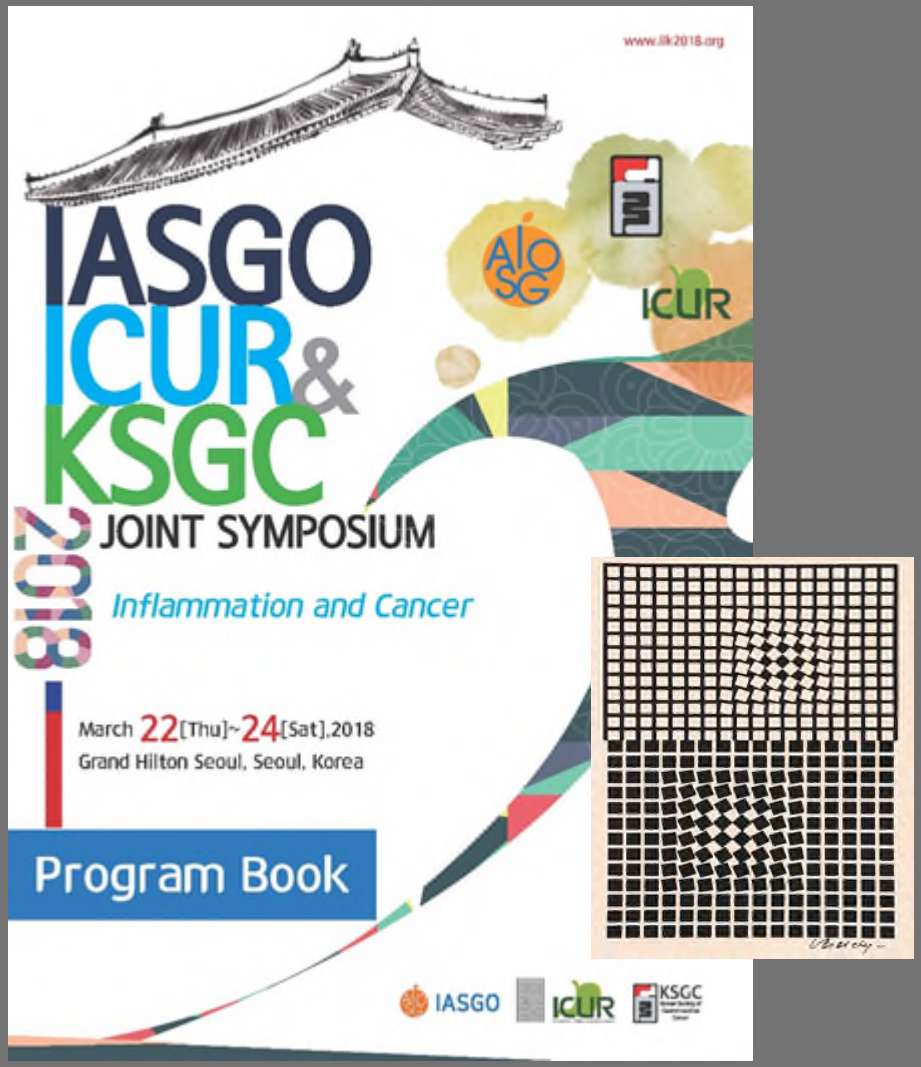
Long history of ICUR/ICEU &
vs. other *GI International Symposia*

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

Sample of the program book

IASGO, ICUR & KSGC Joint Symposium



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:

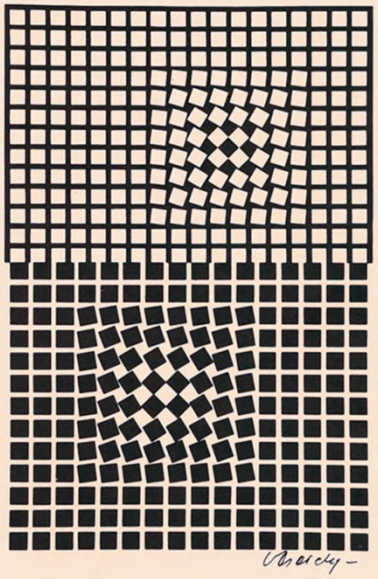
1st: Copenhagen (Denmark): 1970;
2nd: Cologne (Germany): 1972;
3rd: Parádfürdő (Hungary): 1979;
4th: Tokyo (Japan): 1980;
5th: Boston (USA): 1985;
6th: Jerusalem (Israel): 1987;
7th: Berlin (Germany): 1991;
8th: Kyoto (Japan): 1994;
9th: Hong Kong (China): 1997;
10th: Budapest - Pécs (Hungary): 2000;
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

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.

Boston, Mass., May 16-18, 1985

Harvard School of Public Health

Amphitheatres G-1 and G-2

(ground floor)

I invited

5 Nobel Laureates:

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

C I E U

5th International Conference on Experimental Ulcer

May 16-18, 1985
Boston, Massachusetts


C
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The 5th International
Conference on
Experimental
Ulcer
May 16-18, 1985
Boston, Massachusetts

5th 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.

5th 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. MELHUISH, 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.)

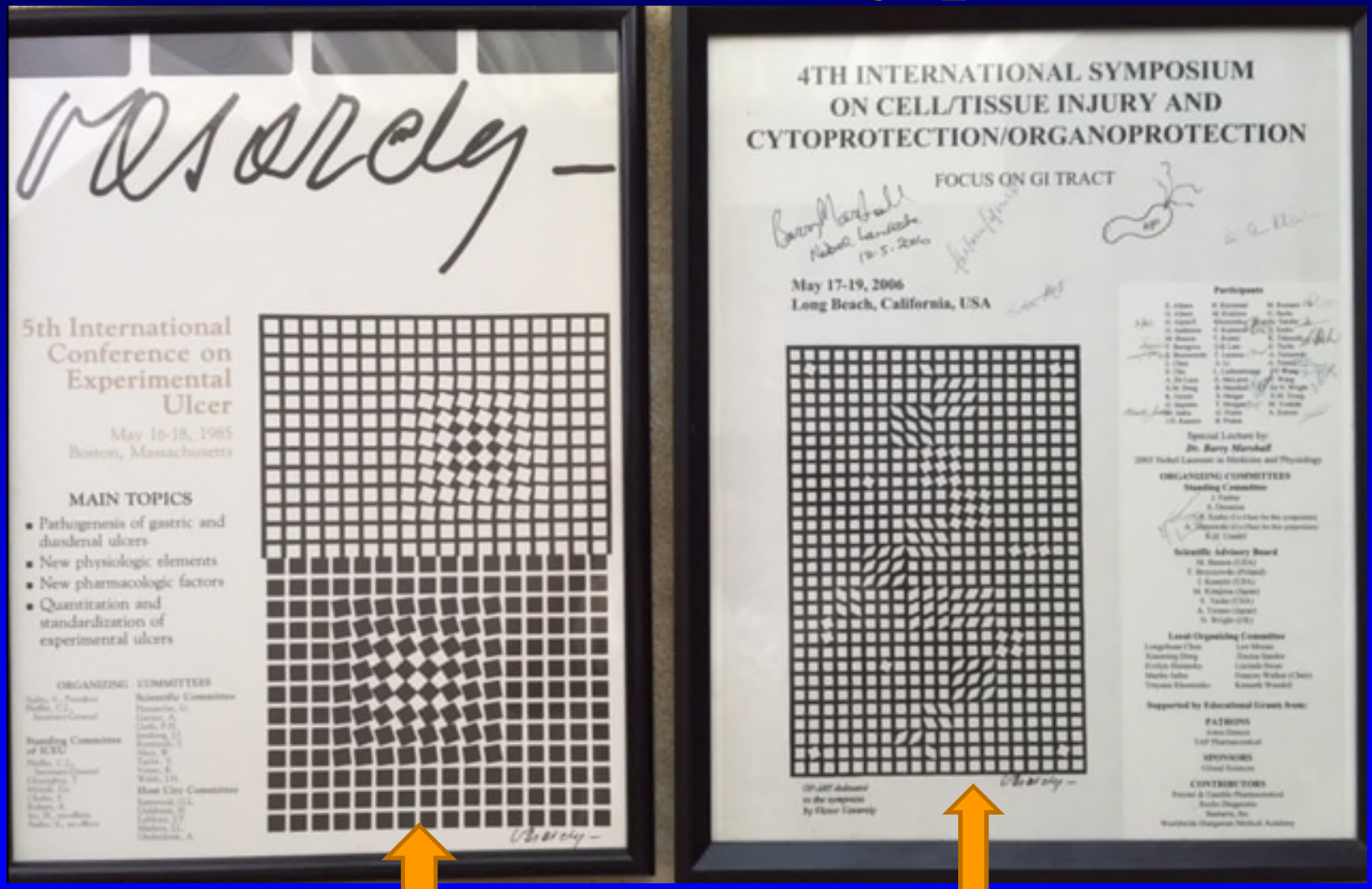
10:20 A.M. **162.** **A. TARNAWSKI**, D. HOLLANDER, W. J. KRAUSE, H. GERGELY (Irvine & Columbia, U.S.A.): Sucralfate protects the gastric mucosa against ethanol injury via prostaglandin mediated mechanisms.

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,

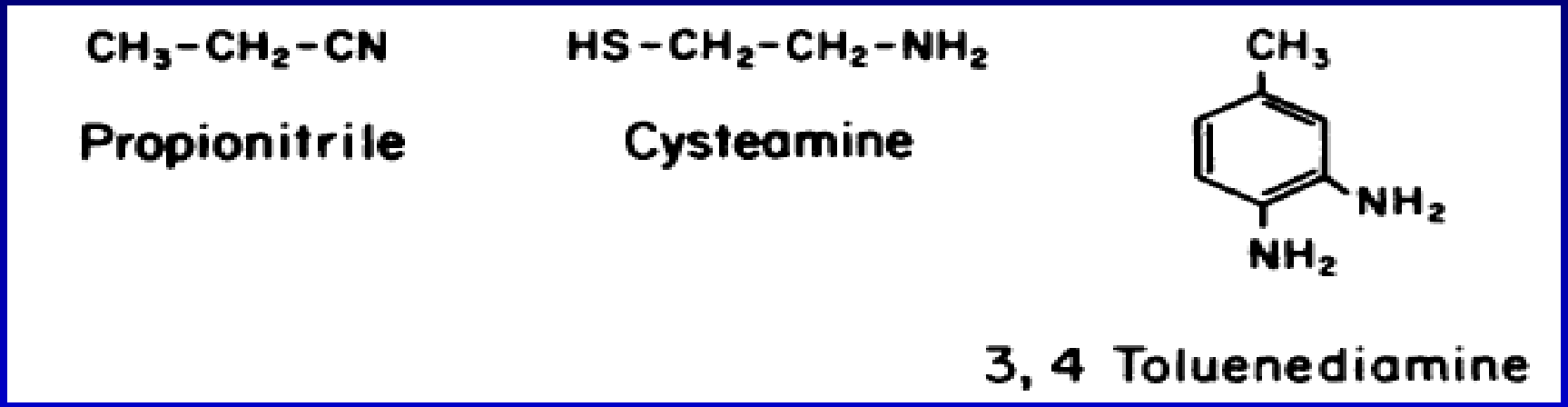
Visiting Professor, Semmelweis University

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



- 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.
EGF	↓	↑	++	+/-	+/-
bFGF	-/↑	-	+	++	++
PDGF	-	-	+	++	+
VEGF	-	NT	-	-	++

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

	bFGF	*PDGF*	*VEGF*	*Cimetidine*
Antiulcerogenic dose (/100g)	100 ng	500 ng	1 µg (1,000 ng)	10 mg (10^{10}pg)
Molecular weight	18,000	34,000	45,000	252
1 pmole	18 ng	34 ng	45 ng	252 pg
Antiulcerogenic dose in pmole/100g	5.6	14.7	22.2	39,682,540.0
Molar comparison	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_2S)**
- (H2-receptor antagonists, PPI & anti-Hp drugs)

Sucralfate (sucrose octasulfate-aluminium salt) similar to heparin…

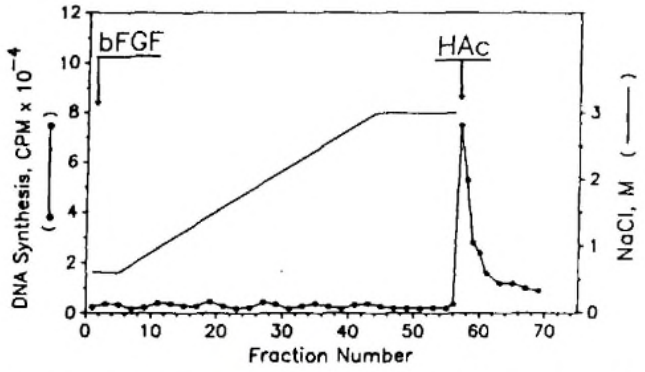
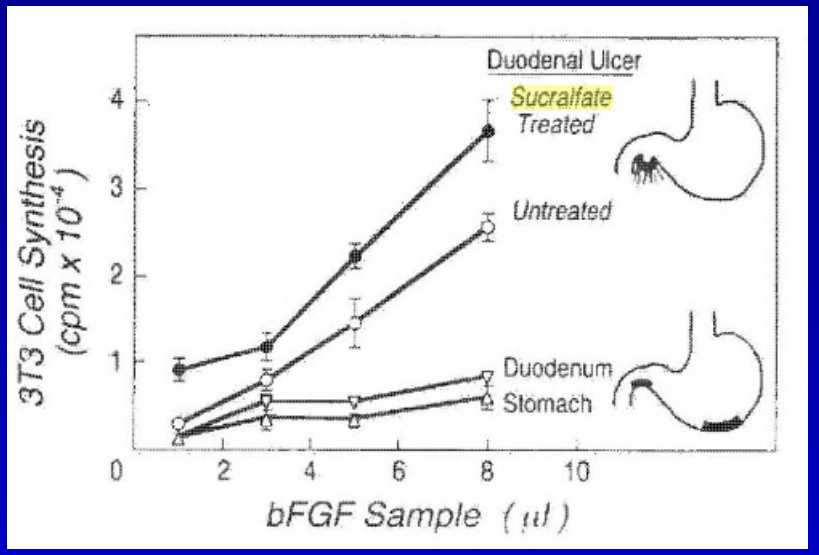


Figure 3. Elution of bFGF from a sucralfate–Sepharose column by acetic acid. The column was rinsed with a 10 ml Tris buffer and 0.6 M NaCl (80 ml) from 0.6 M to 3.0 M, (2) 20 ml of 3 M NaCl, and (3) 30 ml of 1.5 M acetic acid (pH 2.2). (Reproduced with permission from Folkman *et al.*[7])



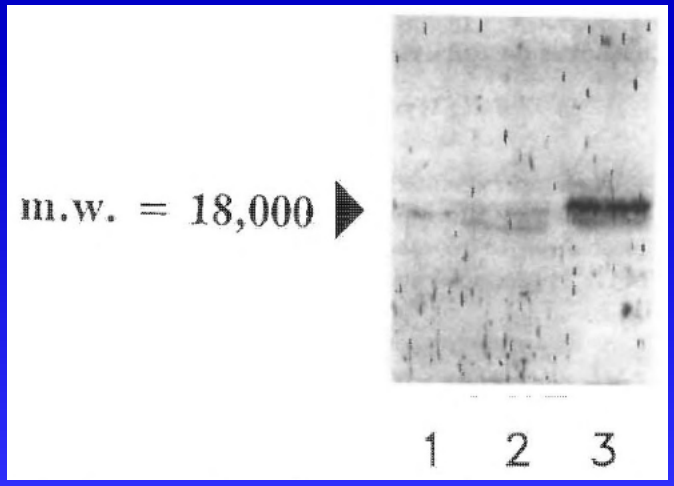
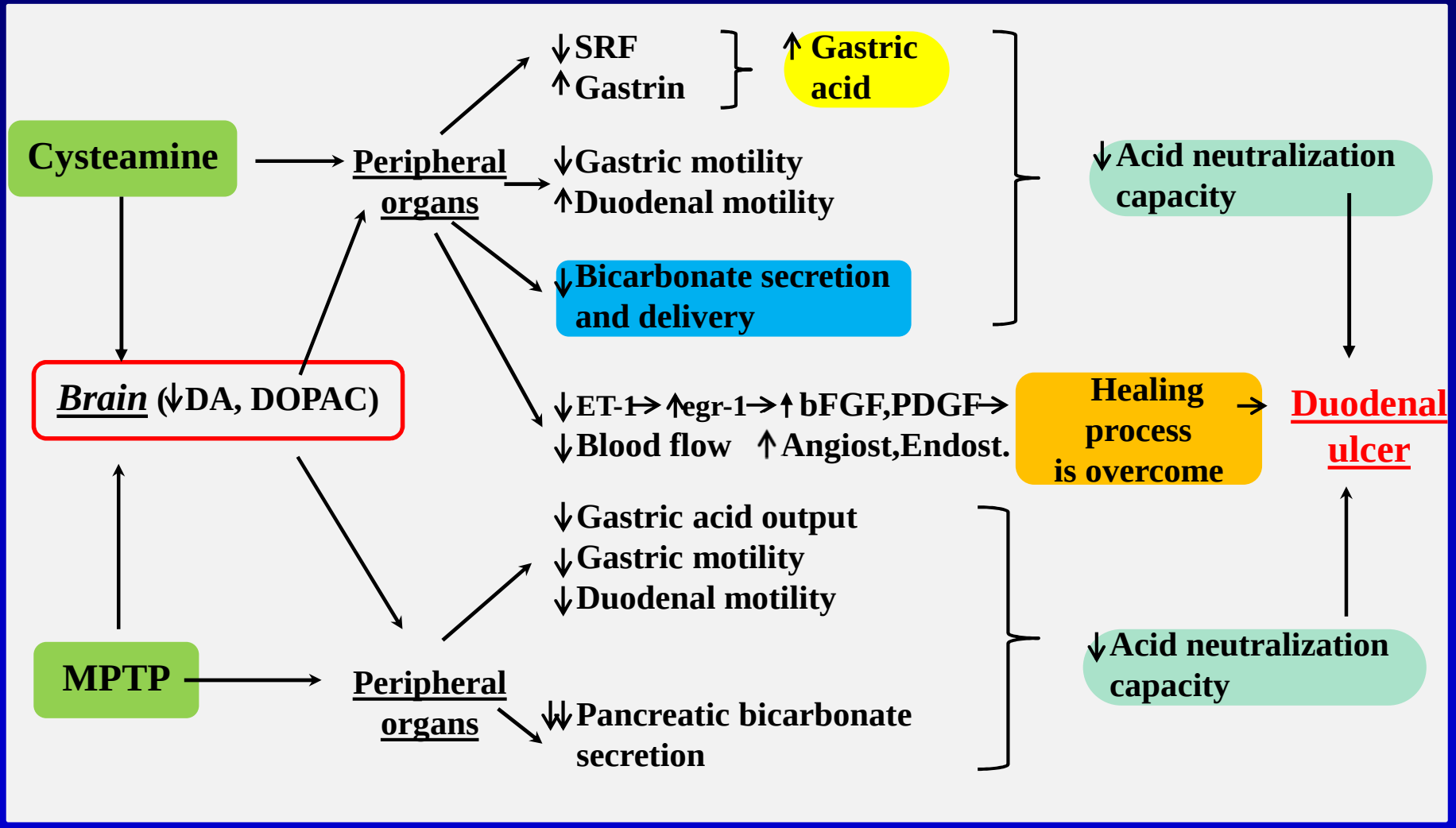


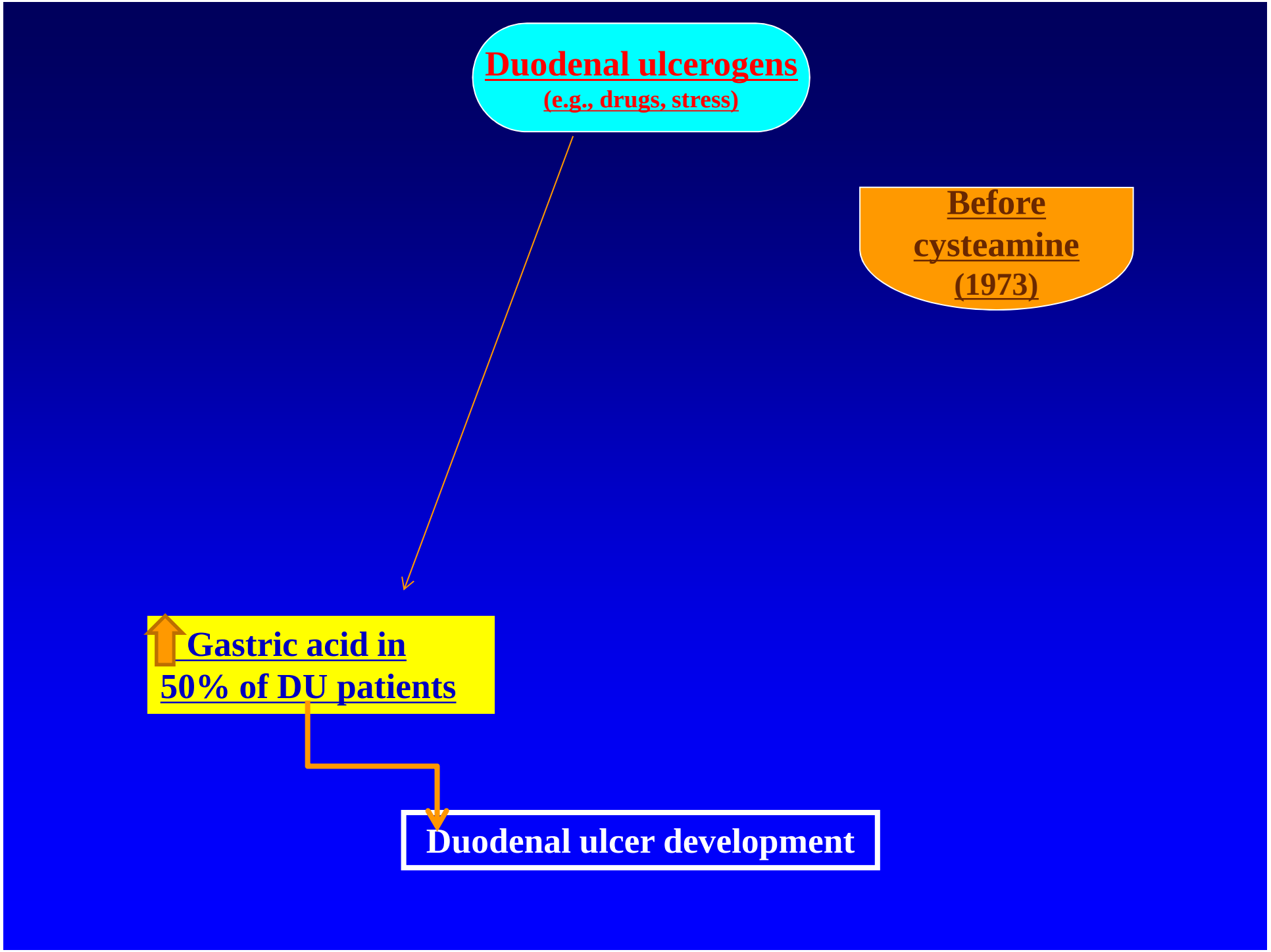
Figure 4. (Top) Effect of sucralfate on endogenous bFGF activity in the rat gastric mucosa. Duodenal ulcers were induced by cystamine and sucralfate was given by gavage (20 mg/100 g, twice daily for 7 days); animals were killed on day 8. One gram of stomach was then incubated in 5 ml NaCl 2.0 M to extract 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.

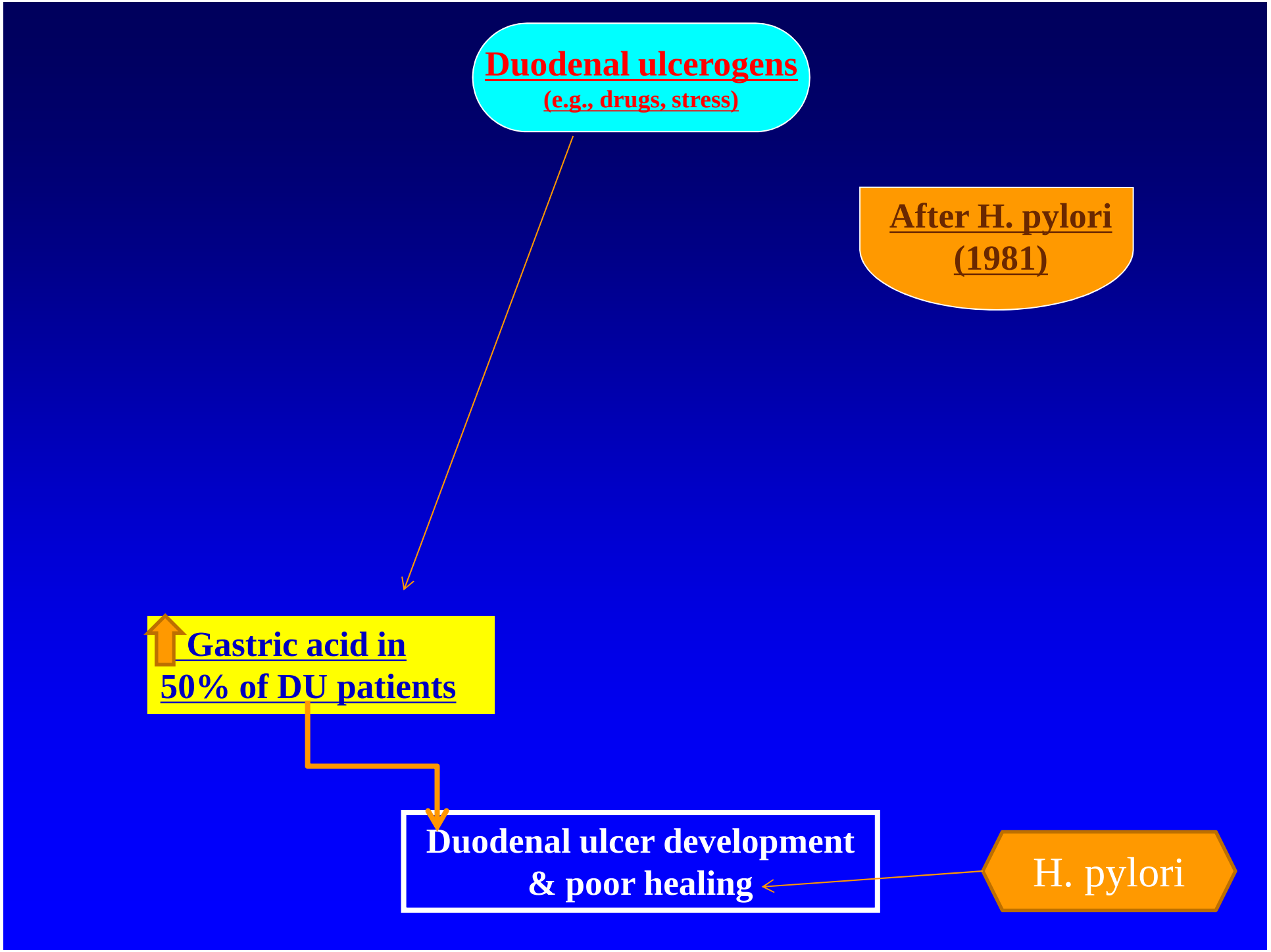
What is still misunderstood in ulcer pathogenesis & gastroprotection

- **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

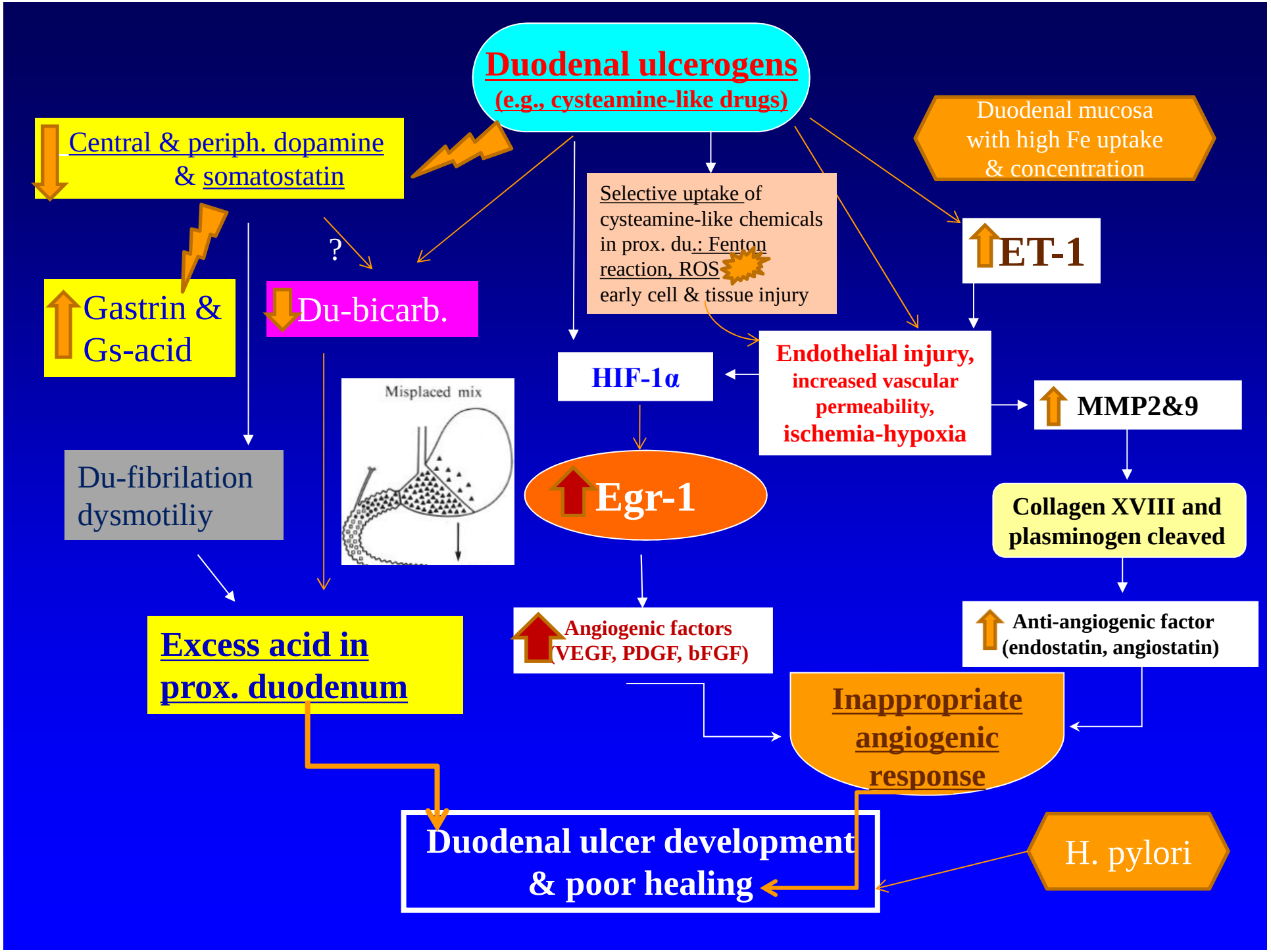
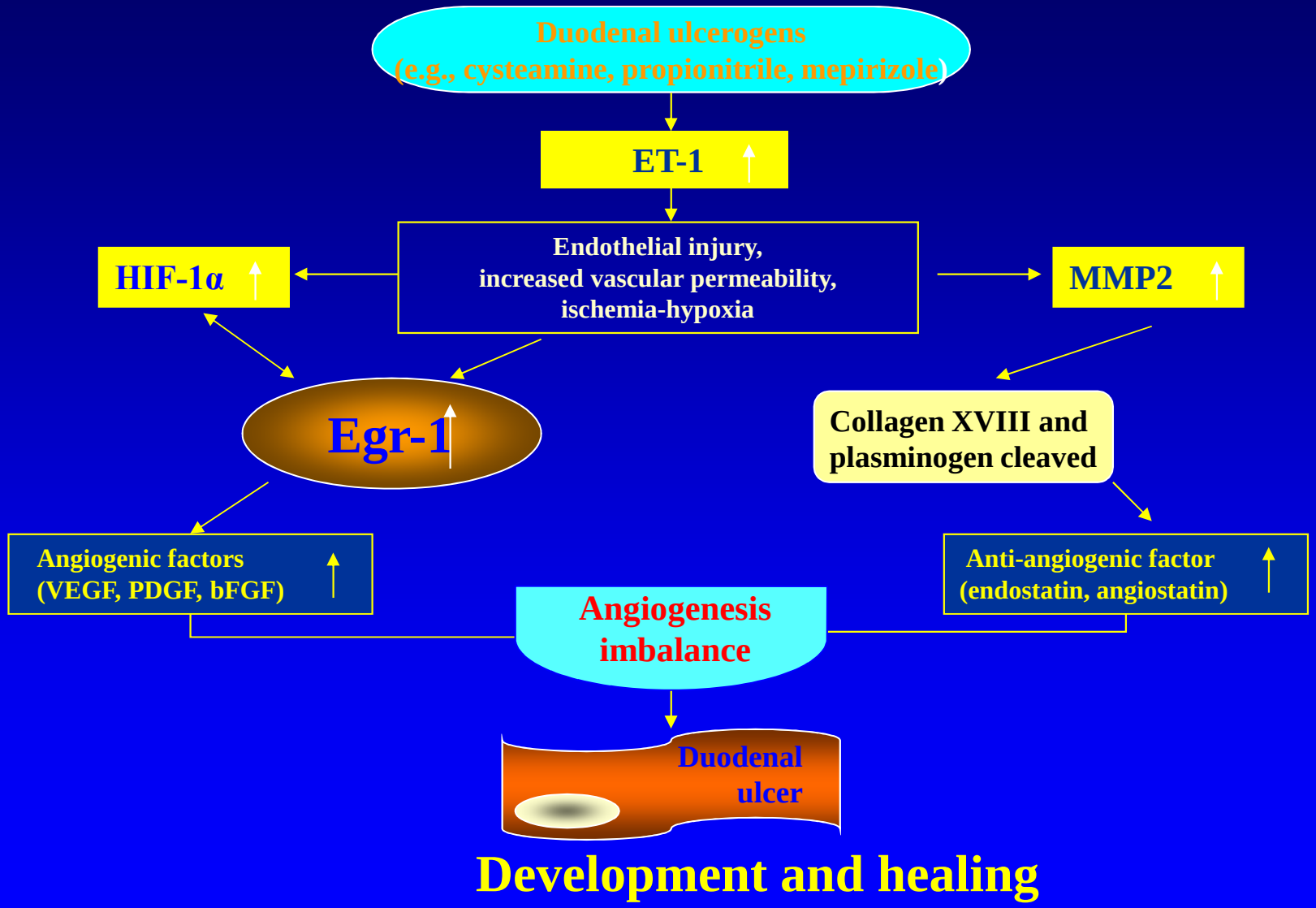
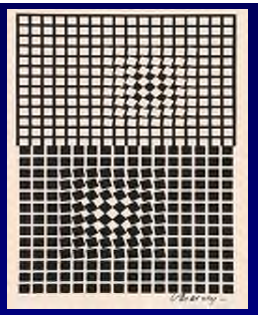

Duodenal ulcerogens
(e.g., cysteamine-like drugs)
Central & periph. dopamine & somatostatin
Duodenal mucosa with high Fe uptake & concentration
Selective uptake of cysteamine-like chemicals in prox. du.: Fenton reaction, ROS early cell & tissue injury
ET-1
?
Gastrin & Gs-acid
Du-bicarb.
Misplaced mix
HIF-1α
Endothelial injury, increased vascular permeability, ischemia-hypoxia
MMP2&9
Du-fibrilation dysmotiliy
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

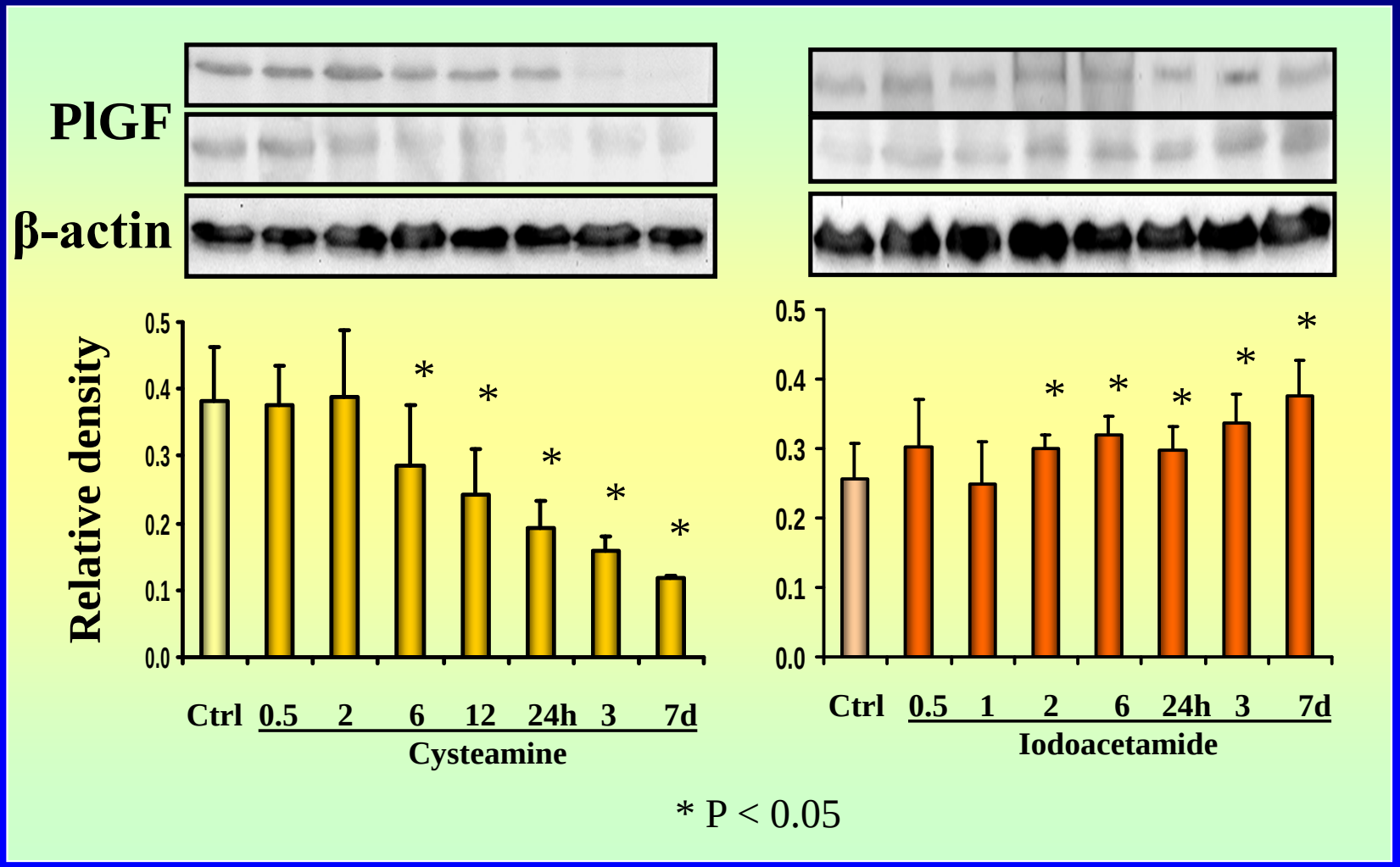


Challenges in ulcer research



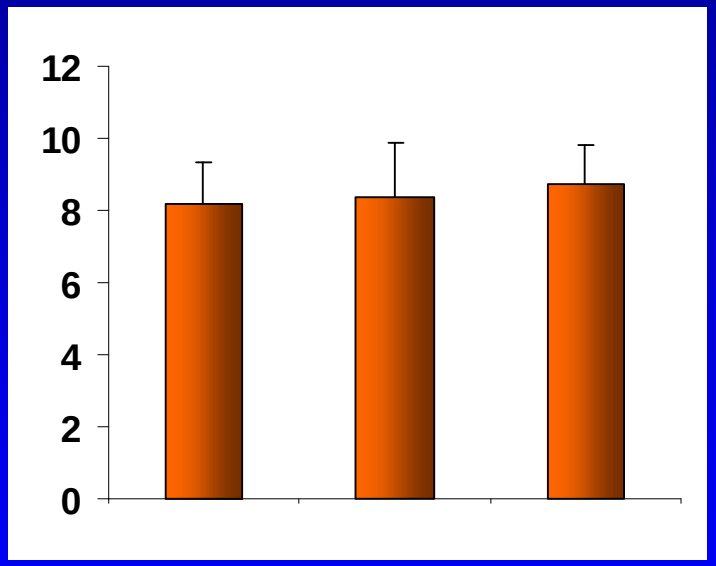
- **Ulcer induction vs. poor healing**
  - Prof. Vincze Varro (Szeged, Hungary): “it’s difficult NOT to induce ulcer” - at least in the stomach...
  - Healing is the problem, not the induction.
- **The balance between damaging & protective factors is still valid!**
  - Look at the Vasarely poster!
- **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’**
  - 15th Taishotoyoma Int. Symp. on Gastroenterology (last: 2013)
  - ICUR (16th in Seoul) & ISCTICO (10th in Kyoto) should continue.

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

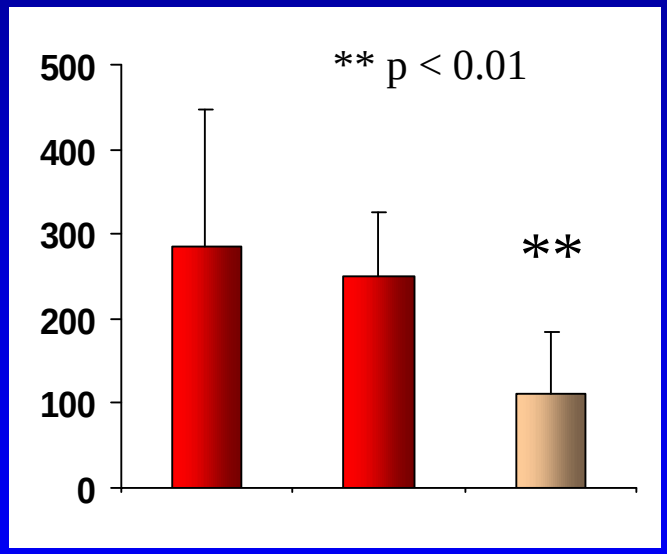


Nuetralization of placental growth factor (PlGF) in cysteamine-induced DU and iodoacetamide-induced UC

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, H2S, dopamine, GC, genes (egr-1, STAT3) & angiogenic growth factors in ulcer development & healing.**
- ***New cellular elements* (e.g., vascular endotehleail 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**

1 **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

2 **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
/simˈpōzēəm/

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

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