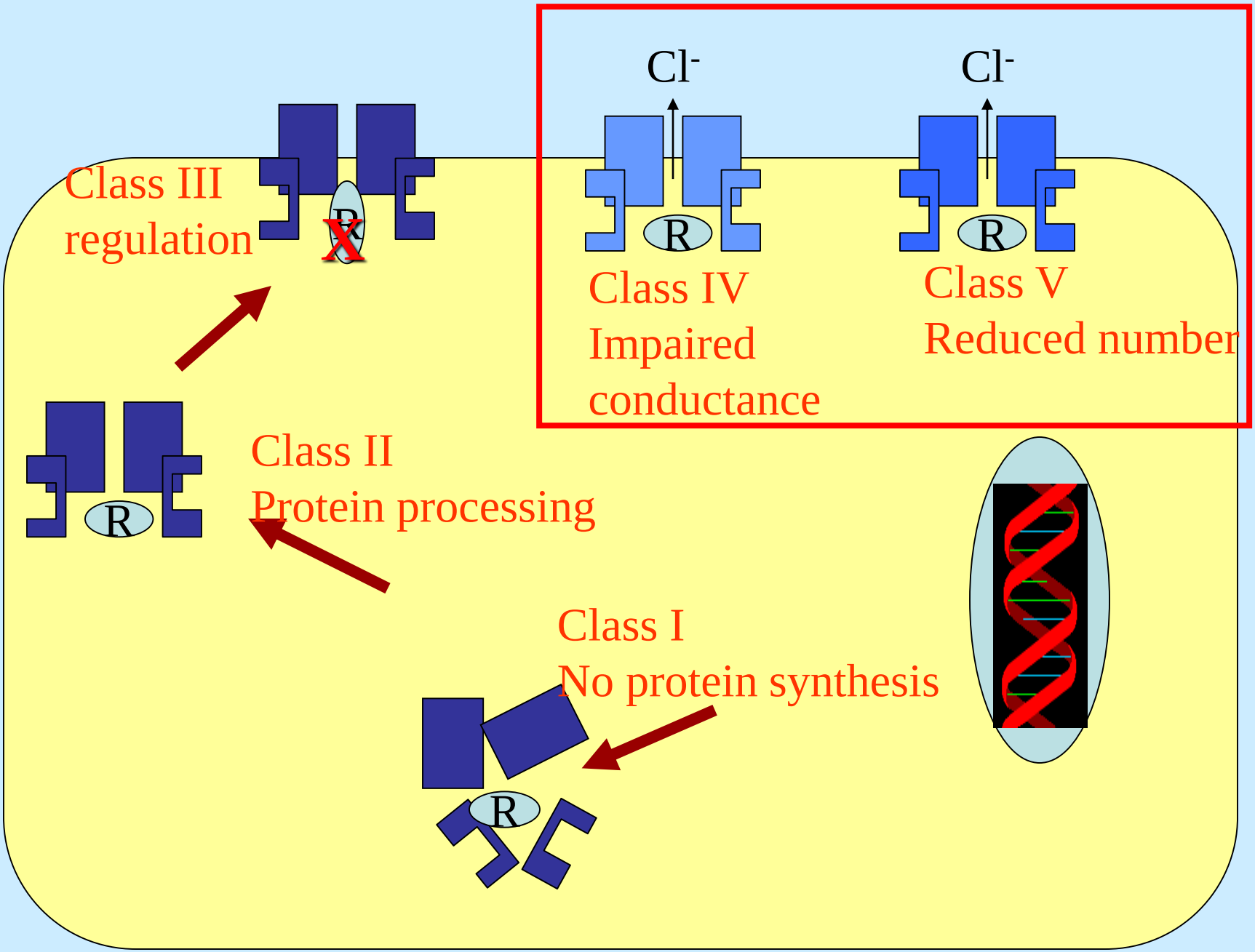
- Later age of diagnosis
- Pancreatic sufficiency.
- Chronic sino-pulmonary disease.
- Sweat chloride levels may not be helpful

Single Organ Presentation of CF

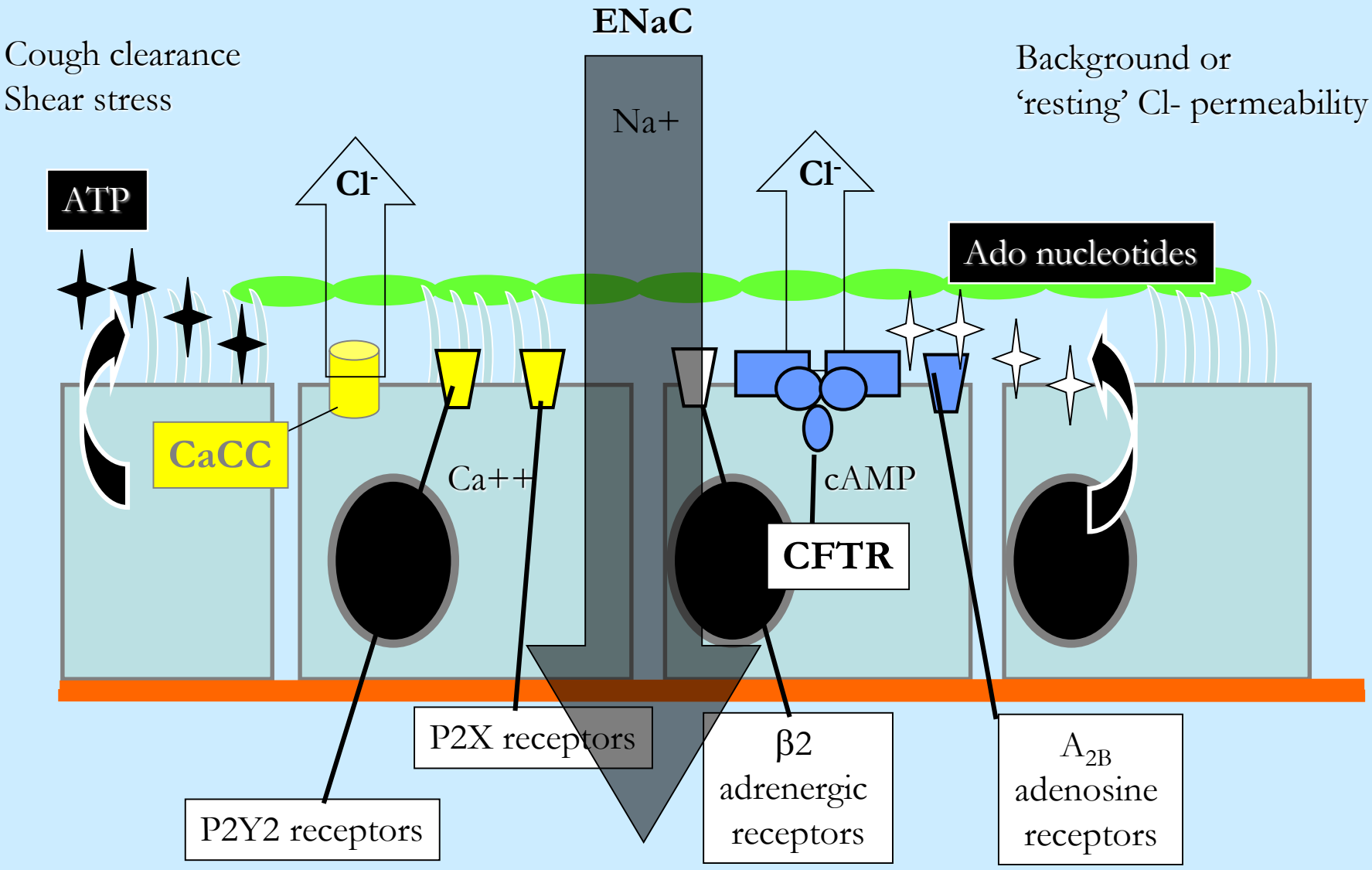
- nasal polyposis
- chronic sinusitis
- CBAVD (Congenital Bilateral Absence of Vas Deferens)
- allergic bronchopulmonary aspergillosis
- unexplained chronic lung disease with no other signs of CF
    - primary sclerosing cholangitis

J Cyst Fibros 2018 Sep;17(5):666-671

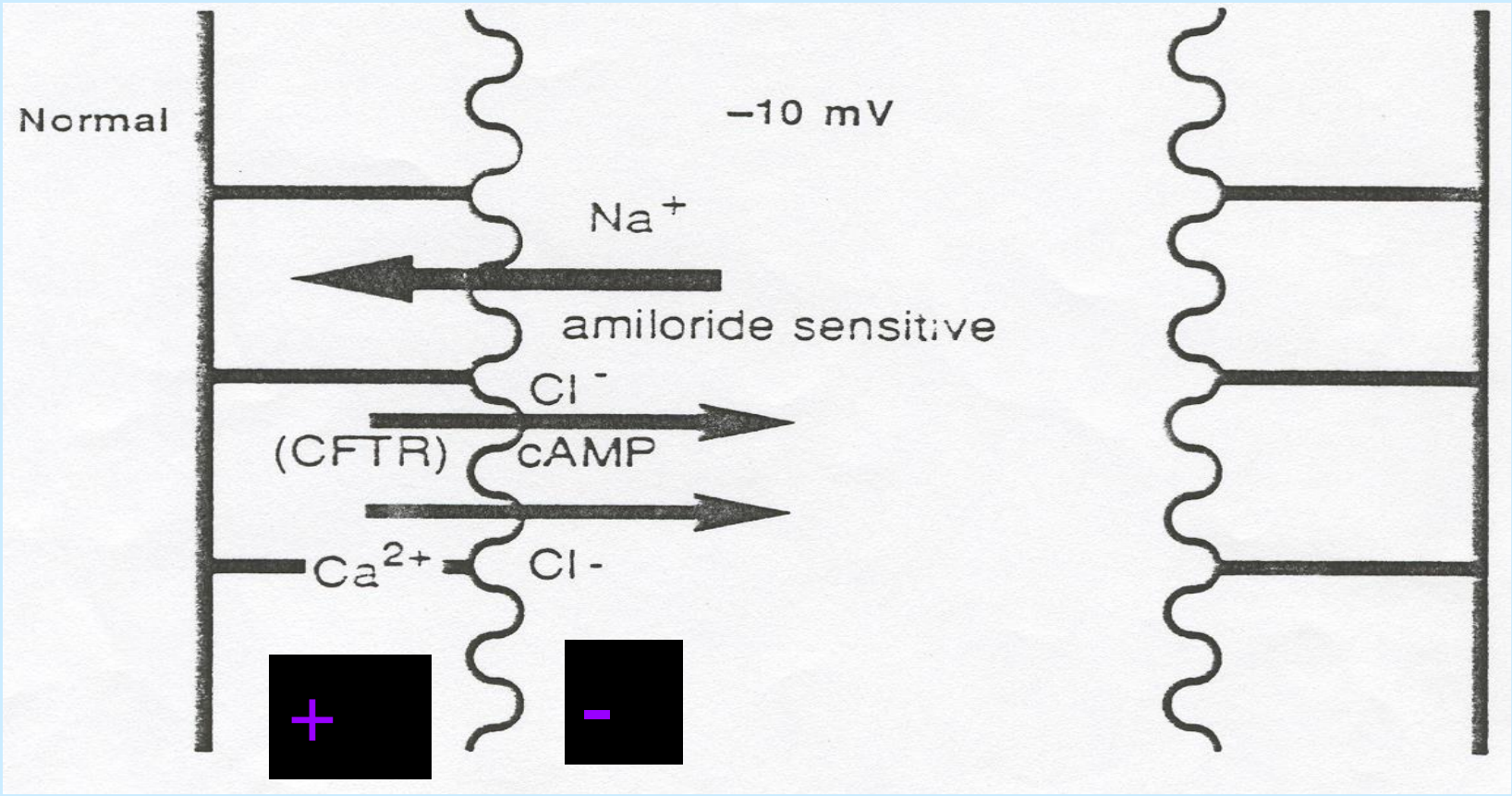
- Acute , recurrent pancreatitis


Cl-
Cl-
Class III
regulation
R
X
R
R
Class IV
Impaired
conductance
Class V
Reduced number
Class II
Protein processing
R
Class I
No protein synthesis
R

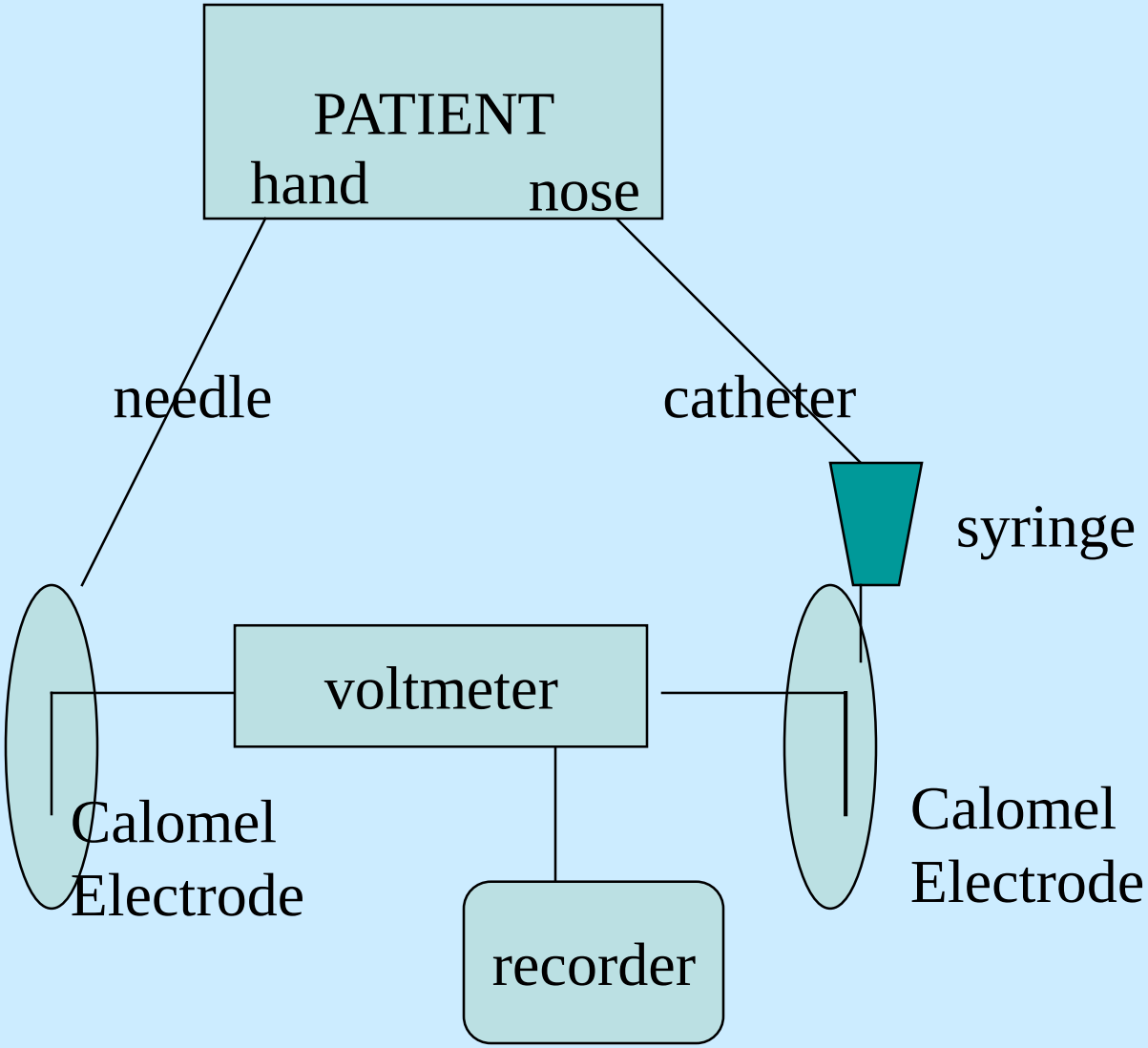
Nasal Potential Difference



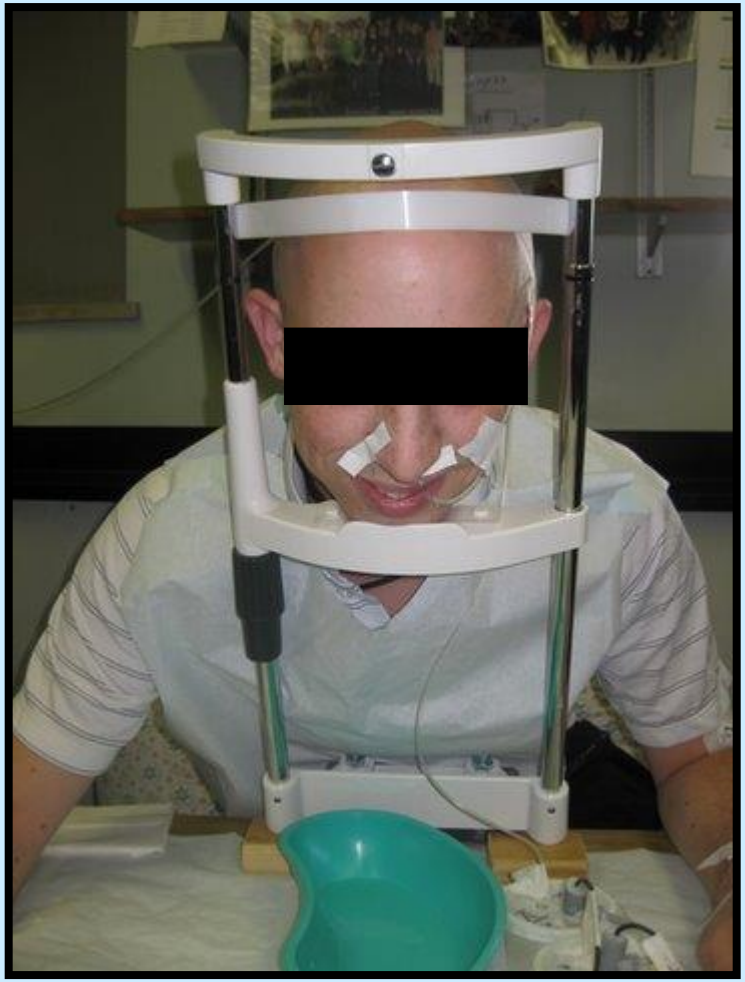
Mechanisms of Cl^- and Na^+ flux across epithelial cells- normal cells



Nasal Potential Difference (NPD)



NPD Technique

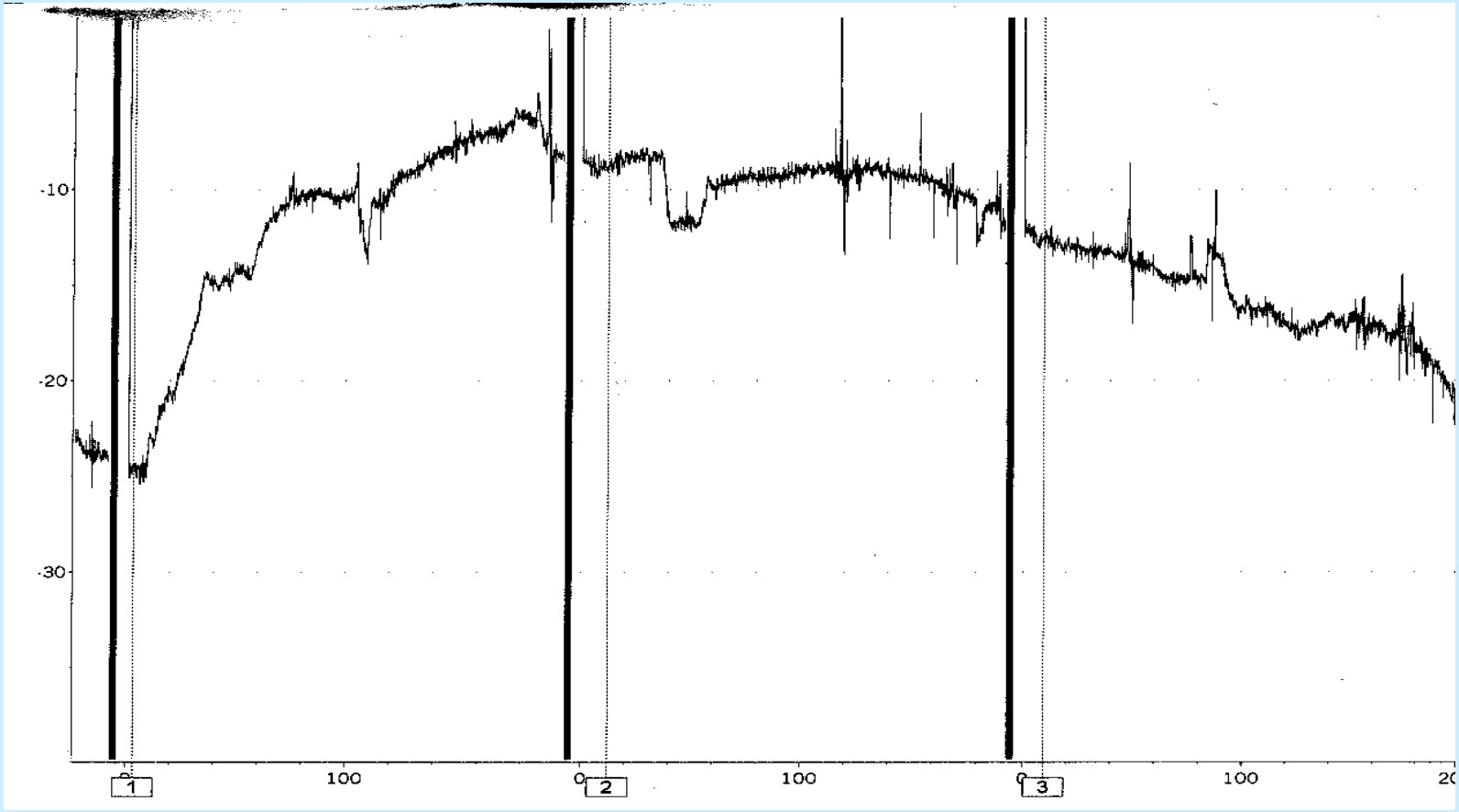


NPD- non CF patient:

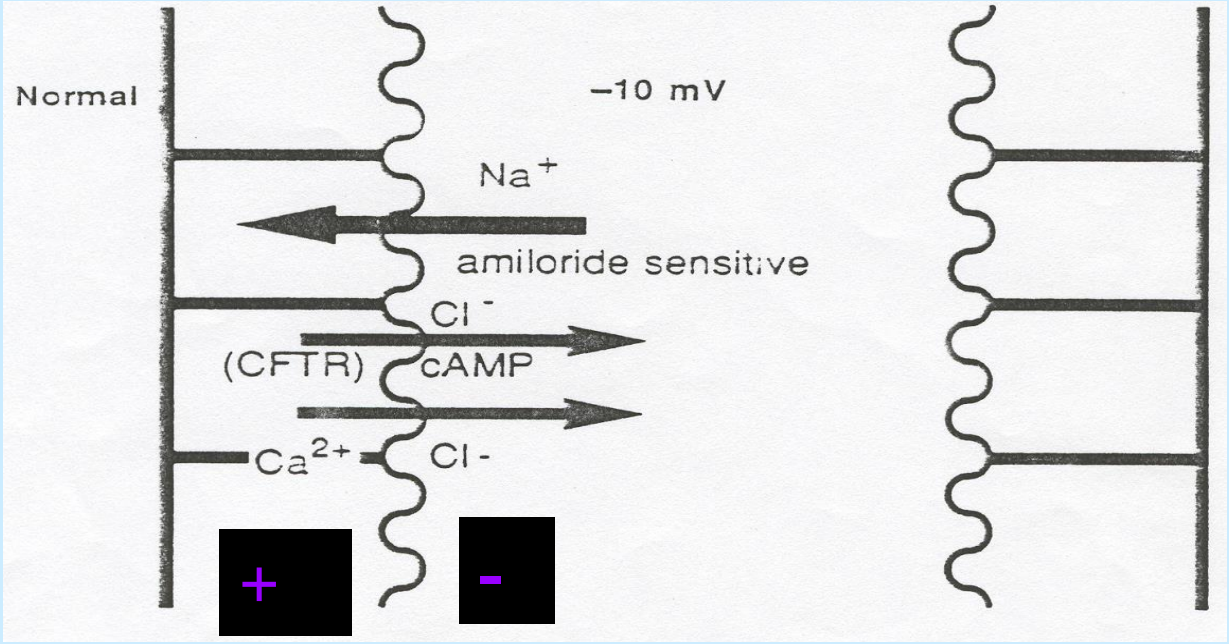
Amiloride

Cl^- free

Isoproteranol



Mechanisms of Cl^- and Na^+ flux across epithelial cells- normal cells

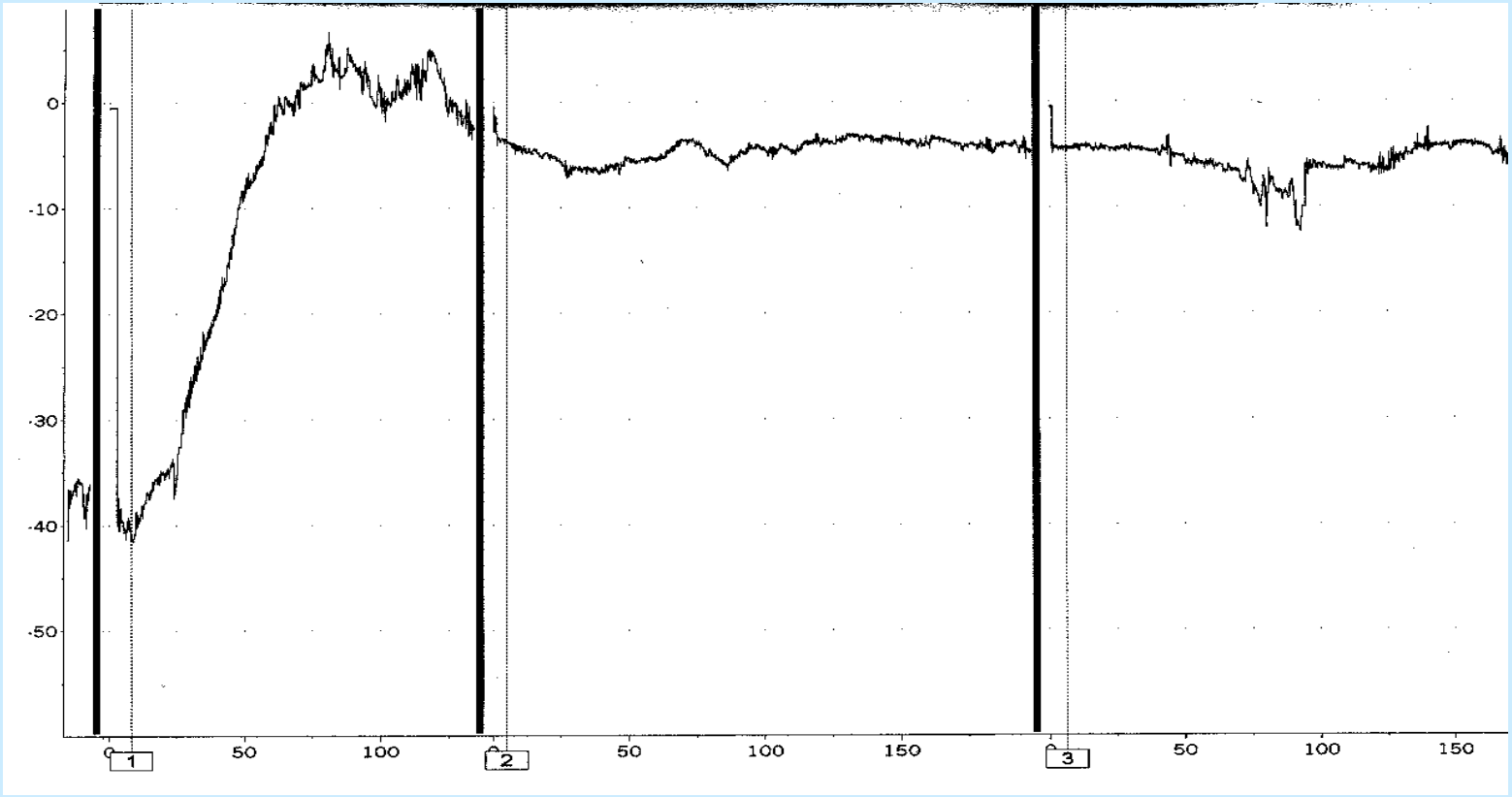


NPD- CF patient:

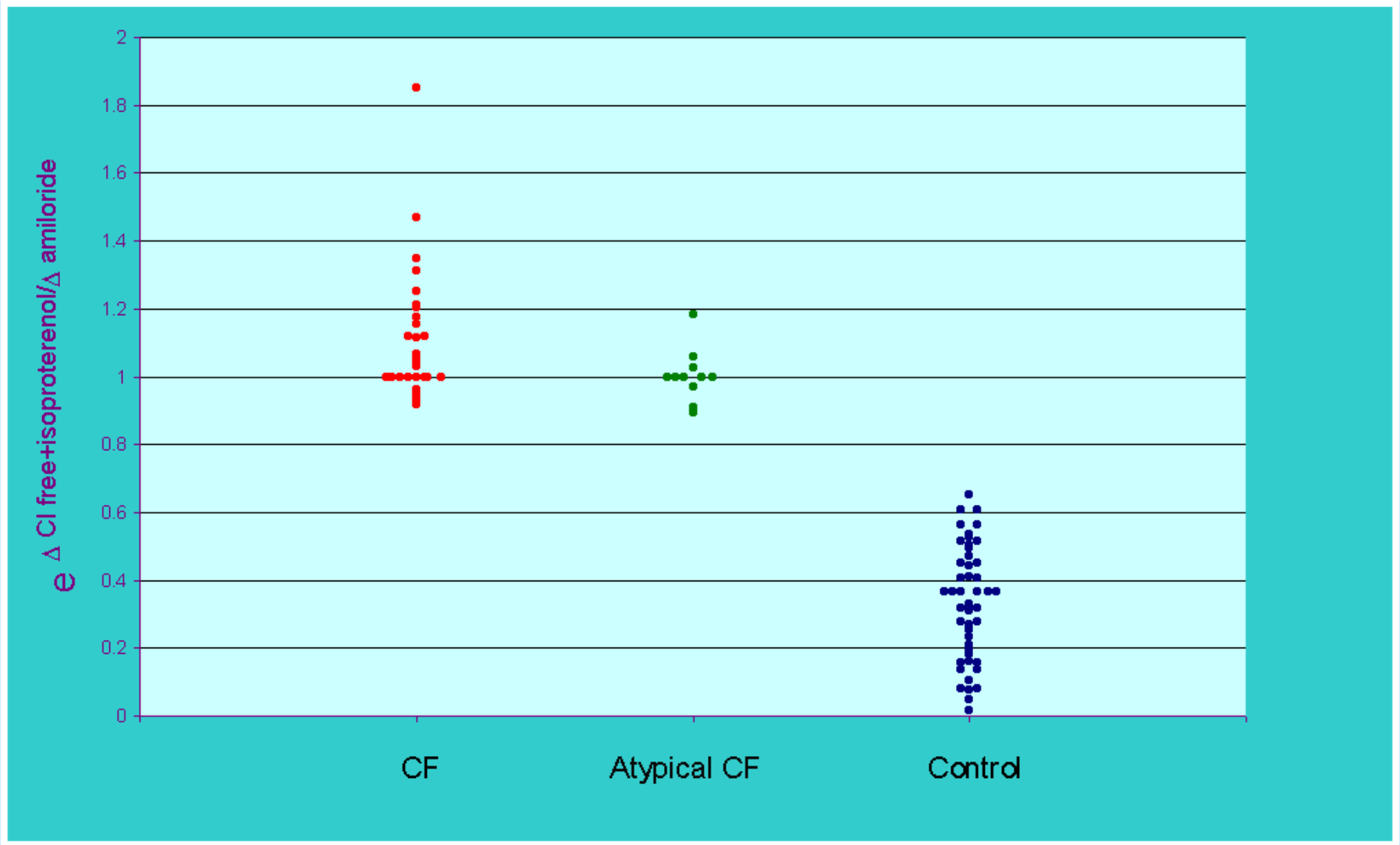
Amiloride

Cl^- free

Isoproteranol



NPD measurements in CF, Atypical CF and Controls

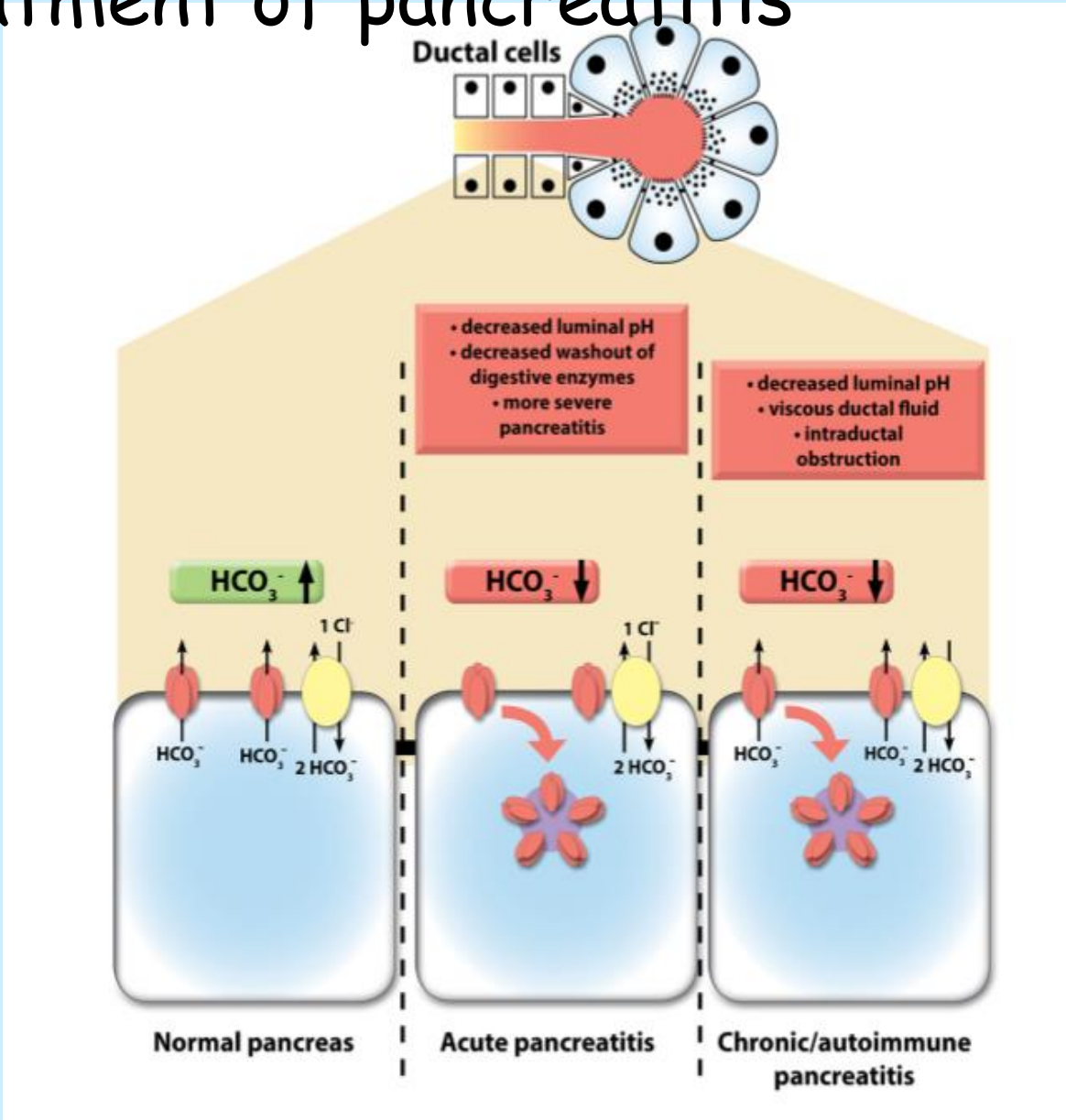


Wilschanski Eur Resp J 2001;17:1208-15

"potential" uses of nasal potentials

- **Diagnosis** ***(European Network)***
- CBAVD/ male infertility
- sinusitis / nasal polyposis
- **pancreatitis**
- **Therapy**
- gene/protein/ "alternative"

CFTR: A new horizon in the pathomechanism and treatment of pancreatitis



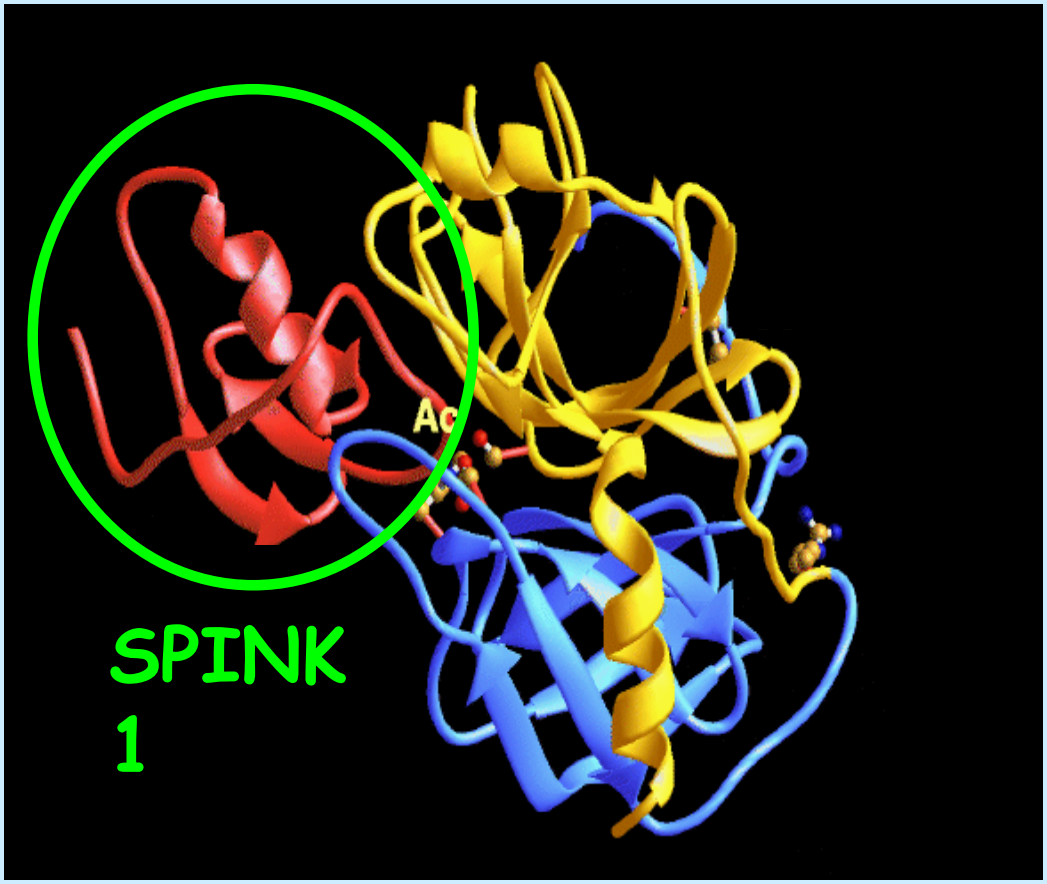
Hegyi P et al. Rev Physiol Biochem Pharmacol . 2016 ; 170: 37-66

Cationic Trypsinogen (PRSS1) - R122H

modified from Whitcomb *et al.*, Nature Genetics 1996

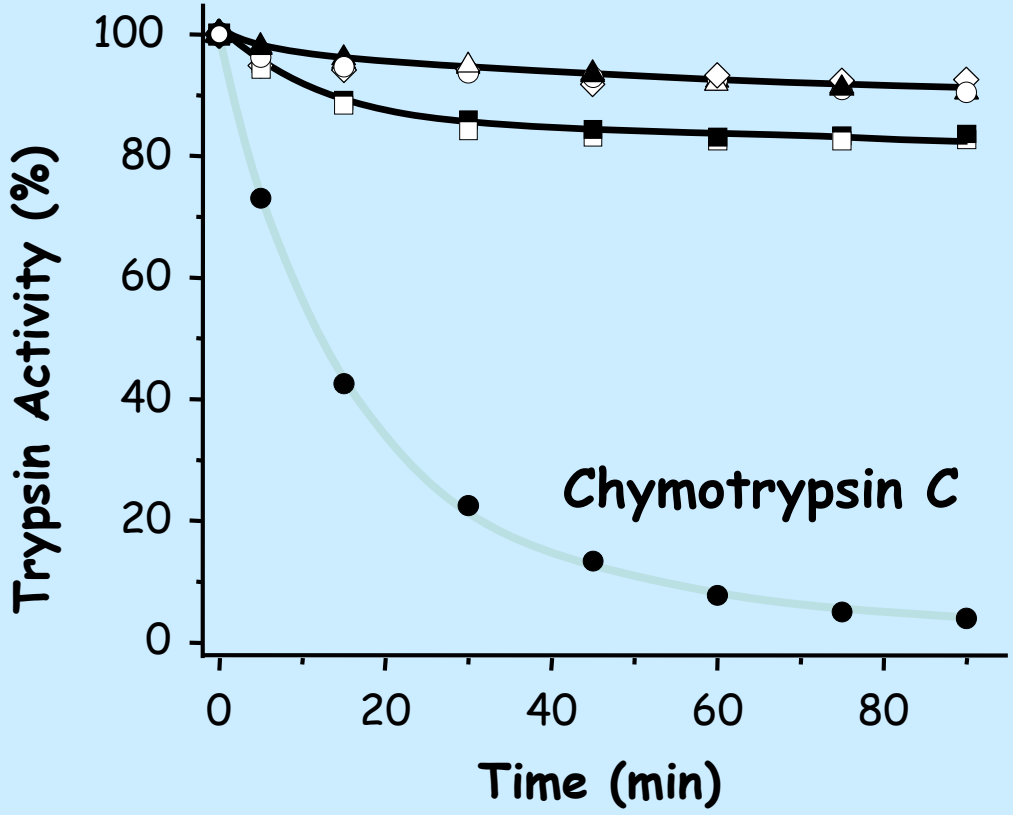
SPINK1

Serine Protease Inhibitor, Kazal Type 1



Chymotrypsin C (*CTRC*)

Degradation of Cationic Trypsin



Szmola & Sahin-Tóth, PNAS 2007

Aim

To present the work-up of children and adults with recurrent pancreatitis referred for genetic analysis and electrophysiological testing

METHODS

- Children and adults with recurrent pancreatitis (at least twice) whose diagnostic work-up (usually extensive including imaging) was negative
- referred for nasal potential difference measurements
- genetic testing PRSS1 , SPINK1, CTRC and CFTR (Paris)

Demographics and clinical data of patients with recurrent acute pancreatitis

No. of patients	158 (96 males, 62 female)
Age (years)	Average: 22yrs (range: 1.5-72 yrs)
No. of episodes	range 2-40
Ethnic origin	85% Jewish 15% Arab
Sweat test	101 out of 158 patients
NPD test	135 out of 158 patients

Sweat chloride results

44/101 patients with results ≤30 mmol/L

57/101 patients with results >30 mmol/L

Nasal Potential Difference (NPD) Results

NPD test was performed on 135 out of 158 patients:

120 patients with normal NPD

15 patients with abnormal NPD

15 patients with abnormal NPD results

Genetic analysis results	Age (yrs)	Sweat test	No. of episodes	Ethnic Origin
R67H/- (SPINK1)	19	33	3	Arab
R117H/Y1014C (CFTR)	7	54	13	Jewish
R117H/- (CFTR)	34	82	20	Jewish
W1282X/Y1014C (CFTR)	67	100	5	Jewish
G85E/- (CFTR)	23	58	4	Arab
ΔF508/- (CFTR)	15	<30	20	Jewish
Negative [9]				

Genetic analysis results of genes *PRSS1, SPINK1, CTRC, CFTR*

CFTR mutations	PRSS1 mutations	SPINK1 mutations	CTRC mutatiuns
R31C/- [2]	R122H/- [4]	I42M/- [1]	V235I/- [1]
L997F/- [1]	K23R/- [9]	R67H/- [2]	G215S/- [1]
ΔF508/- [4]	D21A/- [1]	N34S/- [5]	D171N/- [1]
G85E/- [1]	D19A/- [1]	c.194+2T>C/- [1]	
K172E/- [1]	K23R/K23R [1]		
E217G/- [1]			
E1433K/- [1]			
5T/- [1]			
ΔF508/L997F [1]			
W1282X/5T [1]			
W1282X/D1152H [1]			
E1266K/E1266K [1]			
ΔF508/R31C [1]			

Demographics and clinical data of children with recurrent acute pancreatitis

No. of patients	86 (33 females, 53 males)
Age (years)	10±5 (range: 1-18 yrs)
No. of episodes	range 2-16
Ethnic origin	75% Jewish 25% Arab
Sweat test	65 out of 86 patients
NPD test	76 out of 86 patients

Sweat chloride results

29/65 patients with results ≤30 mmol/L

36/65 patients with results >30 mmol/L

Nasal Potential Difference (NPD) Results

NPD test was performed on 76 out of 86 patients:

70 patients with normal NPD

6 patients with abnormal NPD

6 patients with abnormal NPD Results

Age (years)	CFTR and/or Pancreatitis Mutations	Sweat cl^- (mmol/L)
7	R117H/Y1014C	54
15	ΔF508/-	30
1	ΔF508/-	55
12	-/-	28
7	-/-	61
14	-/-	68

Adults and children

Sweat test (ST) and NPD results for patients who underwent both tests

	ST≤29* (n=41)		30≤ST≤59* (n=46)		ST≥60* (n=14)	
Age<18 yrs Age≥18 yrs	n=28 n=13		n=29 n=17		n=6 n=8	
NPD results:	Normal (28)	Abnormal (3)	Normal (38)	Abnormal (8)	Normal(10)	Abnormal(4)
CFTR mutations [no. of patients]	ΔF508/R31C [1]	-/- [3]	ΔF508/L997F [1]	R117H/Y1014C [1]	L997F/- [1]	W1282X/Y1014C [1]
	-/- [27]		W1282X/5T [1]	G85E/- [1]	D1152H/- [1]	R117H/-[1]
			ΔF508/- [1]	ΔF508/- [1]		-/- [2]
			-/- [35]	-/- [5]		

Mutations in the SPINK1+CTRC+CFTR Genes

Patient no.	Age (yrs)	Mutations	Ethnic origin
035	7	I42M(SPINK1)/V235I(CTRC) ΔF508/5T (CFTR)	Ashkenazi /Iraqi Jewish

Genetics Matters

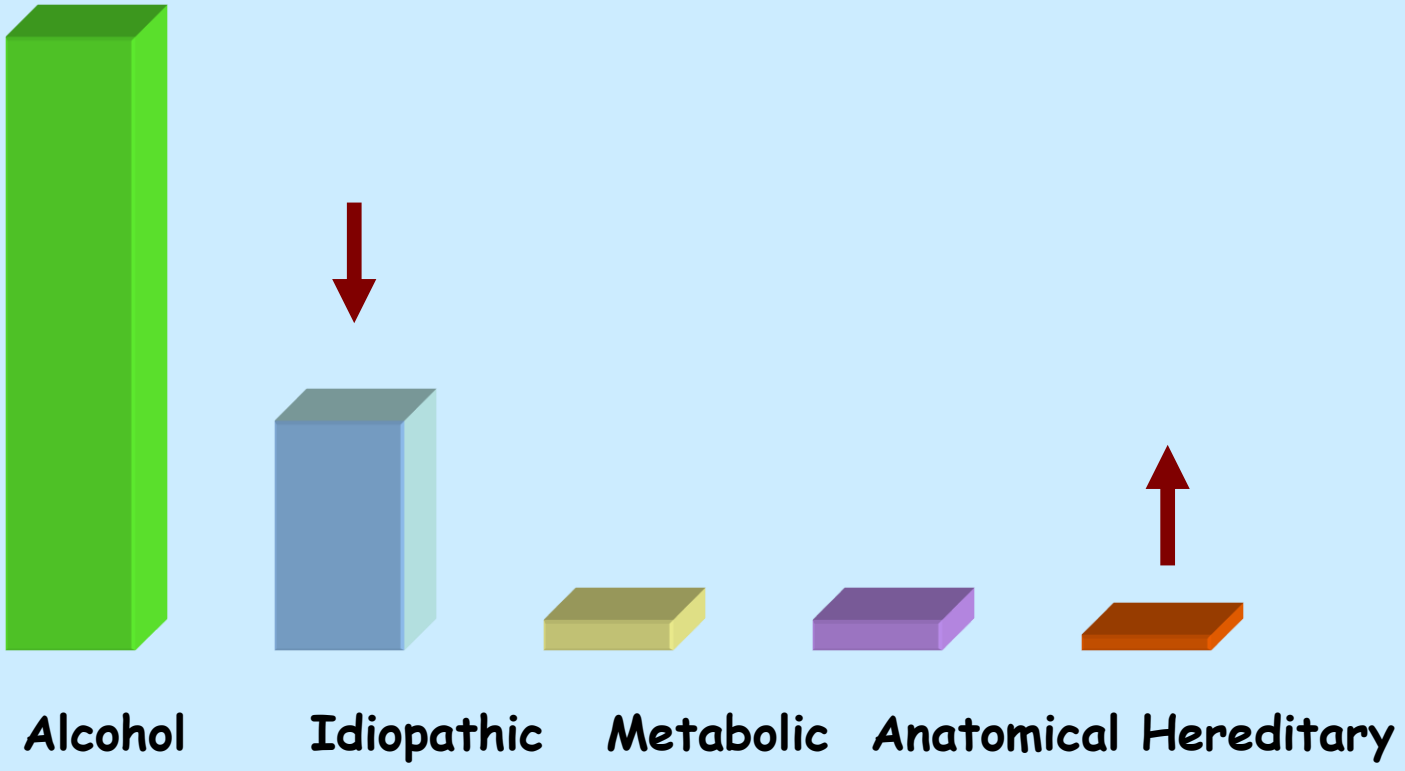
- **Risk Factors for Rapid Progression From Acute Recurrent to Chronic Pancreatitis in Children: Report From INSPPIRE.** Liu QY JPGN May 2019 epub (PRSS1)

- **Association between F508 deletion in CFTR and chronic pancreatitis risk.** ZhaoD Dig Liver Dis. 2017 Sep;49(9):967-972

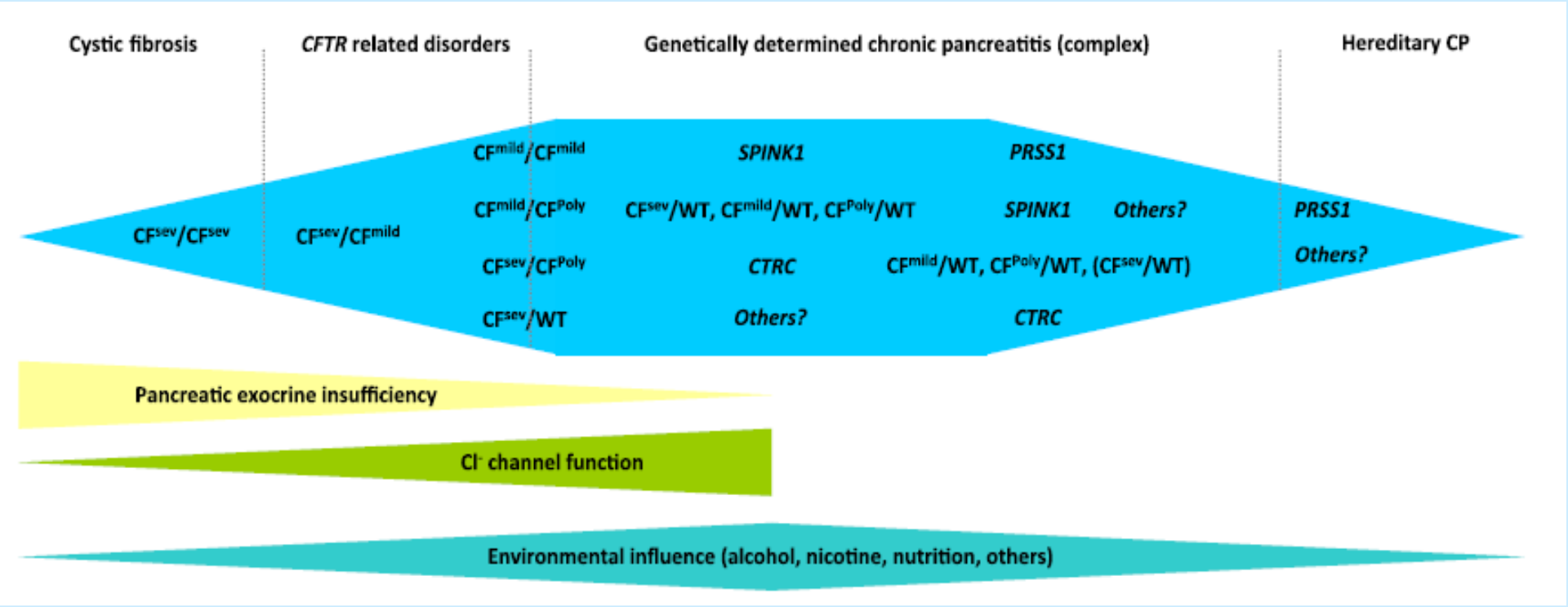
- **Genetic variants in acute, acute recurrent and chronic pancreatitis affect the progression of disease in children.** Abu-El-Haija M Pancreatology 2019 Jun;19(4):535-540 (CFTR)

Recurrent/Chronic Pancreatitis

Aetiology



CHRONIC PANCREATITIS IS A COMPLEX GENETIC DISORDER



Rosendahl J CFTR,SPINK1,CTRC and PRSS1 variants in chronic pancreatitis:is the role of mutated CFTR overestimated ***Gut****. 2013 Apr;62(4):582-92*

Conclusion

- This is the first study on recurrent pancreatitis in Israel examining both the presence of susceptibility gene mutations for pancreatitis and CFTR dysfunction
- A prospective study with a larger number of patients may further clarify the impact of genetic mutations and CFTR dysfunction on the clinical presentation and outcome of recurrent pancreatitis
- (INSPPIRE)

Electrophysiology Lab in Hadassah

Acknowledgements

Santo M, Adler S, Klar A, Broide E, Halpern Z, Konikoff F, Shaoul R, Barkay-Kolker O, Bentur L, Mussaffi H, Kerem E, Arad N, Goldin E, Yaron A, Yerushalmi B, Pinsk V, Shamir R, Shamaly H, Berenstein M, Augarten A, Turner D

Durie P RIP, Whitcomb D, Uc A

Ferec C, Ruszniewski P (France)

THANK YOU!!!!

TABLE 1. ST and NPD results for patients who underwent both tests

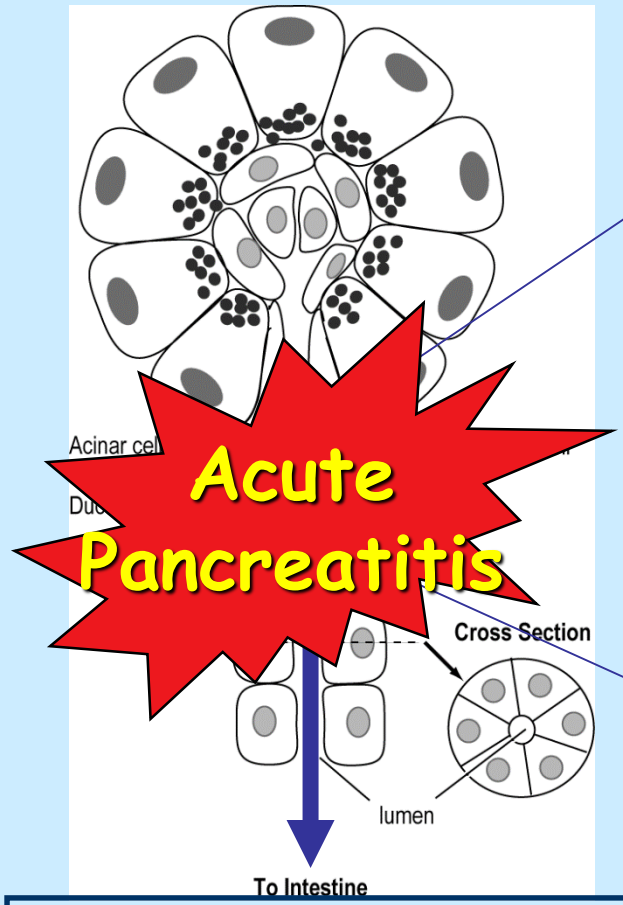
	ST ≤ 39 (N = 22)	40 ≤ ST ≤ 59 (N = 22)		ST ≥ 60 (N = 5)	
Age <18 y	n = 11	n = 15		n = 0	
Age ≥18 y	n = 11	n = 7		n = 5	
NPD results	N (22)	N (21)	A (1)	N (2)	A (3)
Basal NPD	−18.0 ± 6.5	−18.8 ± 5.8	−17.0 ± 0.0	−20.8 ± 2.4	−22.9 ± 5.7
ΔAmil, mV	10.4 ± 6.1	10.9 ± 5.1	13.0 ± 5.7	12.5 ± 3.5	16.2 ± 7.1
$\Delta 0Cl^- + Iso$, mV	−10.7 ± 7.7	−13.2 ± 9.5	−3.5 ± 2.1	−19.5 ± 8.3	−1.0 ± 3.7
$e^{\Delta 0Cl+Iso/\Delta Ami}$, mV	0.4 ± 0.2	0.4 ± 0.2	0.8 ± 0.0	0.2 ± 0.1	1.0 ± 0.3
CFTR mutations [no. patients]	ΔF508/R31C [1] 5T(11TG)/− [1] −/− [20]	ΔF508/L997F [1] W1282X/5T(12TG) [1]−/− [19]	R117H/Y1014C[1]	L997F/− [1] D1152H/− [1]	W1282X/ Y1014C [1] R117H/− [1] −/− [1]

ST is presented in mmol/L. A = abnormal; Amil = amiloride solution; CFTR = cystic fibrosis transmembrane conductor regulator; N = normal; NPD = nasal potential difference; ST = sweat test; $0Cl^- + Iso$ = chloride free + isoproterenol solution; $e^{\Delta 0Cl+Iso/\Delta Ami}$ = exponent of Δchloride free + isoproterenol/ΔAmiloride solution.

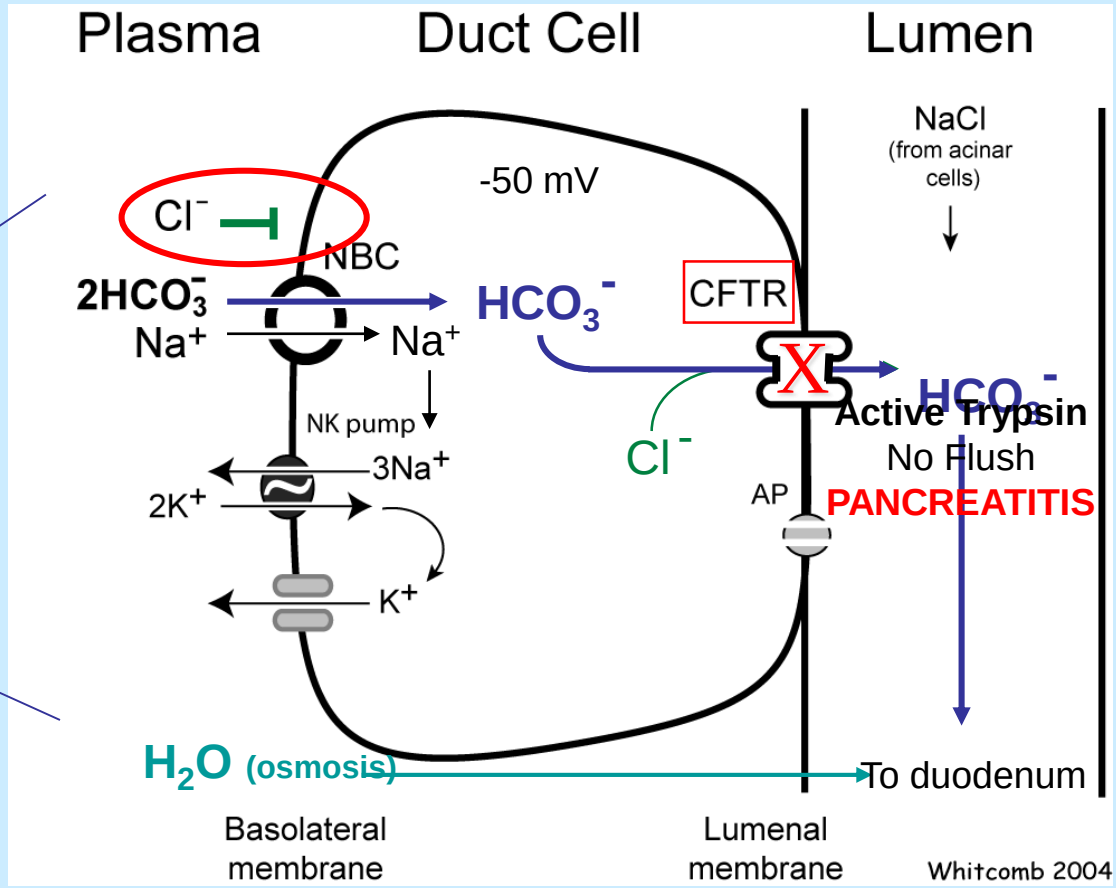
CFTR and Bicarbonate Secretion

Next

Whitcomb DC & Ermentrout DB. *Pancreas* 2004; 29(2):E30-E40



Acute Pancreatitis

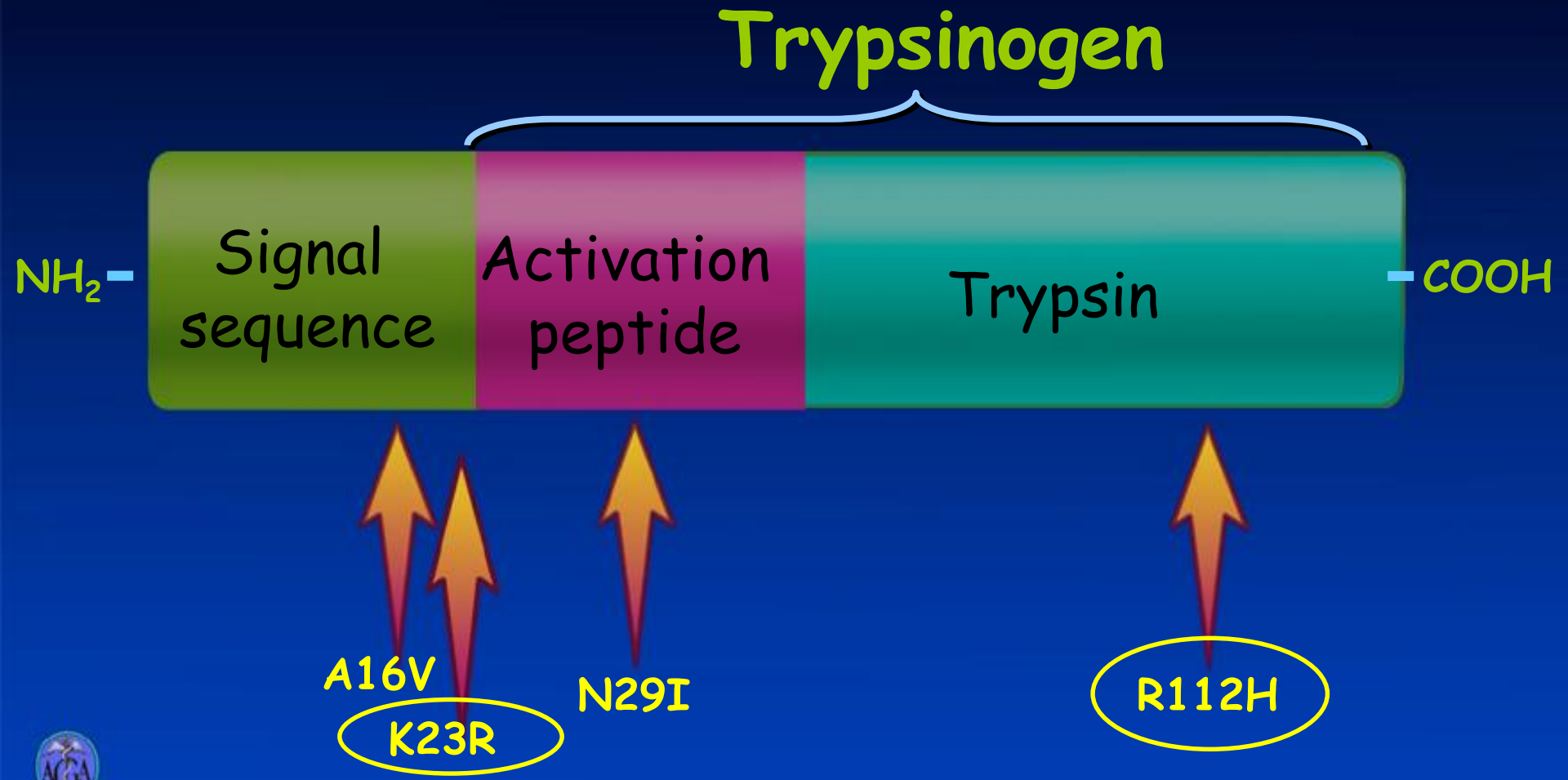


CFTR Mutations limit bicarbonate secretion, increasing susceptibility to pancreatitis.

Opening of CFTR starts ion secretion Chloride washes out and cannot enter on the basolateral side. Chloride is replace by bicarbonate

Hereditary Pancreatitis

Cationic trypsinogen mutations



DC Whitcomb, Med. Clinics of North America 2000; 84:531