

**Long history of ICUR/ICEU &  
vs. other *GI International Symposia***

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and


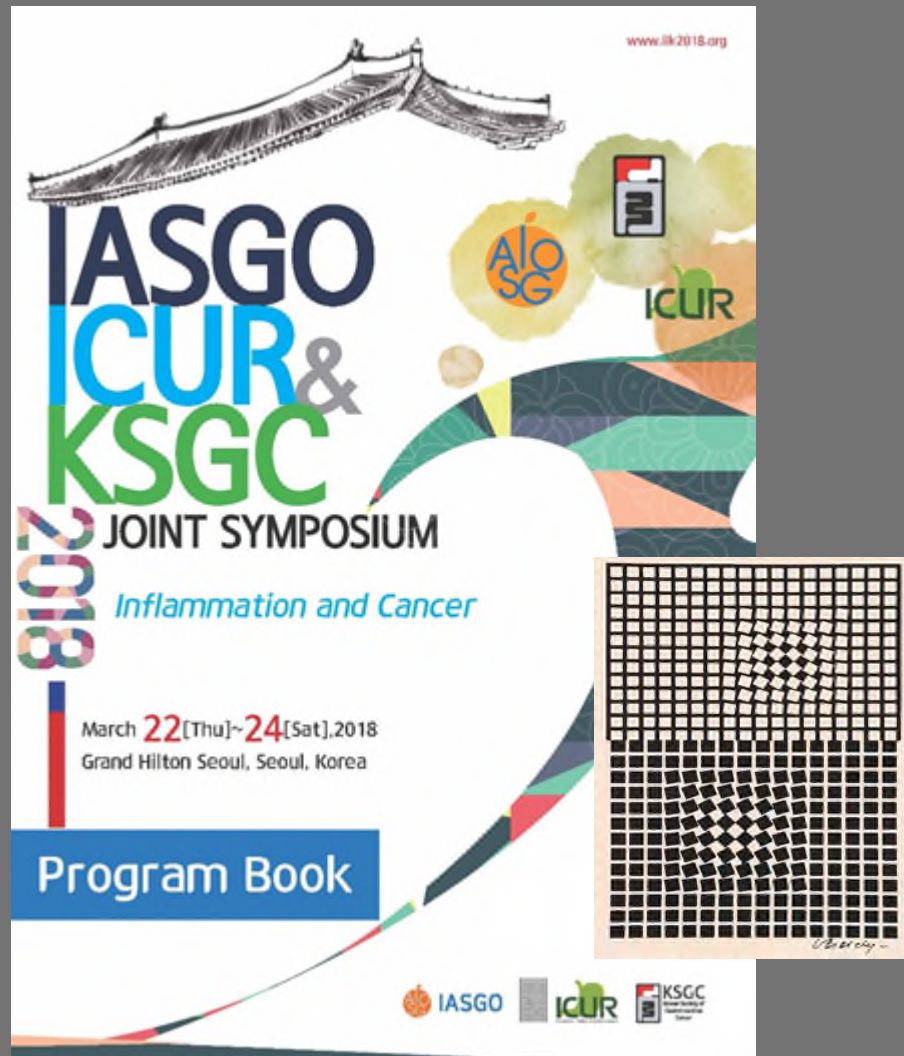
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Visiting Professor, Semmelweis University

Budapest, Hungary

# Sample of the program book

IASGO, ICUR & KSGC Joint Symposium



### Welcome Message ICUR

Welcome to the 16th ICUR (International Conference on Ulcer Research) – the first ever held in Korea! This, well focused conference series started by Dr. Carl Pfeiffer (then at Univ. of Pennsylvania) as ICEU (International Conference on Experimental Ulcer), which had its first meeting in 1970 in Copenhagen, Denmark. Reflecting the global reach of ulcer research, the meetings were held all over the world, e.g., I had the privilege to organize the 5th ICEU when I was in Boston & other conferences were held four times in Japan, twice in Croatia, Germany, Hungary, & once in Canada, Denmark, Israel & USA. It took us about 15 years to convince the Standing Committee of ICEU (then led by Carl Pfeiffer) to change the name from ICEU to ICUR in order to better reflect the current trends of ulcer research, i.e., not to concentrate only on experimental ulcers in laboratory animals but include in vitro studies with cell & organ cultures as well as clinical research on ulcers in the upper & lower GI tract.



*Szabo*  
Sandor Szabo  
ICUR President

The tremendous progress in ulcer research happened during the life-time of ICEU-ICUR... Just think it over: when this collaborative, often contentious conference series started, there was only two widely used rodent model gastric ulcers (actually, mostly erosions) induced by severe stress or pylorus ligation (Shay ulcer). Never mind that the majority of 'peptic ulcers' in patients were in the duodenum (except in Japan & Chile). The first rat models of duodenal ulcers (e.g., produced by acetic acid or cysteamine) were developed during the first decade of ICEU meetings. Furthermore, before the ICEU-ICUR there were no H2 blockers & PPI, H. Pylori was not (re)discovered yet, no growth factors, no interleukins & genes now known to be involved in the pathogenesis of IBD. This does not mean that these discoveries happened because of this conference series; rather that these developments & explorations were greatly enhanced by preparations of the data to be presented at these conferences & accelerated by creative discussions & exchange of ideas.

One more historic fact: ICEU-ICUR is the longest running research conference series focused on ulcerative & inflammatory lesions in the GI tract. Namely, the very successful Taisho-Toyoma Conferences on Gastroenterology had its last, 15th meeting a few years in Japan, while the even more focused ISCTICO (Int. Symp. on Cell/Tissue Injury & Cytotrop./Organoprot.) will have its 10th reunion this June in Kyoto, Japan & hopefully it will be running for a long time, now under the auspices of IUPHAR GI Section.

We should all thank & congratulate Prof. Baik Hahm for bringing ICUR to Korea – a land of tremendous progress not only in electronics & car industry, but in medical research, esp., in gastroenterology & cancer! Furthermore, for the first time, our conference in Korea is a joint meeting with clinicians & other investigators: I hope that the IASGO, ICUR & KSGC joint meeting will be especially successful.



OP-ART dedicated to the symposia by Victor Vasarely

5

# Long history of ICUR/ICEU

**John L. Wallace, PhD, MBA, FRSC**  
**Antibe Therapeutics Inc.**  
15 Prince Arthur Avenue  
Toronto, ON, Canada M5R 1B2

Dear John,  
Here are the ICUR Meetings:

1st: Copenhagen (Denmark): 1970;  
2nd: Cologne (Germany): 1972;  
3rd: Parádörd (Hungary): 1979;  
4th: Tokyo (Japan): 1980;  
5th: **Boston (USA): 1985;**  
6th: Jerusalem (Israel): 1987;  
7th: Berlin (Germany): 1991;  
8th: Kyoto (Japan): 1994;  
9th: Hong Kong (China): 1997;  
10th: Budapest - Pécs (Hungary): 2000;  
11th: Dubrovnik (Croatia): 2003;  
12th: Osaka (Japan): 2007;  
13th: Split (Croatia): 2009;  
14th: Tokyo (Japan): 2012,  
and the 15th is your Meeting at Ottawa.

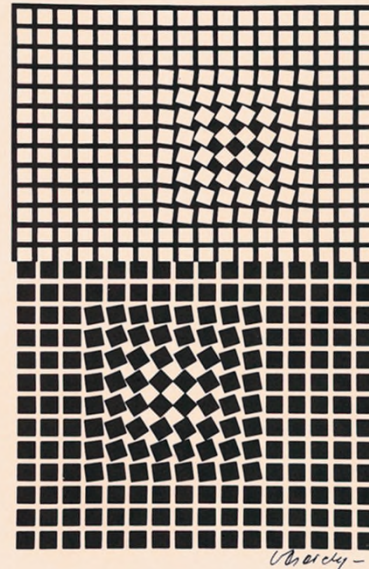
With my best wishes,

Gyula

—  
Gyula Mózsik MD PhD ScD (med)  
Professor of Medicine  
First Department of Medicine,  
Medical and Health Centre,  
University of Pécs Hungary

The 5th International Conference on Experimental Ulcer

May 16-18, 1985  
Boston, Massachusetts



PROGRAM

Boston, Mass., May 16-18, 1985  
Harvard School of Public Health  
Amphitheatres G-1 and G-2  
(ground floor)

## ORGANIZING COMMITTEES

Szabo, S., President  
Pfeiffer, C. J., Secretary-General

## STANDING COMMITTEE OF ICEU

Gheorghiu, T.  
Mozsik, Gy.  
Okabe, S.  
Pfeiffer, C.J., Secretary-General

Robert, A.  
Ito, H., ex-officio  
Szabo, S., ex-officio

## SCIENTIFIC COMMITTEE

Flemstrom, G.  
Garner, A.  
Guth, P.H.  
Isenberg, J.I.  
Konturek, S.

Silen, W.  
Tache, Y.  
Vener, K.  
Walsh, J.H.

I invited

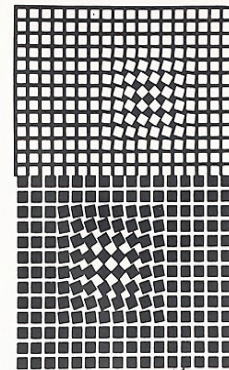
**5 Nobel Laureates:**

- **Julius AXELROD**
- **Christian De DUVE**
- **Linus PAULING**
- **John VANE**
- **Albert SZENT-GYORGYI**



# 5th International Conference on Experimental Ulcer

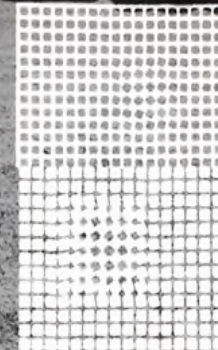
May 16-18, 1985  
Boston, Massachusetts





The 5th International  
Conference on  
Experimental  
Ulcer

May 16-18, 1985  
Boston, Massachusetts



# 5<sup>th</sup> ICEU, Boston, MA, 1985

## PROGRAM

Thursday, May 16, 1985  
Amphitheatre G-1

2:00 P.M.

### Opening Addresses

DANIEL C. TOSTESON, Dean, Harvard Medical School

HARVEY V. FINEBERG, Dean, Harvard School of Public Health

CARL J. PFEIFFER, Secretary General, Standing Committee, ICEU

PETER J. GOMES, Plummer Professor of Christian Morals, Harvard University (Cambridge, U.S.A.): The place of healing.

### Introductory Lectures

- 2:40 P.M. 1. G. WORMSLEY (Dundee, U.K.): New elements in aetiology & pathology of ulcer disease.
- 3:00 P.M. 2. A. SONNENBERG (Boston, U.S.A.): Pathogenetic implications for ulcer disease from epidemiologic studies.
- 3:20 P.M. 3. F. P. BROOKS (Philadelphia, U.S.A.): The role of CNS in gastric functions and ulcerogenesis.
- 3:40 P.M. 4. L. A. TURNBERG (Manchester, U.K.): An evaluation of the relevance of experimental ulcers to human disease.

### Special Lecture

Chairman: W. Silen (Boston, U.S.A.) & B. J. R. Whittle (Kent, UK)

- 4:00 P.M. 5. C. DE DUVE (New York, U.S.A.): Do cells have ulcers?

4:20 P.M. Coffee Break



12:05

132. A. ROBERT, K. TABATA, S. N. JOFFE, E. D. JACOBSON (Kalamazoo & Cincinnati, U.S.A.): Duodenal ulcers produced by mepirizole are not due only to prostaglandin deficiency.

12:10 P.M.

Discussion

1:00 P.M.

Lunch

### Special Lecture

Chairman: J. H. Walsh (Los Angeles, U.S.A.)

- 2:00 P.M. 133. J. AXELROD (Bethesda, U.S.A.): The interaction of stress hormones, ACTH, catecholamines and glucocorticoids.



# 5<sup>th</sup> ICEU, Boston, MA, 1985

## Special Lecture

Chairman: S. Konturek (Krakow, Poland)

10:45 A.M. 123. J. VANE (Kent, U.K.): Prostanoids and the cardiovascular system.



“Hot” Topics for Discussion: 4b. Prostanoids and ulcer disease.

Chairmen: A. Robert (Kalamazoo, U.S.A.)

11:10 A.M. 124. A. BENNETT, P. O. COLLINS, P. B. MELHUIJSH, L. E. PEACOCK, I. F. STAMFORD, I. A. TAVERES (London, U.K.): Drugs affecting eicosanoids in gastric mucosa and gastrointestinal muscle.

11:20 A.M. 125. B. J. R. WHITTLE, J. L. WALLACE (Kent, U.K.): Assessment of prostanoid protection of the gastric mucosa using *in vivo* and *in vitro* techniques.

11:30 A.M. 126. A. ROBERT (Kalamazoo, U.S.A.): On the mechanism(s) of cytoprotection.

## Special Lecture

Chairman: A. Dubois (Bethesda, U.S.A.)

10:00 A.M. 161. L. PAULING (Palo Alto, U.S.A.): Ascorbic acid and other vitamins in gastrointestinal functions and diseases.



Pharmacology: 3b. New drugs for ulcer prevention and treatment.

Chairmen: S. Okabe (Kyoto, Japan) & I. Szelenyi (Nuernberg, F.R.G.)

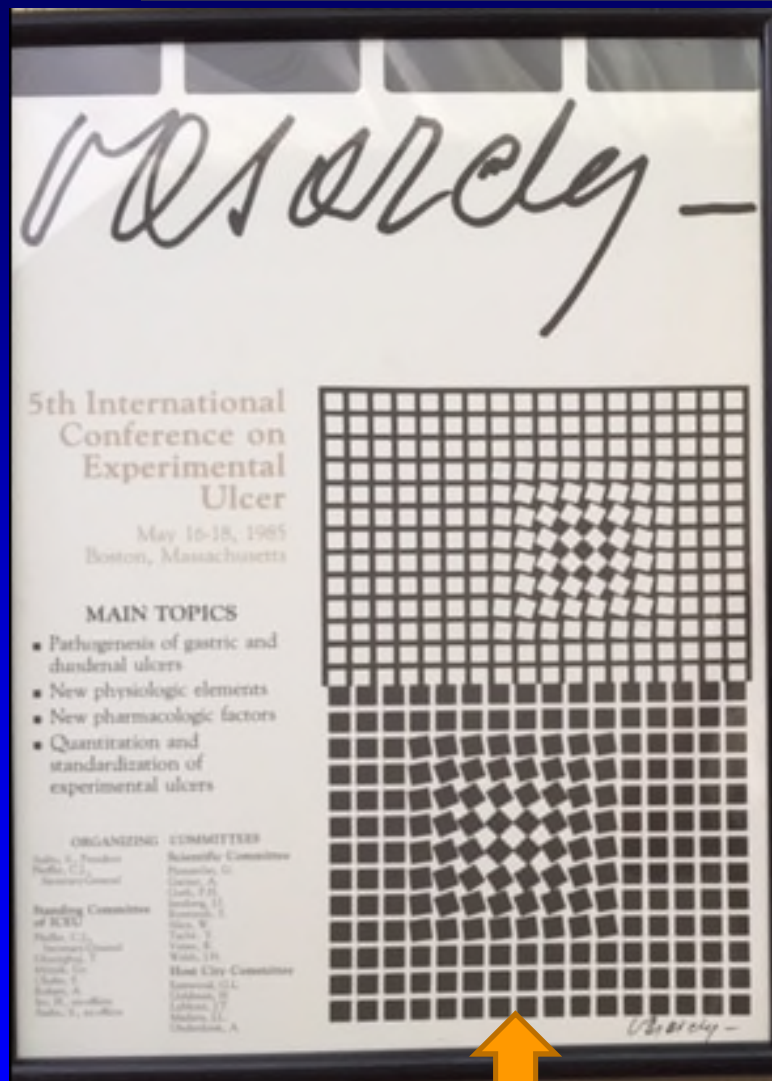
10:20 A.M. 162. A. TARNAWSKI, D. HOLLANDER, W. J. KRAUSE, H. GERGELY (Irvine & Columbia, U.S.A.): Sucralfate protects the gastric mucosa against ethanol injury via prostaglandin mediated mechanisms.

10:40 A.M. 163. A. GARNER, J. R. HEYLINGS, J. P. KEOGH, A. M. STANIER, J. M. WILKES (Cheshire, U.K.): Pharmacologic modulation of duodenal bicarbonate secretion.

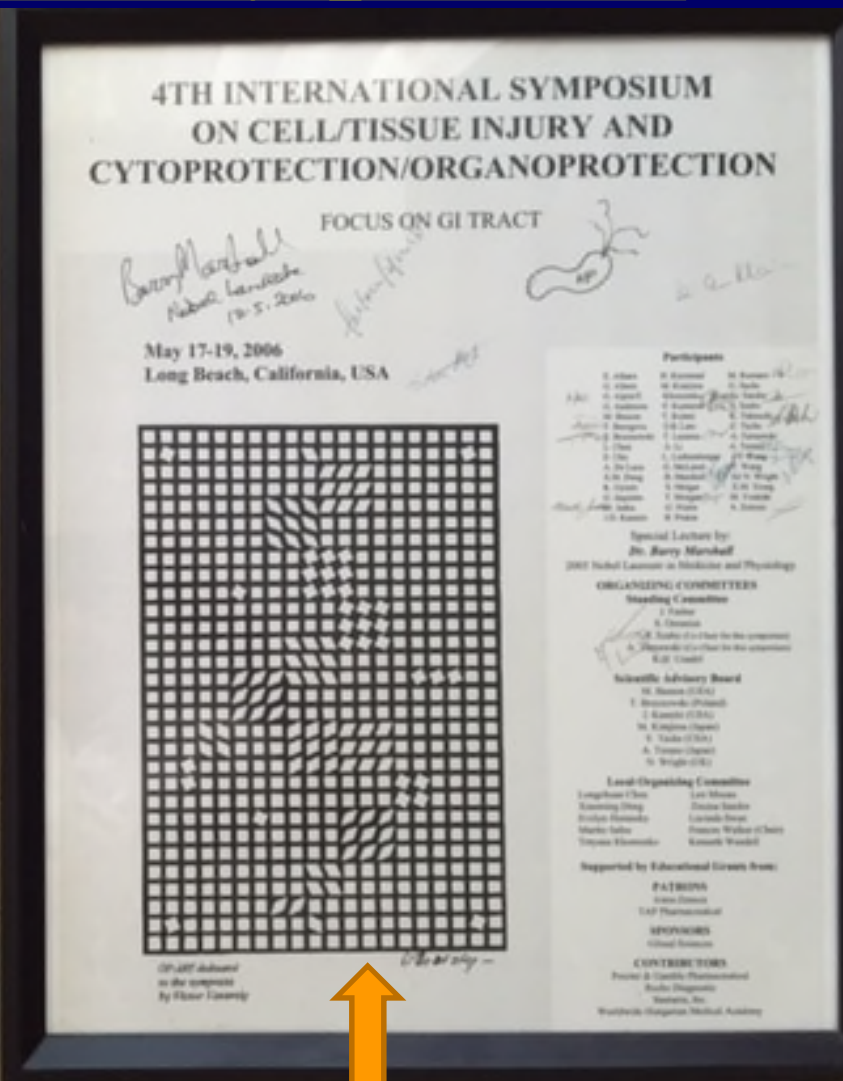
11:00 A.M. 164. V. SCHUSDZIARRA, K. H. USADEL (Munich & Heidelberg, F.R.G.): Somatostatin in gastric and duodenal ulceration.

11:20 A.M. 165. E. Z. DAJANI, R. G. BIANCHI, D. G. COLTON, D. A. CALLISON, D. DRISKILL, E. L. PHILLIPS, L. KESSLER, R. PAPPO (Skokie, U.S.A.): Perspectives on the pharmacology of misoprostol.

# The TWO Vasarely posters



Now dedicated to ICUR



Will remain logo of ISCTICO/IUPHAR GI Section



**Molecular & cellular pathogenesis of**  
**GI ulceration: Data that could only**  
**have been obtained with animal**  
**models**

**Sandor Szabo**, MD (Belgrade), PhD (Montreal), MPH (Harvard)

Professor of Pathology & Pharmacology,

School of Medicine, University of California,

Irvine, CA, USA

and

External Member, Hungarian Academy of Sciences,

Visiting Professor, Semmelweis University

Budapest, Hungary

# Novel animal models & new molecular - cellular elements during ICUR history

- Novel animal models

- Gastric & duodenal ulcers by *acetic acid* (rats)
- Duodenal ulcers by *cysteamine & its derivatives* (rats, mice)
- Acute & chronic gastritis by *SH alkylators* (rats, mice)
- Enteritis by *indomethacin* (rats) & *IL-10 deficiency* (mice)
- Ulcerative colitis by *TNBS or SH alkylators* (rats, mice)

- New molecules

- *Prostaglandins (PG) & sulfhydryls (SH)* in gastroprotection
- *Glucocorticoids* (physiologic doses!) in gastroprotection
- *Dopamine* in duodenal ulceration & IBD
- *Genes: egr-1, STAT3* in duodenal & gastric ulceration
- *Angiogenic growth factors: bFGF, PDGF, VEGF* for ulcer healing

- New cellular elements

- *Vascular endothelial cells*
- *Angiogenesis*

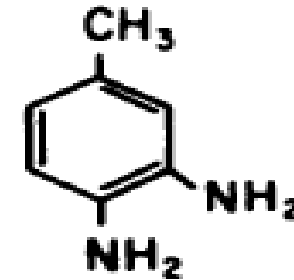
# The first duodenal ulcerogens



Propionitrile



Cysteamine



3, 4 Toluenediamine

- DU potency:

- Weak

Potent

Moderate

- Published:

- Szabo & Selye,
  - Arch. Pathol., 1972

Selye & Szabo.,  
Nature, 1973

Selye,  
Proc.Soc.Exp.Biol.Med.,1972

- Structure-activity:

- Szabo, Lancet, 1979
  - Szabo et al., JPET, 1982
  - Onishi et al., PNAS, 1991

## Comparative effect of growth factors on gastroduodenal secretion, cell proliferation, and angiogenesis

Peptides	Gs-acid	Du-bicarb.	Epith. ↑	Fibrobl. ↑	Angiog.
<b>EGF</b>	↓	↑	++	+/-	+/-
<b>bFGF</b>	-/↑	-	+	++	++
<b>PDGF</b>	-	-	+	++	+
<b>VEGF</b>	-	NT	-	-	++

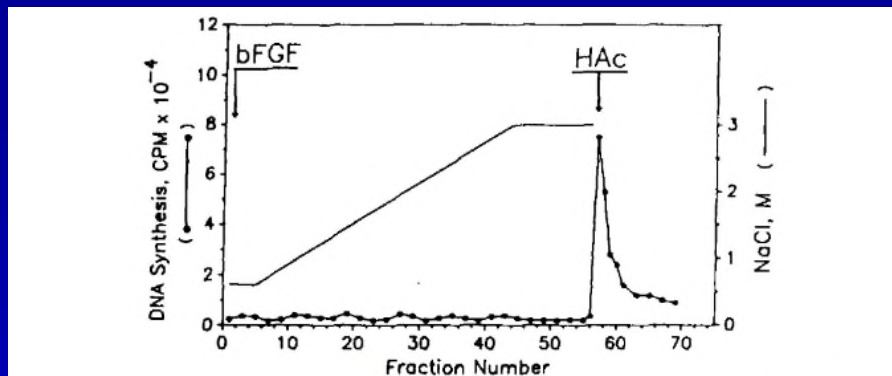
**The major comparison of antiulcerogenic doses of  
bFGF, PDGF, VEGF, and cimetidine in the rat  
model of cysteamine-induced chronic duodenal ulcer**

	<i>bFGF</i>	<i>PDGF</i>	<i>VEGF</i>	<i>Cimetidine</i>
<b>Antiulcerogenic dose (/100g)</b>	100 ng	500 ng	1 µg (1,000 ng)	10 mg (10 <sup>10</sup> pg)
<b>Molecular weight</b>	18,000	34,000	45,000	252
<b>1 pmole</b>	18 ng	34 ng	45 ng	252 pg
<b>Antiulcerogenic dose in pmole/100g</b>	5.6	14.7	22.2	39,682,540.0
<b>Molar comparison</b>	7,086.168	2,699.492	1,787.502	1

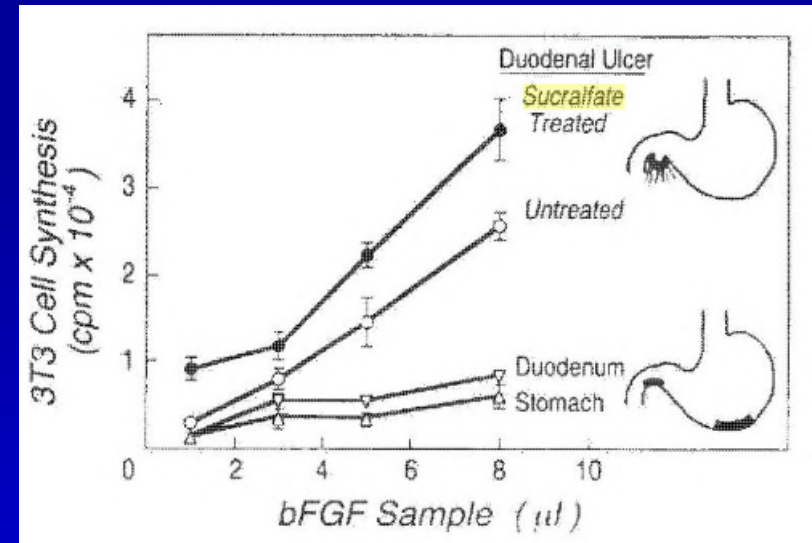
# New GI drugs developed during the history of ICEU/ICUR

- **PG derivatives**
  - Misoprostol (USA) & other PGs (Japan, China)
- **Gastroprotective drugs**
  - Sucralfate (Japan & worldwide)
  - Sofalcone (Japan: synthetic flavonoid derivative)
  - BPC-157 (Croatia)
- **NSAID-PL** (with phospholipid attachments)
  - Aspirin-PC (just approved by FDA)
- **NASID-NO & NSAID-hydrogen sulfide (H<sub>2</sub>S)**
- (H<sub>2</sub>-receptor antagonists, PPI & anti-Hp drugs)

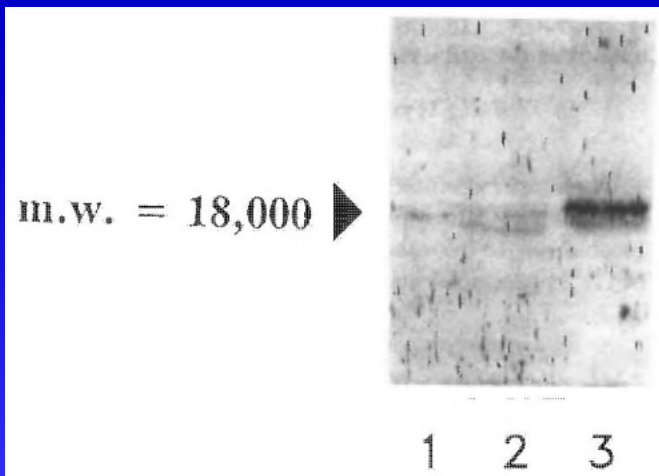
# Sucralfate (sucrose octasulfate-aluminium salt) similar to heparin...



**Figure 3.** Elution of bFGF from a **sucralfate**-Sepharose column by acetic acid. The column was rinsed with a 10 ml Tris buffer and 0.6 M NaCl (80 ml) from 0.6 M to 3.0 M, (2) 20 ml of 3 M NaCl, and (3) 30 ml of 1.5 M acetic acid (pH 2.2). (Reproduced with permission from Folkman *et al.*?)



**Figure 4.** (Top) Effect of **sucralfate** on endogenous bFGF activity in the rat gastric mucosa. Duodenal ulcers were induced by cystamine and **sucralfate** was given by gavage (20 mg/100 g, twice daily for 7 days); animals were killed on day 8. One gram of stomach was then incubated in 5 ml NaCl 2.0 M to extract bFGF from the tissues at 4°C for 12 hr. The extractant was centrifuged and the supernatant was diluted fourfold with 10 mM Tris buffer to lower the salt concentration. The diluted supernatant was then applied to a heparin-affinity column. The column was rinsed with 0.6 M NaCl and eluted with 2.0 M NaCl, and the fractions were assayed for mitogenic activity on 3T3 fibroblasts. All of the mitogenic activity was in the 2.0 M NaCl fraction.



m.w. = 18,000 ▶

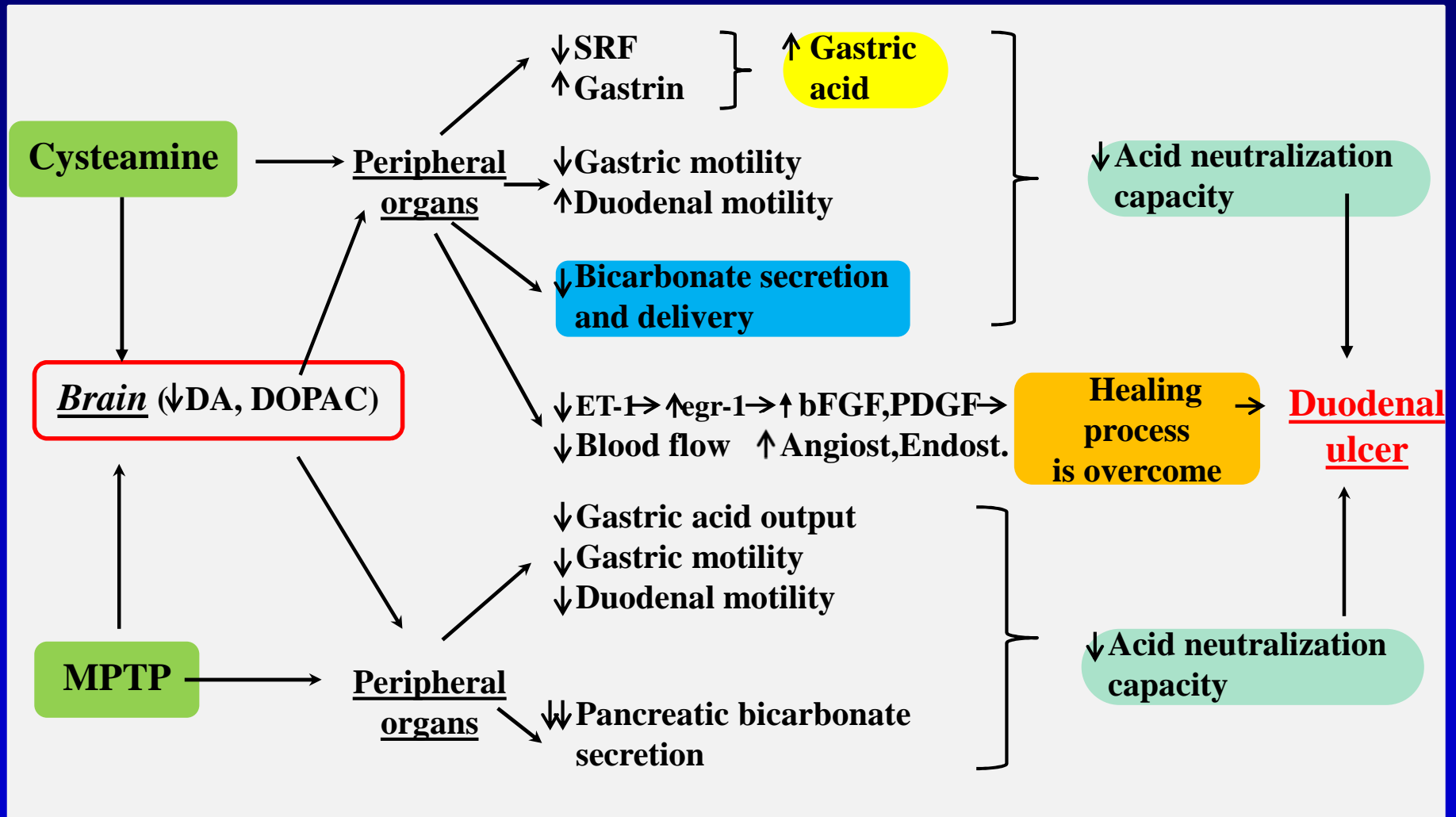
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# What is still misunderstood in ulcer pathogenesis & gastroprotection

- **In interpretation & evaluation:**
  - Acute erosions (heal spontaneously) vs.
  - Ulcers (need granulation tissue/angiogenesis for healing)
- **In ulcer induction:**
  - Local irritants (e.g., acetic acid, ethanol) vs.
  - Systemic ulcerogens (e.g., cysteamine, MPTP)
- **Mechanisms of gastroprotection:**
  - Indomethacin (COX inhibitor) counteracts some but not all forms of gastroprotection
  - SH alkylators (e.g., NEM) block every gastroprotective agent
  - Thus, both endogenous PG & SH are important for gastroprotection



# Pathogenesis of pre-ulcer stages of duodenal ulceration induced by cysteamine or the dopaminergic neurotoxin MPTP



**Duodenal ulcerogens**  
(e.g., drugs, stress)

**Before**  
**cysteamine**  
**(1973)**

**↑ Gastric acid in**  
**50% of DU patients**

**Duodenal ulcer development**

**Duodenal ulcerogens**  
(e.g., drugs, stress)

**After H. pylori**  
**(1981)**

↑ **Gastric acid in**  
**50% of DU patients**

**Duodenal ulcer development  
& poor healing**

**H. pylori**

# Duodenal ulcerogens (e.g., cysteamine-like drugs)

↓ Central & periph. dopamine & somatostatin

↑ Gastrin & Gs-acid

↓ Du-bicarb.

Selective uptake of cysteamine-like chemicals in prox. du.: Fenton reaction, ROS early cell & tissue injury

Duodenal mucosa with high Fe uptake & concentration

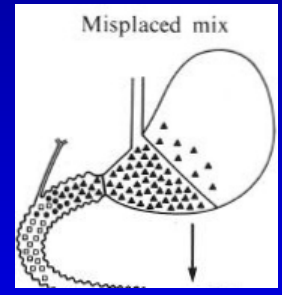
↑ ET-1

Endothelial injury, increased vascular permeability, ischemia-hypoxia

HIF-1 $\alpha$

↑ MMP2&9

Du-fibrillation dysmotility



↑ Egr-1

Collagen XVIII and plasminogen cleaved

Excess acid in prox. duodenum

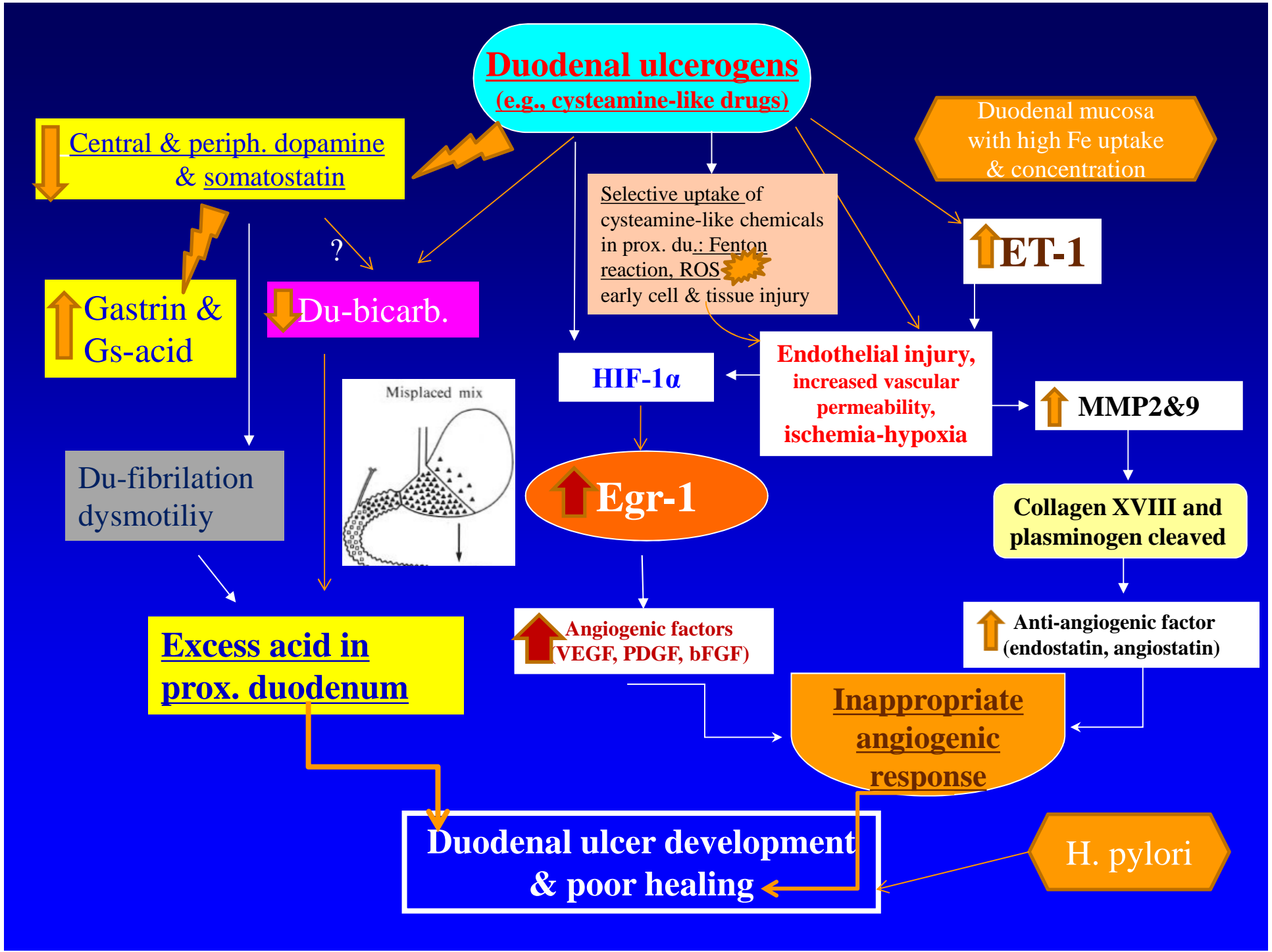
↑ Angiogenic factors (VEGF, PDGF, bFGF)

↑ Anti-angiogenic factor (endostatin, angiostatin)

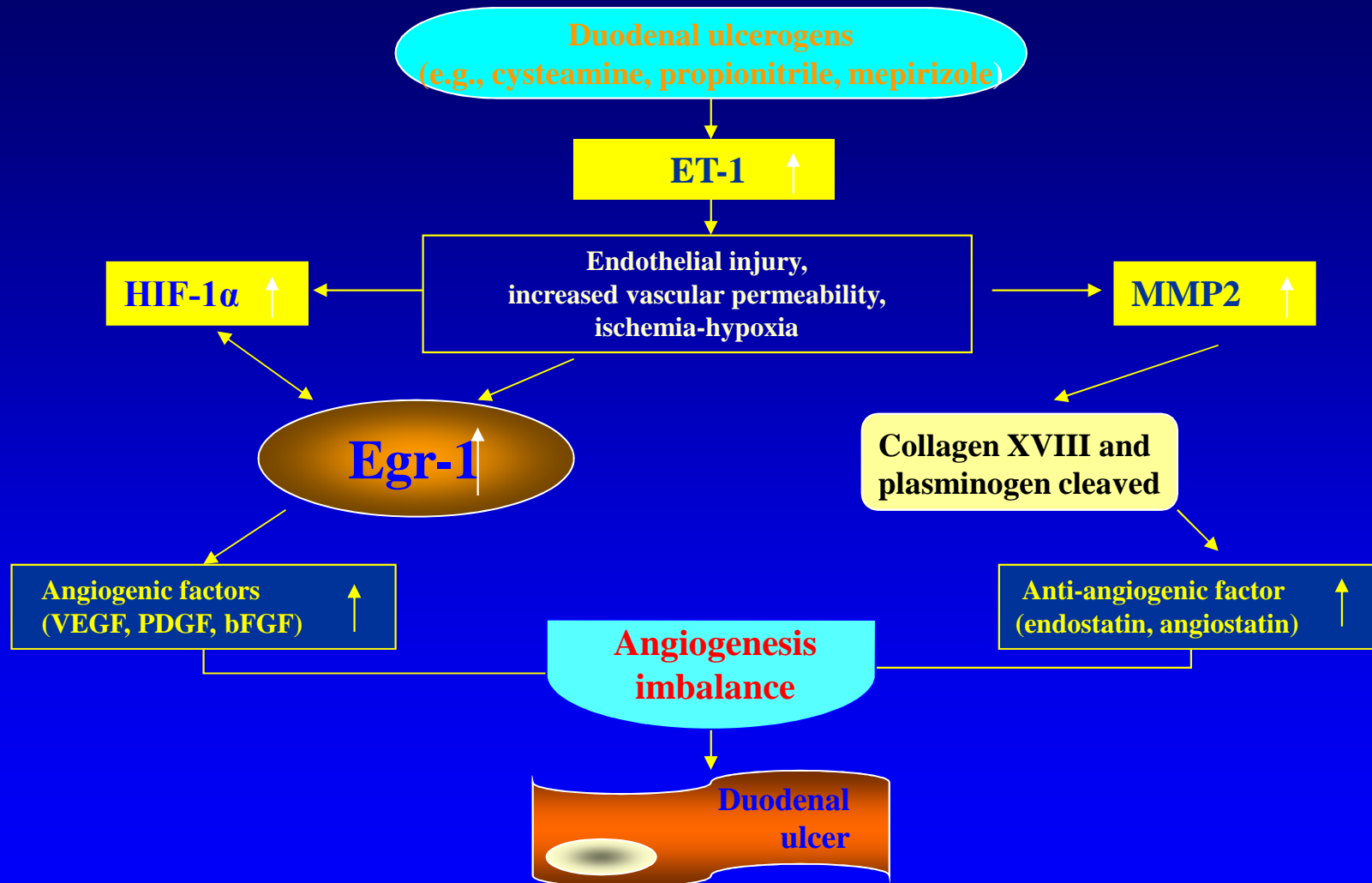
Inappropriate angiogenic response

Duodenal ulcer development & poor healing

H. pylori

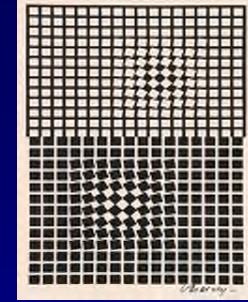


# Diagram of summary



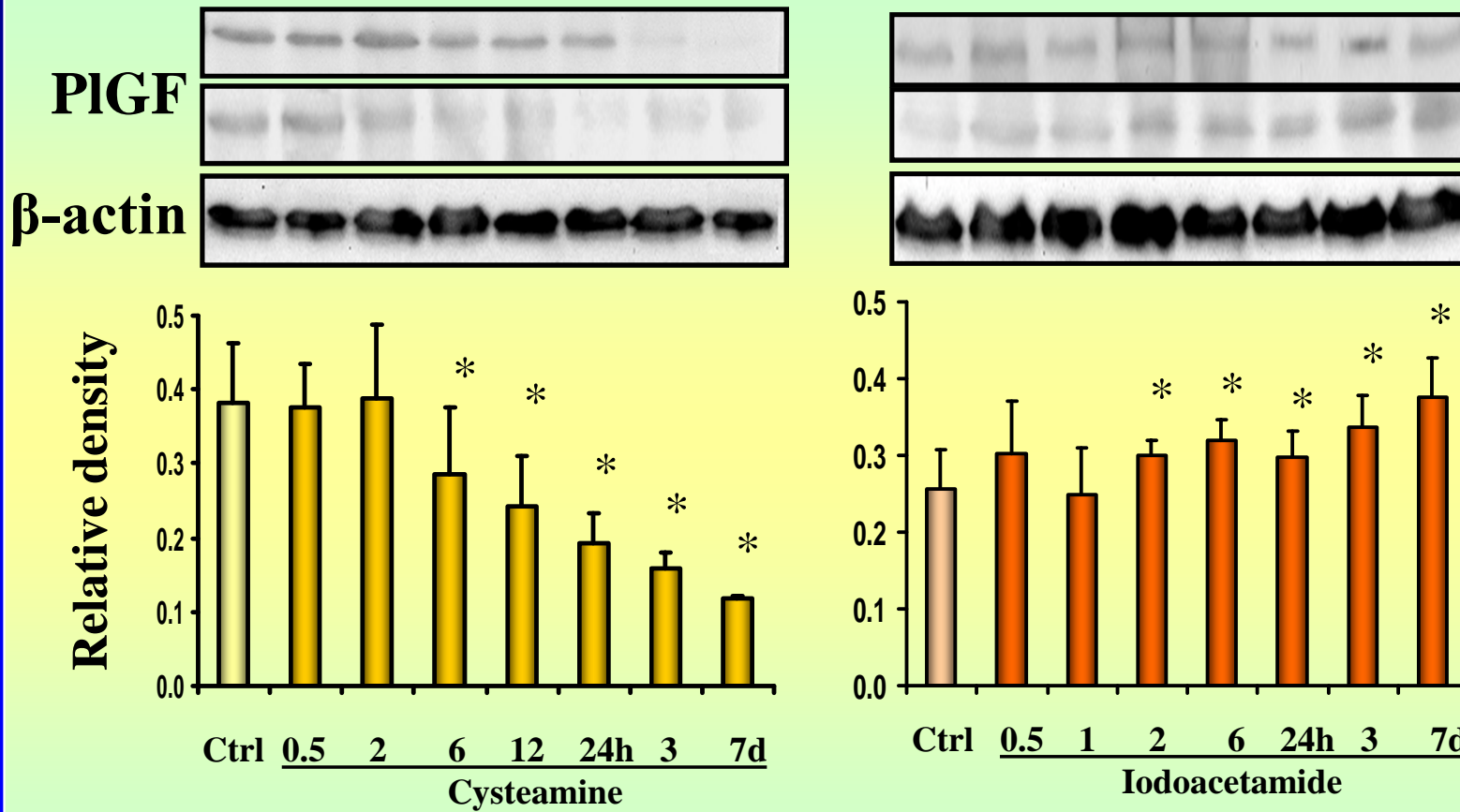
**Development and healing**

# Challenges in ulcer research



- **Ulcer induction vs. poor healing**
  - Prof. Vincze Varro (Szeged, Hungary): “it’s difficult NOT to induce ulcer” - at least in the stomach...
  - Healing is the problem, not the induction.
- **The balance between damaging & protective factors is still valid!**
  - Look at the Vasarely poster!
- **Molecular & cellular mechanisms of healing** are still not completely clear, esp., in the lower GI tract: **PlGF!**
- **GI ulcer/inflammation & cancer connection!?**
- **Role of ‘ulcer conferences/symposia’**
  - 15<sup>th</sup> Taishotoyoma Int. Symp. on Gastroenterology (last: 2013)
  - ICUR (16<sup>th</sup> in Seoul) & ISCTICO (10<sup>th</sup> in Kyoto) should continue.

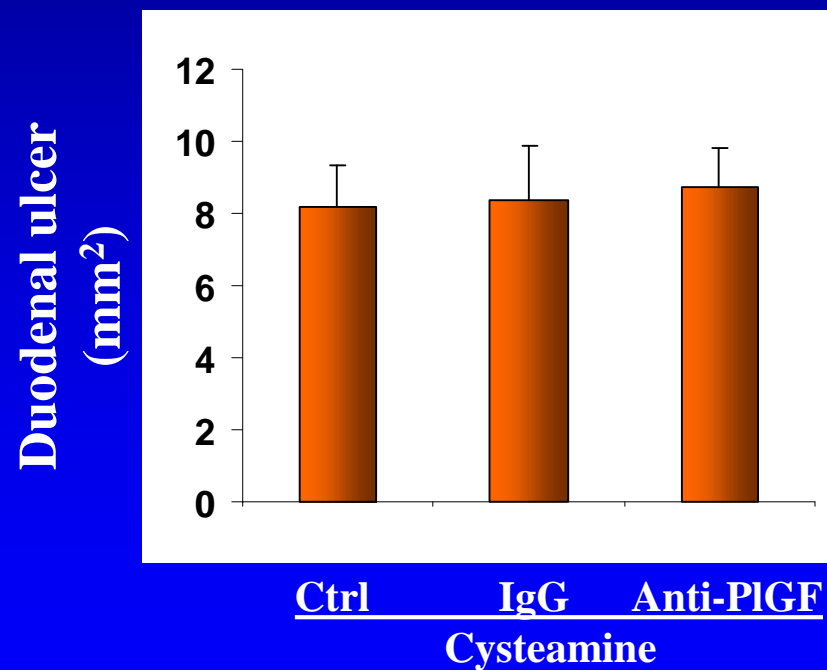
# Western blot of placental growth factor (PIGF) expression in experimental DU and UC in rats



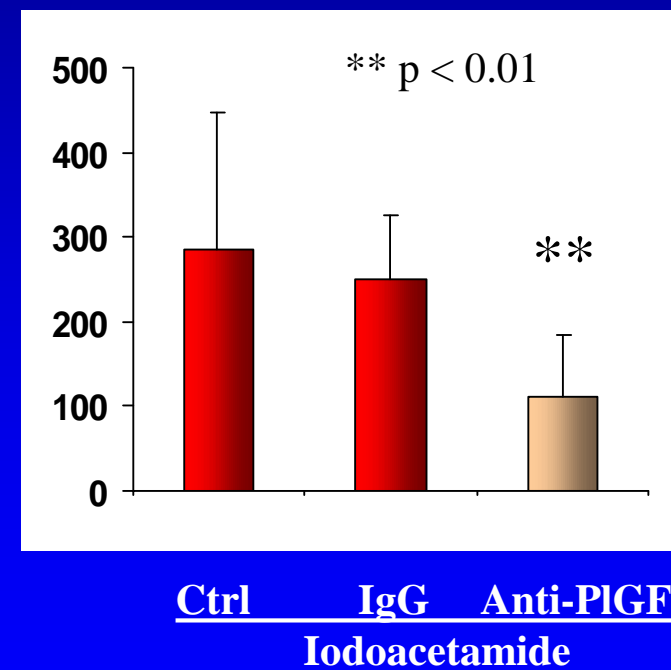
\*  $P < 0.05$

# Neutralization of placental growth factor (PIGF) in cysteamine-induced DU and iodoacetamide-induced UC

## Duodenal ulcer



## Ulcerative colitis






# Conclusions

- The almost 40 years of ICUR/ICEU lead to productive discussions & creative discoveries.
- During this period novel animal models (e.g., acetic acid, cysteamine) have been discovered.
- Also identified were new molecules: PG, SH, H<sub>2</sub>S, dopamine, GC, genes (egr-1, STAT3) & angiogenic growth factors in ulcer development & healing.
- New cellular elements (e.g., vascular endothelial cells & angiogenesis) also became targets of ulcer research.
- Thus, series like ICUR & ISCTICO are very useful & productive – not only because of the original Greek meaning of “symposion”...

# Symposium - Conference

## Definition of SYMPOSIUM

plural *symposia*  \-zē-ə, -zh(ē-)ə\ or *symposiums*

- a : a convivial party (as after a banquet in ancient Greece) with music and conversation

b : a social gathering at which there is free interchange of ideas
- a : a formal meeting at which several specialists deliver short addresses on a topic or on related topics — compare **COLLOQUIUM**

b : a collection of opinions on a subject; *especially* : one published by a periodical


c : **DISCUSSION**

Dictionary

symposium



sym·po·si·um

/sim'pōzēəm/ 

noun

noun: *symposium*; plural noun: *symposia*; plural noun: *symposiums*

a conference or meeting to discuss a particular subject.

- a collection of essays or papers on a particular subject by a number of contributors.
- a drinking party or convivial discussion, especially as held in ancient Greece after a banquet (and notable as the title of a work by Plato).

Origin

GREEK

sun-  
together

GREEK

potēs  
drinker

GREEK  
sumpotēs  
fellow drinker

GREEK

sumposion

GREEK

sumposion

→

LATIN

→ symposium

late 16th century

late 16th century (denoting a drinking party): via Latin from Greek *sumposion*, from *sumpotēs* 'fellow drinker,' from *sun-* 'together' + *potēs* 'drinker.'

Use over time for: symposium

Mentions

1800 1850 1900 1950 2010



Show less

Feedback