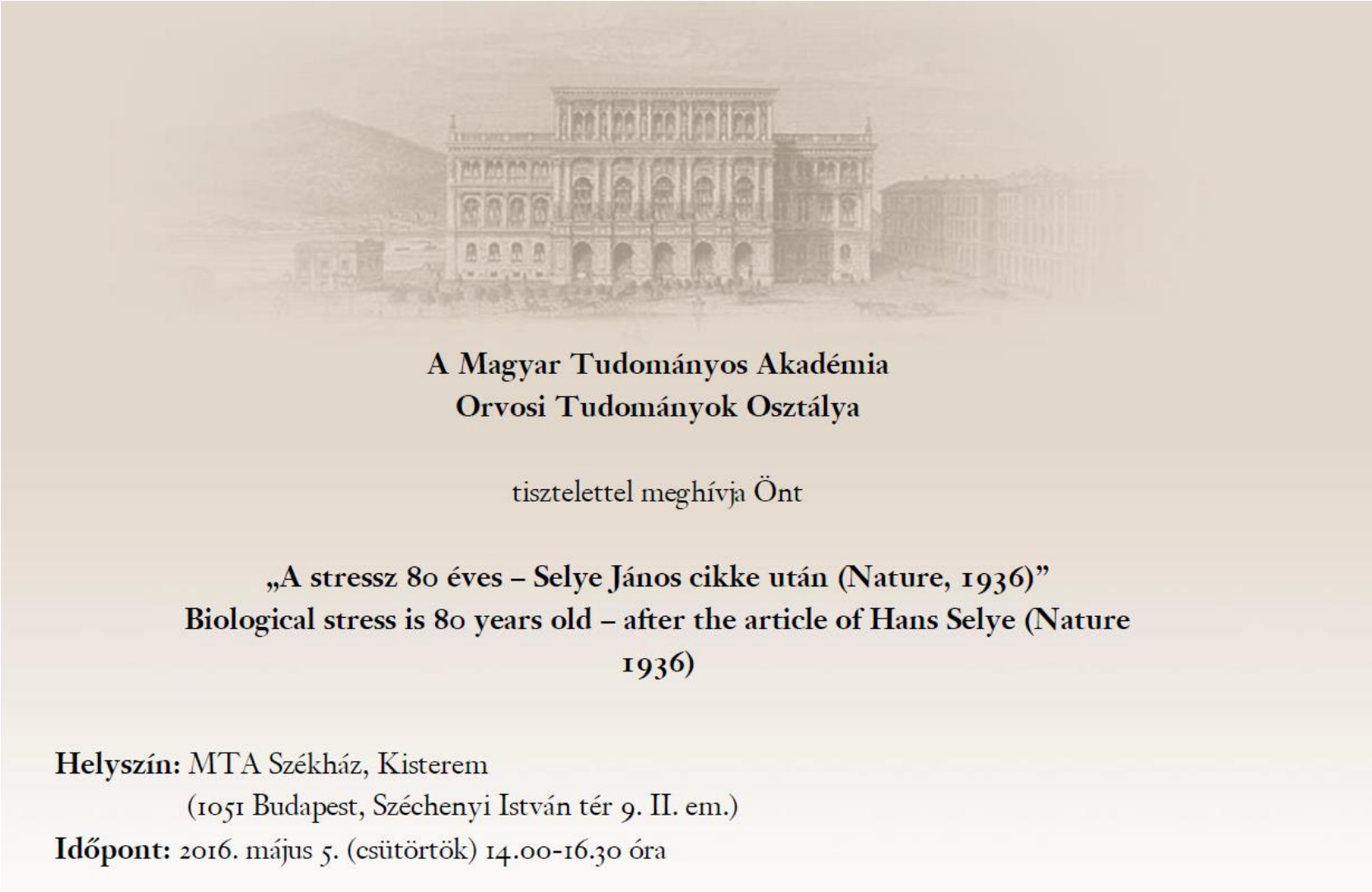
May 5th, 2016, Budapest, Hungary



A Magyar Tudományos Akadémia
Orvosi Tudományok Osztálya

tisztelettel meghívja Önt

„A stressz 80 éves – Selye János cikke után (Nature, 1936)"
Biological stress is 80 years old – after the article of Hans Selye (Nature 1936)

Helyszín: MTA Székház, Kisterem
(1051 Budapest, Széchenyi István tér 9. II. em.)
Időpont: 2016. május 5. (csütörtök) 14.00-16.30 óra

Stress-related gastroduodenal ulcers: Perspectives from academic surgeons

Masashi Yoshida, M.D., PhD, FACS

Visiting Professor,
Department of Surgical Research and Techniques,
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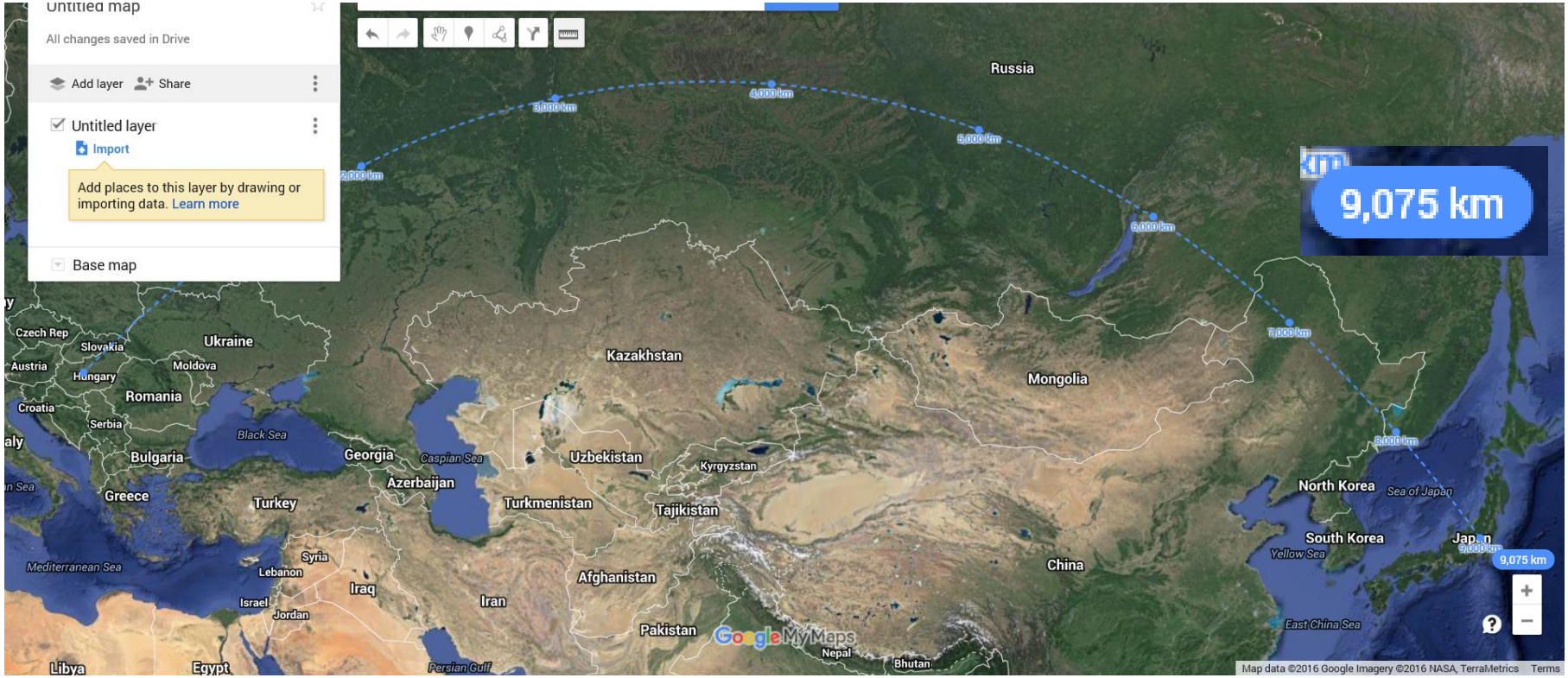
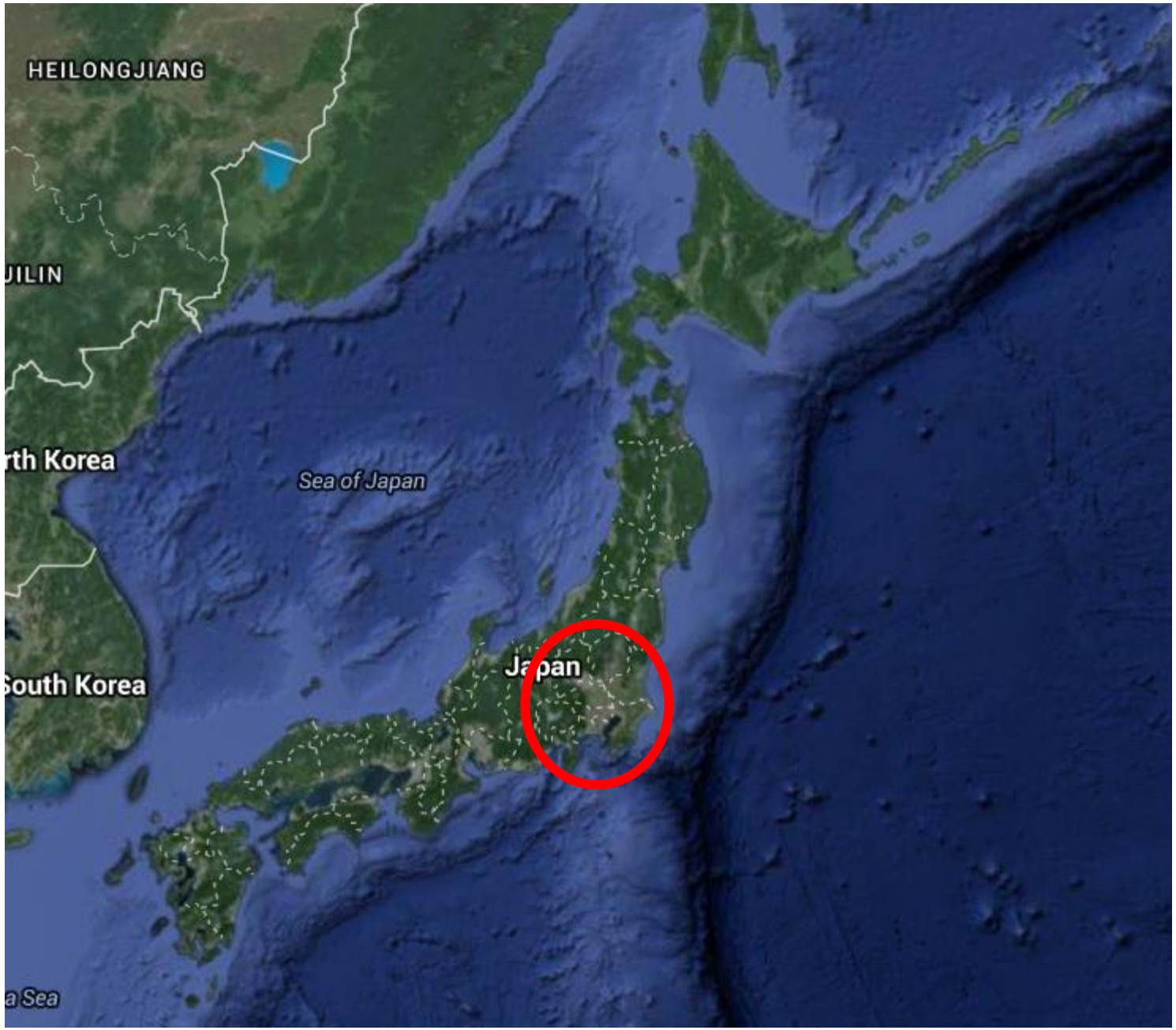
Professor,
Department of Surgery,
International University of Health and Welfare Hospital,
Tochigi, Japan

Masashi Yoshida, Masaki Kitajima, Yutaka Suzuki

International University of Health and Welfare Hospital,
Tochigi, Japan




HEILONGJIANG
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rth Korea
Sea of Japan
South Korea
Japan
a Sea

IUHW Hospital

IUHW:
International University of Health and Welfare

IUHW Mita Hospital

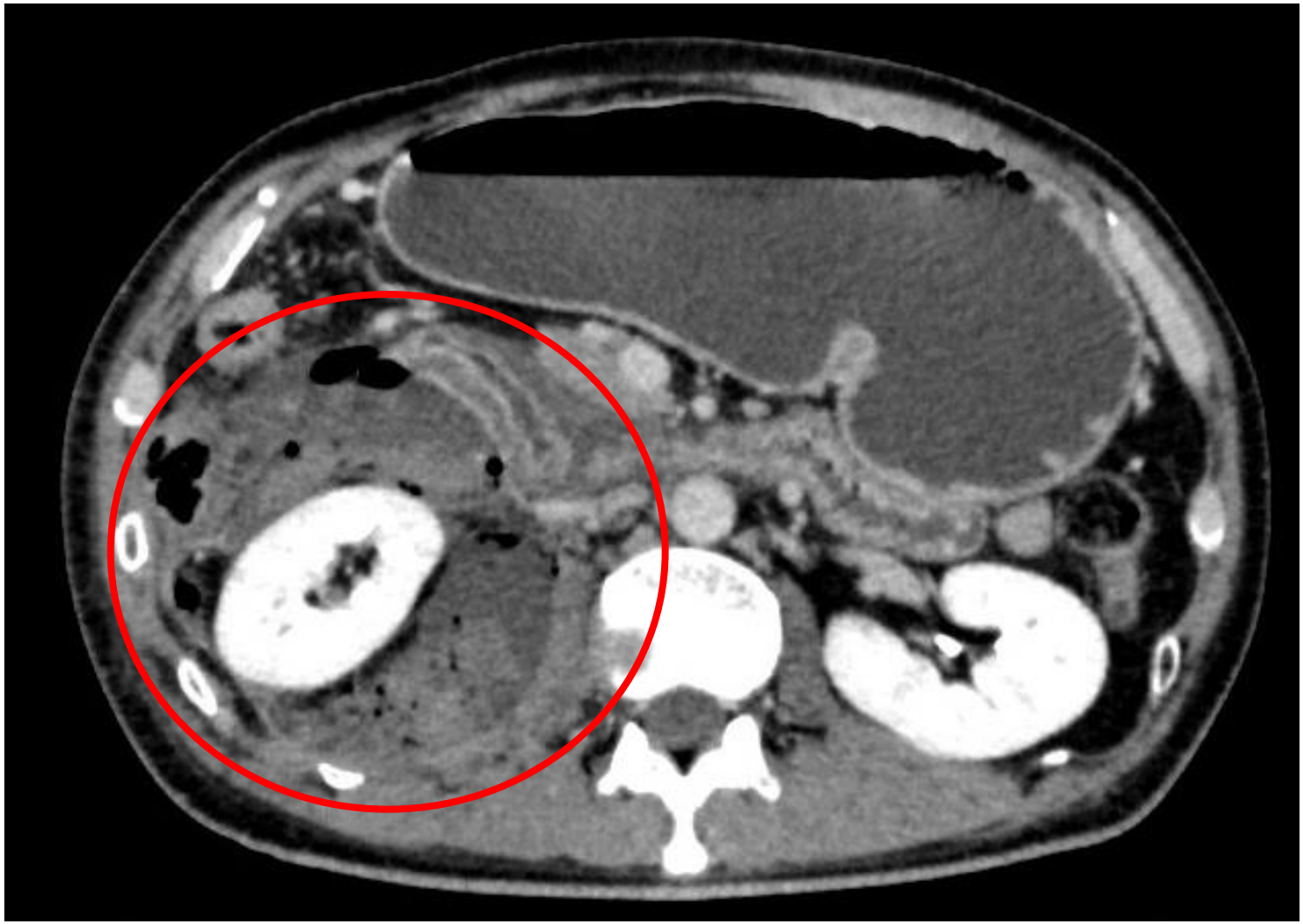
IUHW Hospital

IUHW:International University of Health and Welfare
Established in 1995

School of Medicine, 2017

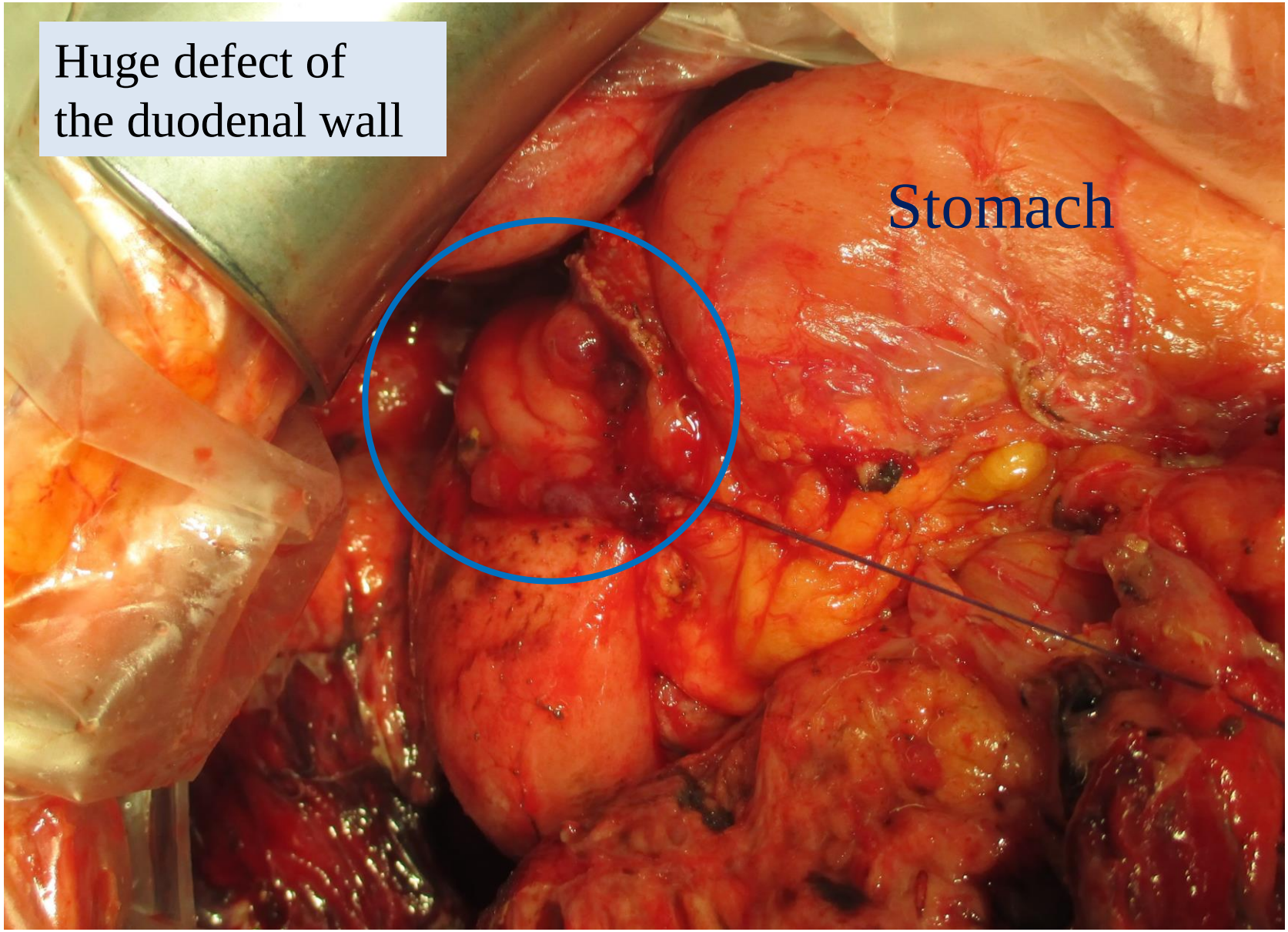
Duodenal Ulcer Perforation

Sept. 2014
57 year old
Male



Retroperitoneal abscess

Duodenal Ulcer Perforation



J Gastrointest Surg (2014) 18:1261–1268
DOI 10.1007/s11605-014-2485-5

ORIGINAL ARTICLE

What Is the Best Predictor of Mortality in Perforated Peptic Ulcer Disease? A Population-Based, Multivariable Regression Analysis Including Three Clinical Scoring Systems

Kenneth Thorsen · Jon Arne Søreide · Kjetil Søreide

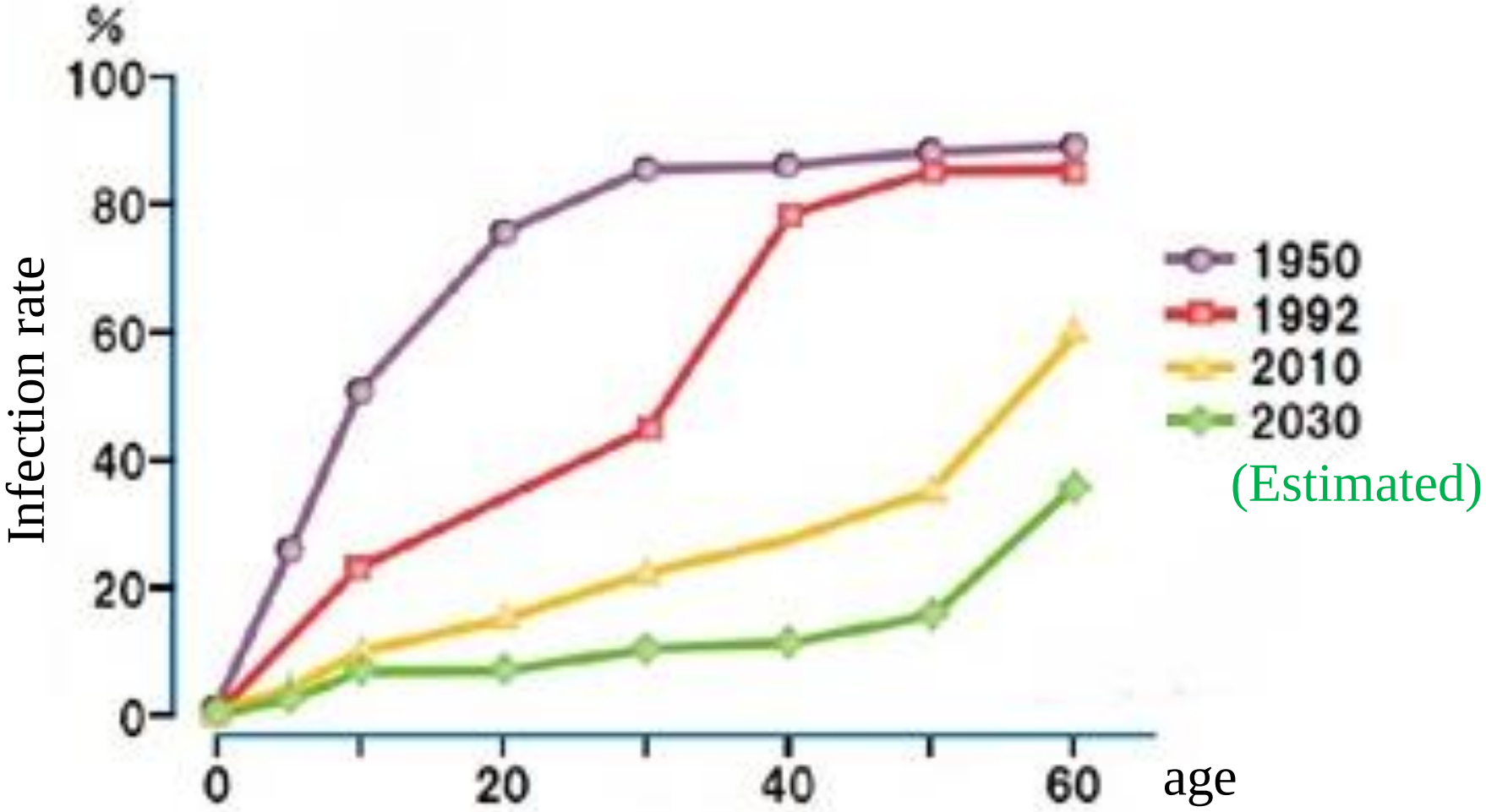
K. Thorsen (✉) · J. A. Søreide · K. Søreide
Department of Gastrointestinal Surgery, Stavanger University Hospital, PO Box 8100, 4068 Stavanger, Norway

A total of 172 patients were included, of whom 28 (16 %) died within 30 days.

Table 4 Multivariable regression analysis of factors associated with 30-day mortality

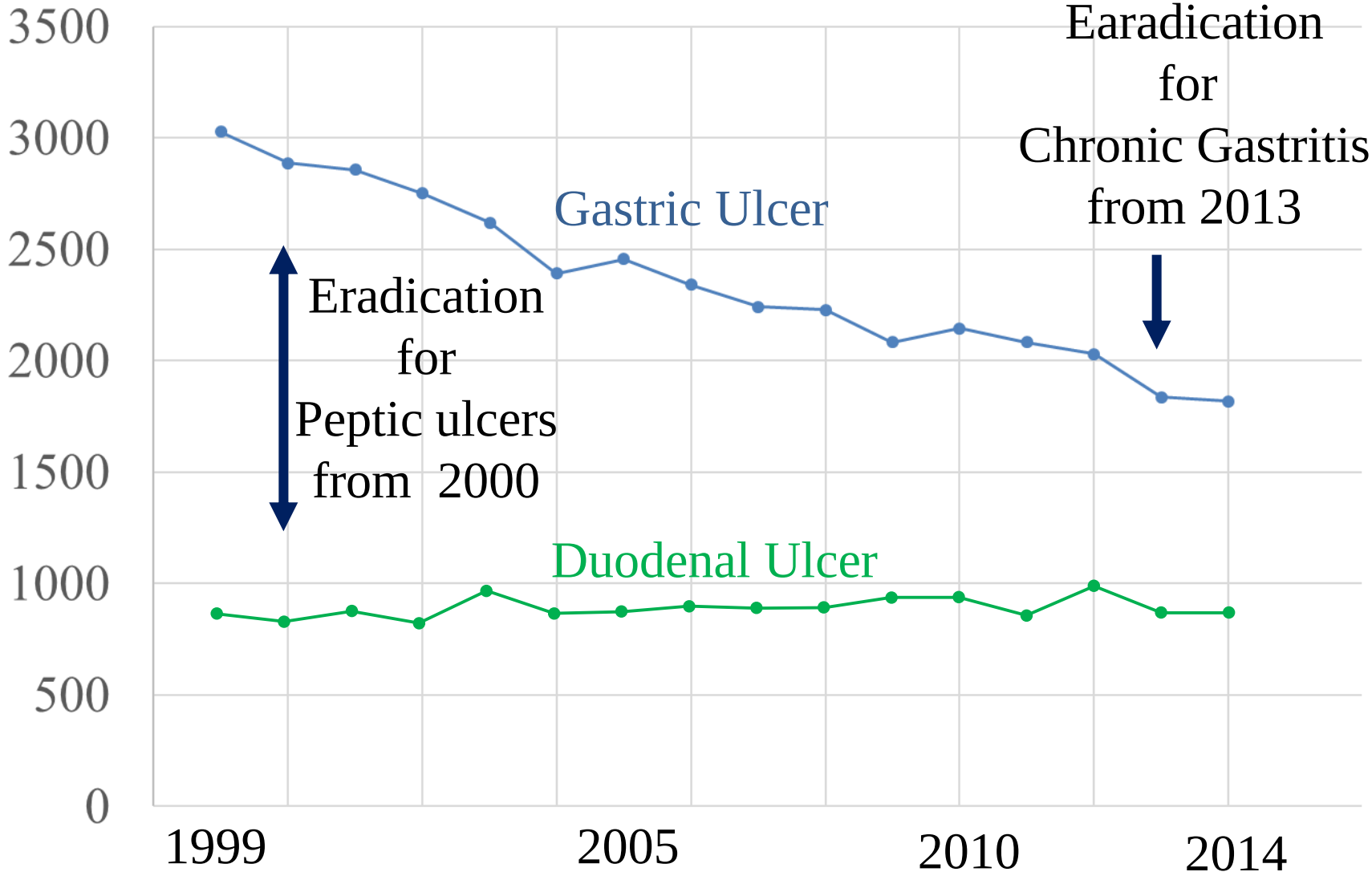
Factors	Wald	*p* value	Odds ratio (95 % CI)
Age	10.2	0.001	1.1 (1.0–1.1)
Delay >24 h	4.4	0.035	3.5 (1.1–11.3)
Active cancer	7.8	0.005	7.6 (1.8–31.7)
Albumin ≤37 g/l	5.6	0.018	4.1 (1.3–13.8)
Bilirubin >19 μmol/l	6.5	0.011	5.1 (1.5–18.2)
Creatinine >118 μmol/l	4.4	0.036	3.5 (1.1–11.1)

Adjusted for gender



Shift of the *Helicobacter pylori* infection in Japan

(Asaka et al.)



Number of People Died of Peptic Ulcers in Japan

Experimental Model for Production of Perforating Duodenal Ulcers by Cysteamine in the Rat

NATURE VOL. 244 AUGUST 17 1973

many of these studies sublethal and even lethal amounts were used, we could find no description of any duodenal lesions.

This work was supported in part by the Medical Research Council of Canada, the Ministère des Affaires Sociales, Quebec, and the Colonial Research Institute, Freeport, Bahamas. S. S. is a fellow of the Medical Research Council of Canada.

HANS SELYE
SANDOR SZABO

Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Montreal 101, Quebec

Received May 11; revised June 25, 1973.

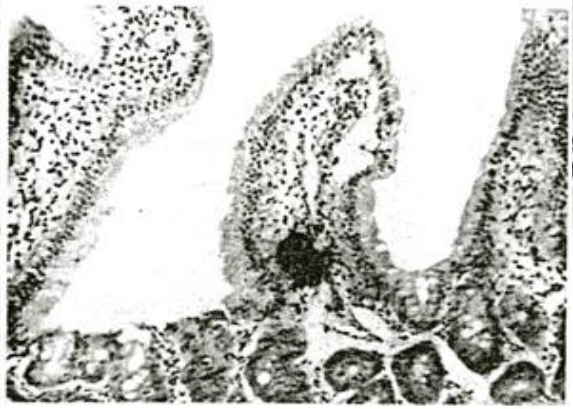


Fig. 6 Autoradiographical picture reveals that 35S-Cyst. labelled cells are observed at mucosal layer after administration (30min.) (×200)

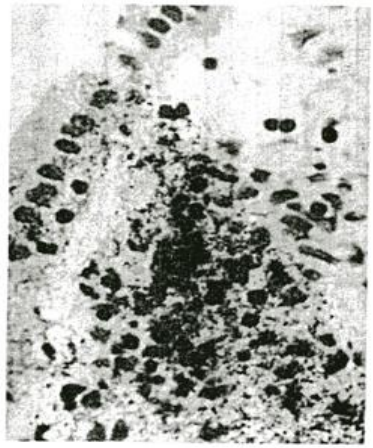
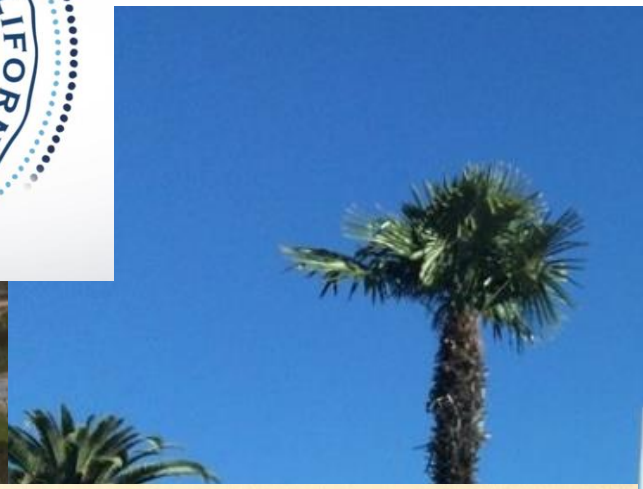


Fig. 9 Polymorphonuclear cells are observed around 35S-Cyst. labelled cells (1hour) (×400)

May,1998~ May, 2000



VA Medical Center
Long Beach, CA

University of California, Irvine
College of Medicine

CERTIFICATE OF RESEARCH FELLOWSHIP

Awarded to

MASASHI YOSHIDA, MD

For his productive research fellowship in the Experimental Pathology and Pharmacology Laboratory in the Diagnostic and Molecular Medicine Health Care Group in the Pathology and Laboratory Medicine Service at the VA Medical Center, Long Beach, CA, which is affiliated with the University of California, Irvine, CA, College of Medicine. He performed mechanistic and clinically relevant studies on the role of vascular injury and increased vascular permeability in the pathogenesis of chemically induced duodenal ulceration, participated in cellular and molecular biologic studies on the role of VEGF, gene expression and gene therapy studies using the cysteamine-induced duodenal ulcer model. He also participated in our weekly lab meetings and delivered several impressive presentations in the Macro, Micro and Molecular conferences of our Health Care Group as well as presented some of his findings at national and international meetings.

May 1, 1998 to May 3, 2000

Sandor Szabo, MD, PhD,MPH
Chief, Diagnostic & Molecular Medicine Health Care Group
Professor of Pathology & Pharmacology

May 12,2000
Date

Duodenal ulcerogens:

Cysteamine-HCl (25mg/100g)

Propionitrile (10mg/100g)

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-HCl (5mg/100g)

Control: Ethanolamine (ET),

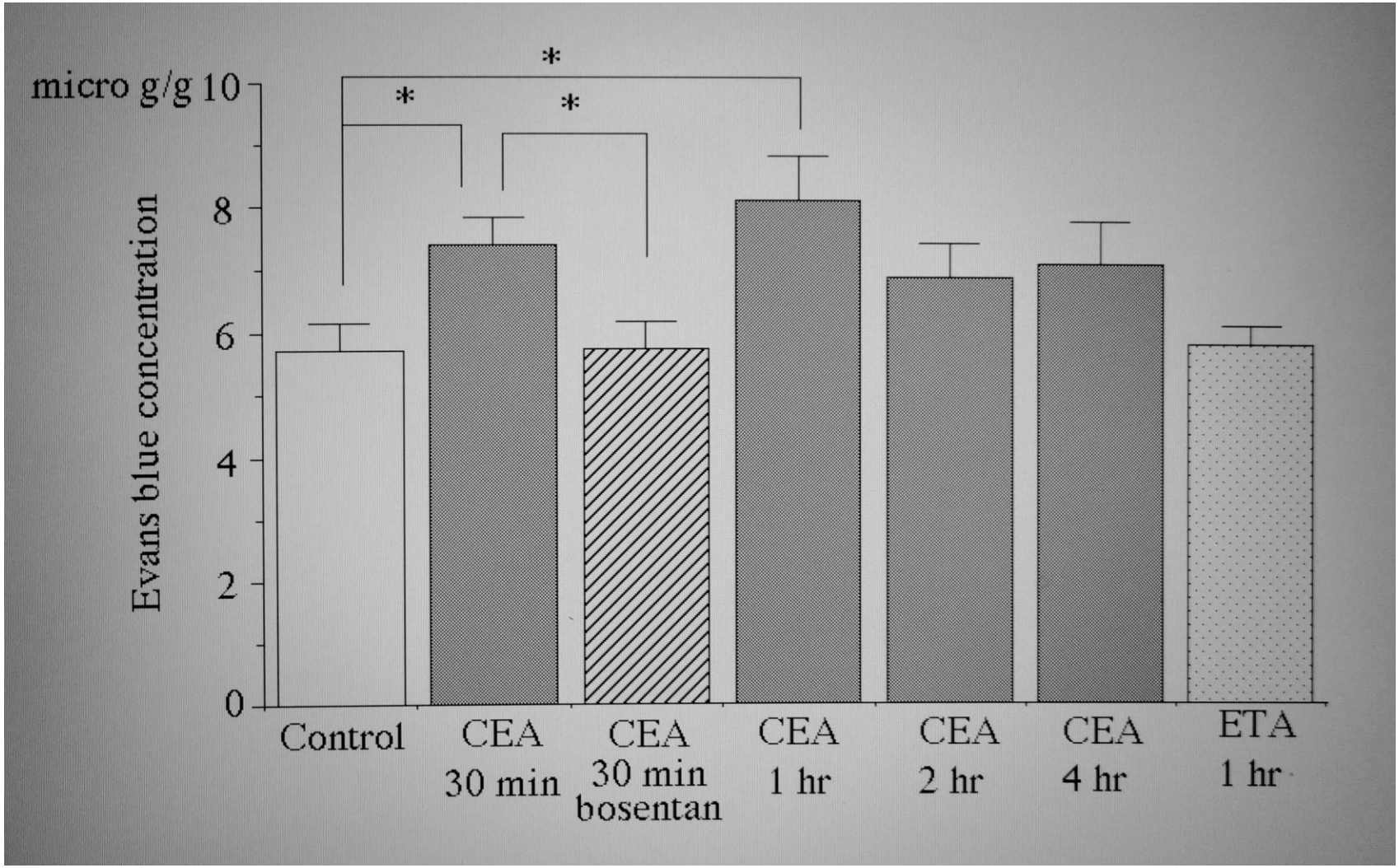
a non-ulcerogenic structural analogue of cysteamine

Pretreatments with endothelin (ET) A and B receptor antagonist,

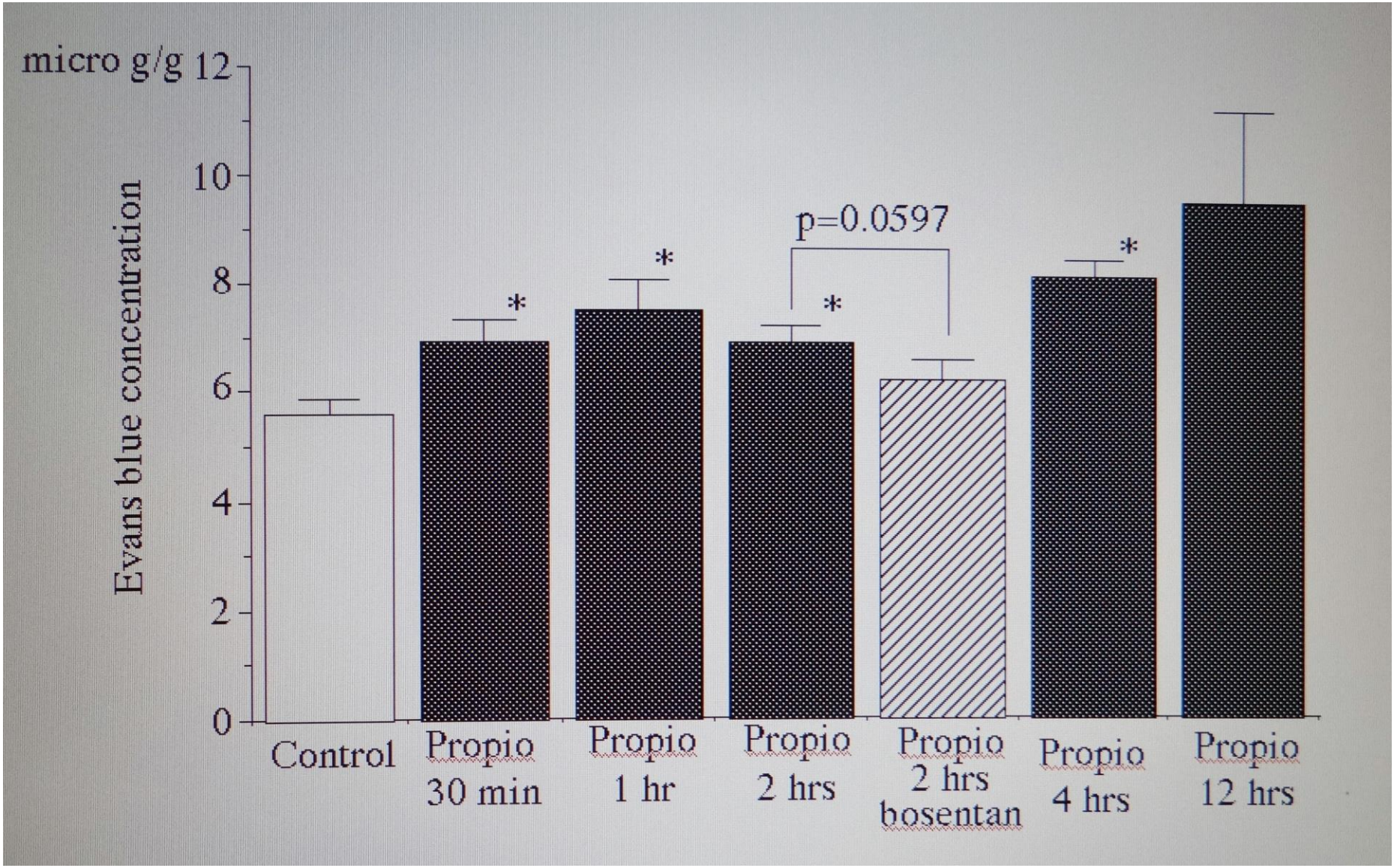
bosentan (10 mg/100g)

Evan's blue (1mg/100g) iv,

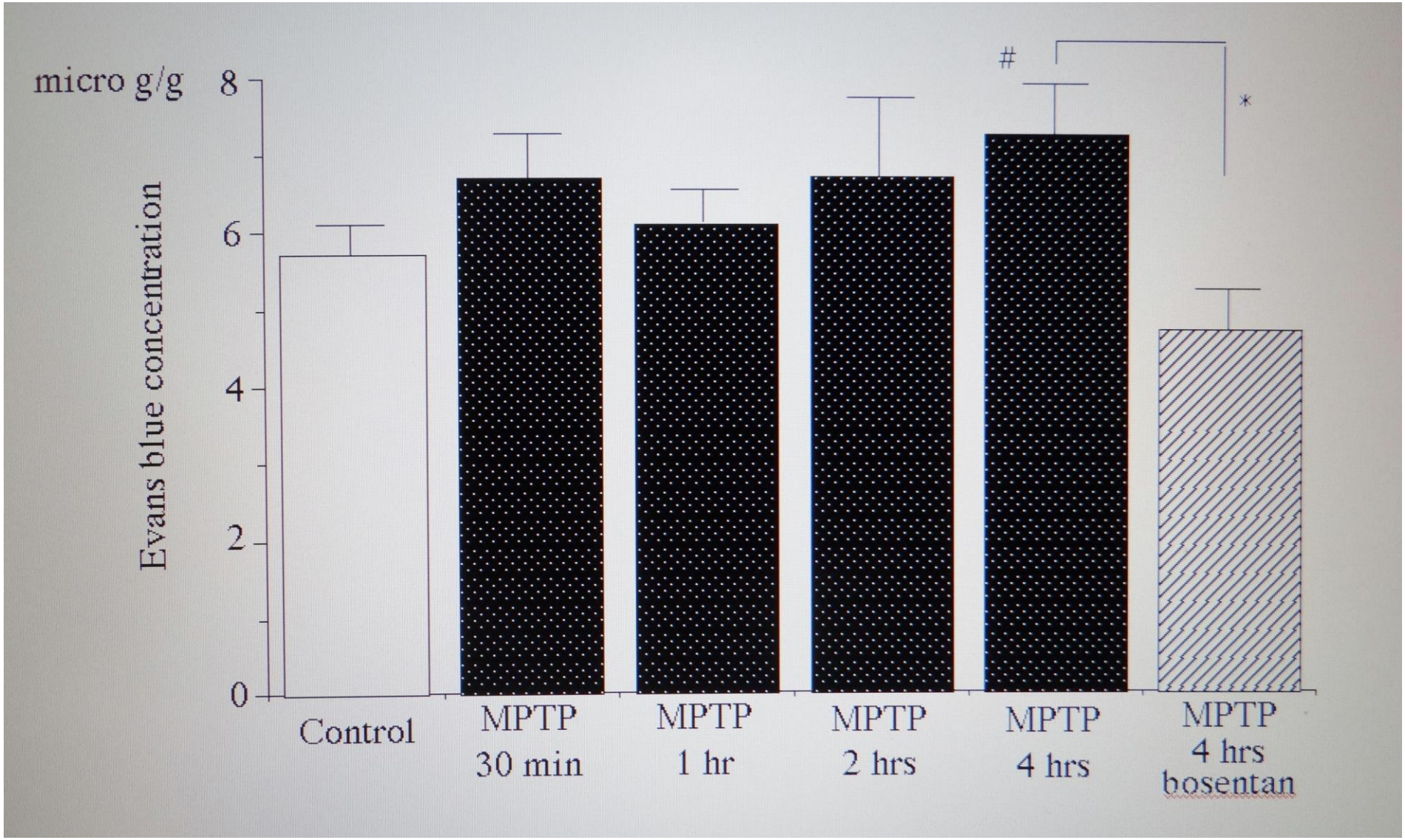
Mucosal concentration was measured spectrophotomedtrically



Effects of Cysteamine on Vascular permeability of the duodenal mucosa



Effects of Propionitrile on Vascular permeability of the duodenal mucosa



Effects of MPTP on Vascular permeability of the duodenal mucosa

Endotheline related duodenal vascular permeability increase may be a comon element in the early phase of duodenal ulceration.

Stress: Burn injury to rat's back skin

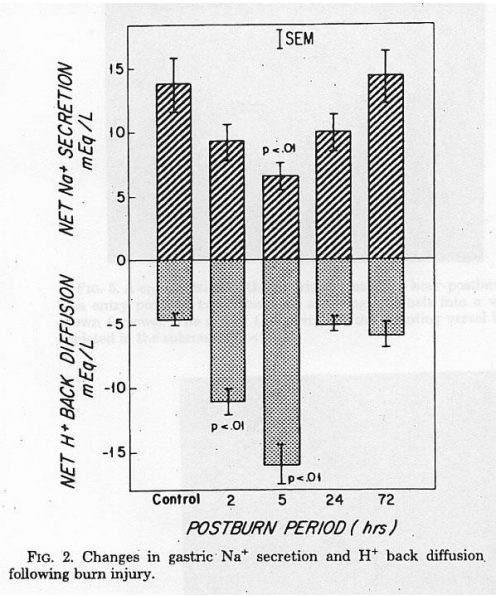


FIG. 2. Changes in gastric Na^+ secretion and H^+ back diffusion following burn injury.

0022-5282/78/1809-0644$02.00/0
THE JOURNAL OF TRAUMA
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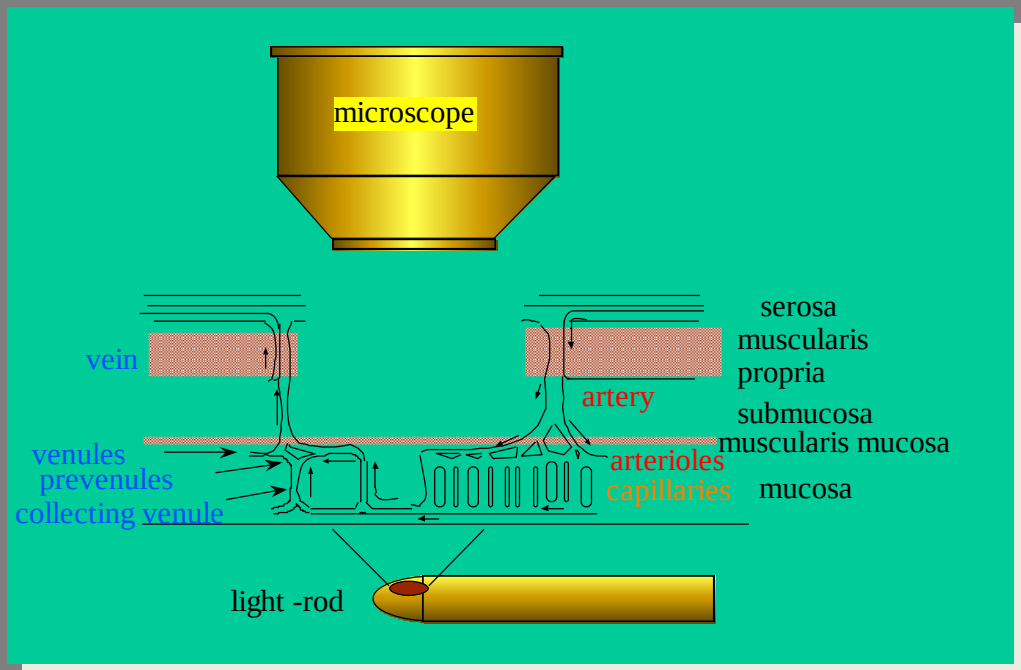
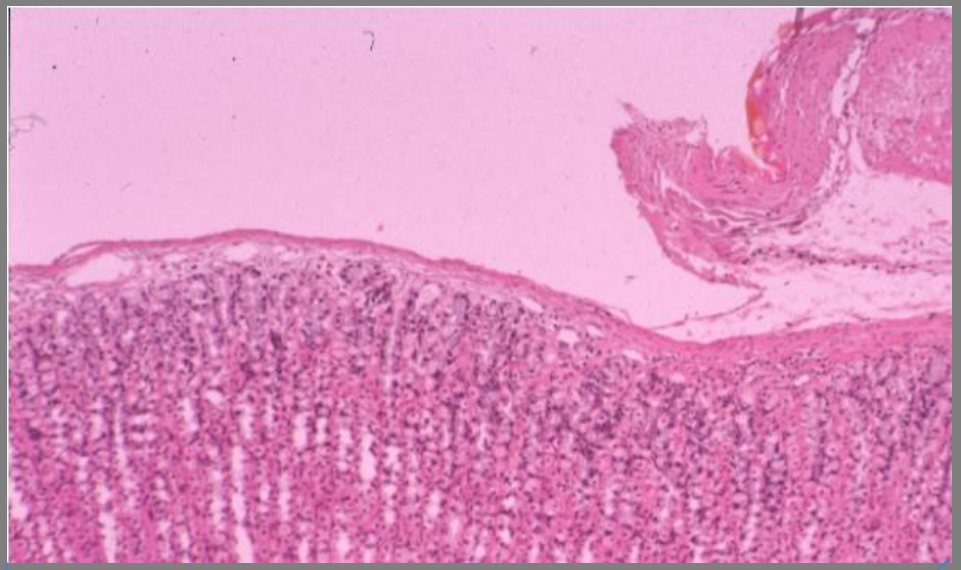
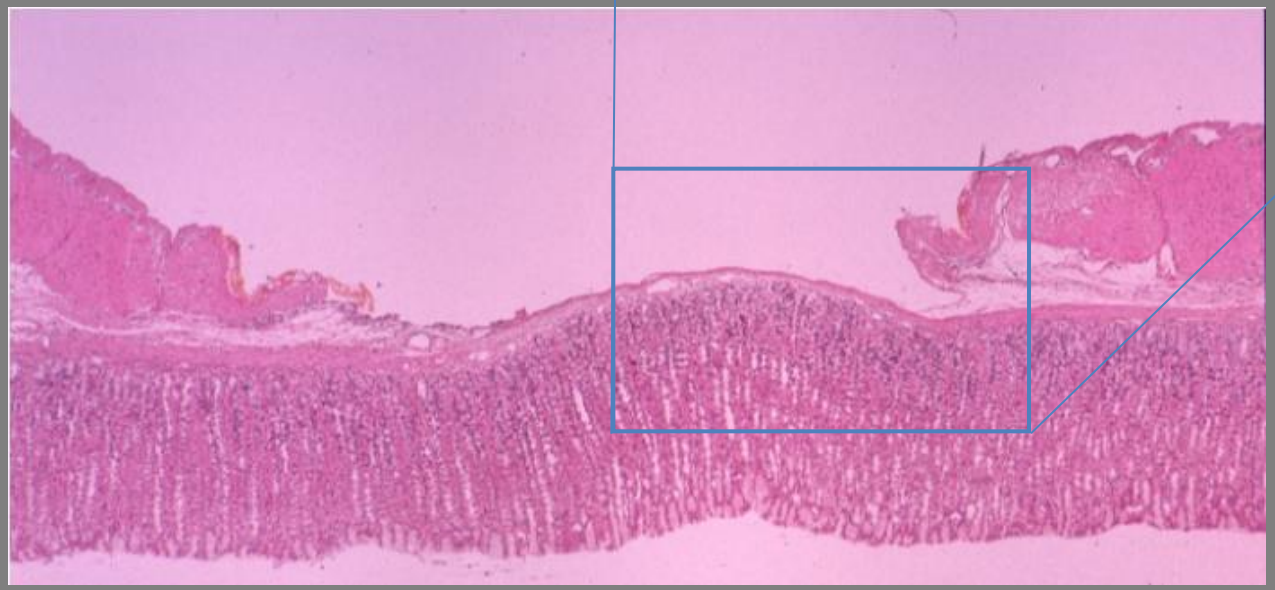
Vol. 18, No. 9
Printed in U.S.A.

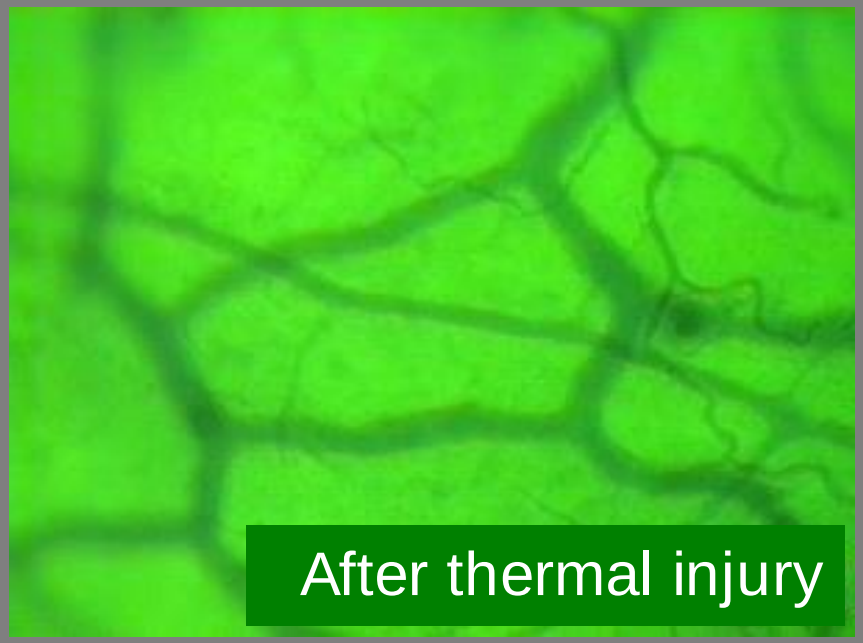
Gastric Mucosal Lesions After Burn Injury: Relationship to H^+ Back-diffusion and the Microcirculation

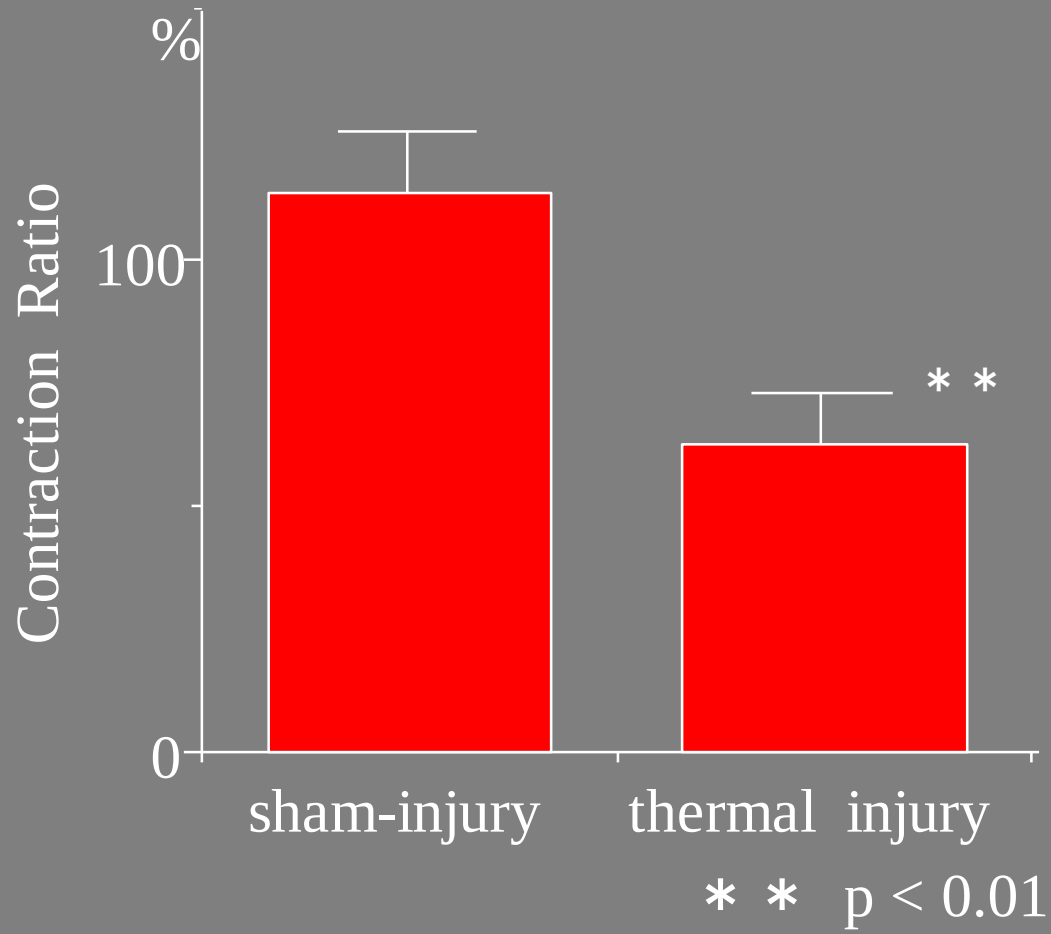
MASAKI KITAJIMA, M.D., ROBERT R. WOLFE, PH.D., ROBERT L. TRELSTAD, M.D., JOHN R. ALLSOP, M.D., AND JOHN F. BURKE, M.D.


microscope
vein
artery
venules
prevenules
collecting venule
arterioles
capillaries
serosa
muscularis
propria
submucosa
muscularis mucosa
mucosa
light -rod

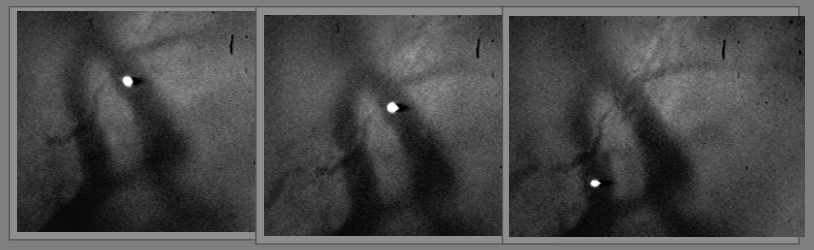






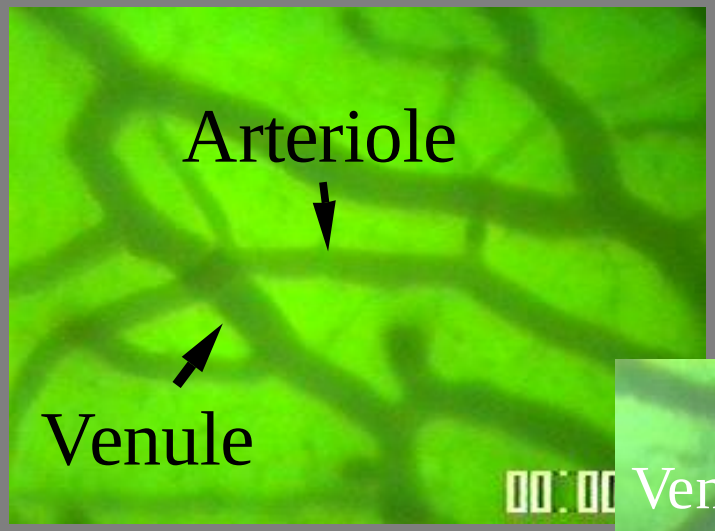


Arteriole contraction ratio
15 minutes after thermal injury

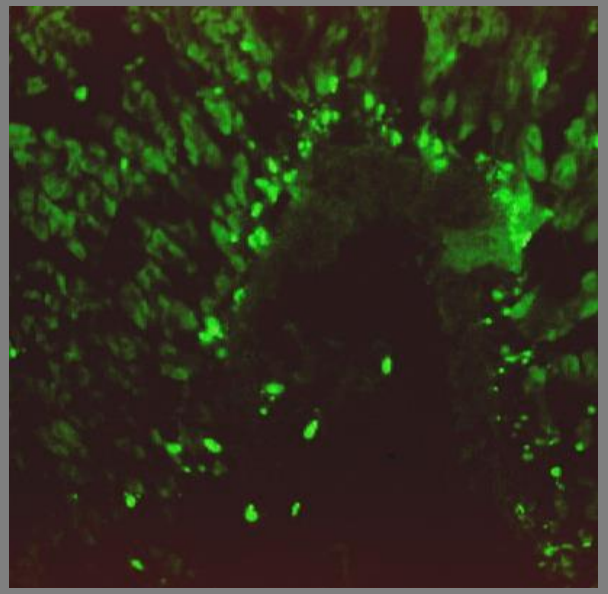


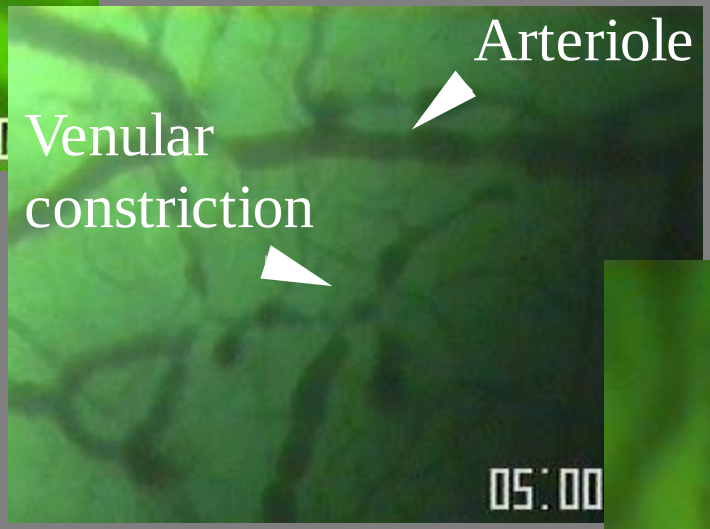
*p<0.05 VS pre-thermal injury and 15 minutes post sham-injury.

The percentage of rolling leukocytes in venules

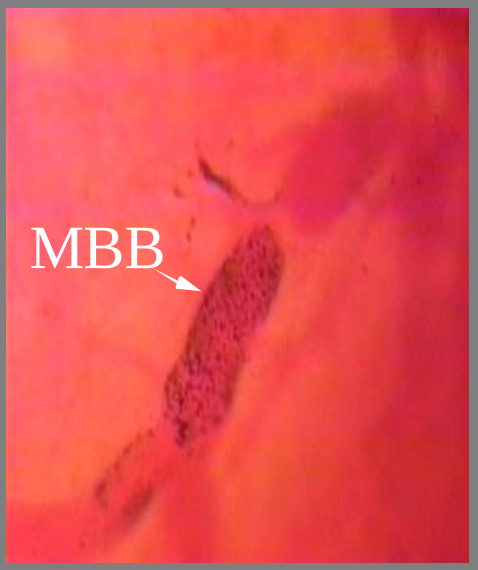


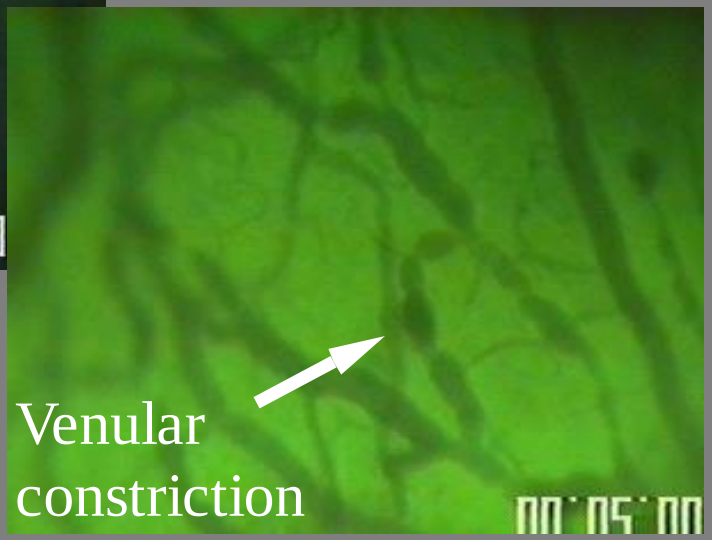
Control group





5-hr without
water resuscitation





5-hr with
water resuscitation

Gastroenterology. 1985 Jan;88(1 Pt 2):228-36.

Early vascular injury and increased vascular permeability in gastric mucosal injury caused by ethanol in the rat.

Szabo S, Trier JS, Brown A, Schnoor J

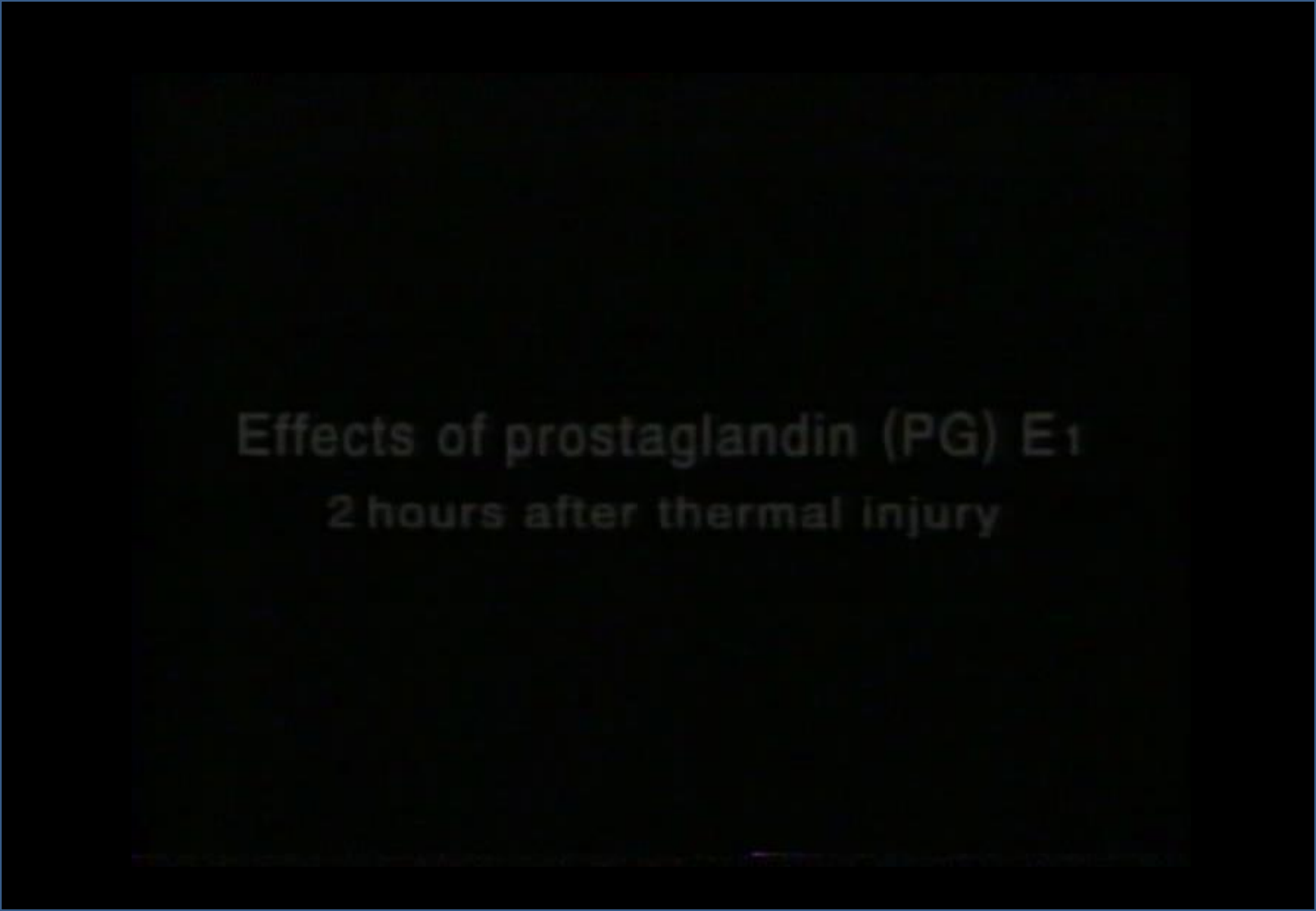
Abstract

The hypothesis that vascular injury contributes to the development of hemorrhagic erosions after intragastric administration of ethanol has been examined in the rat using vascular tracers. Extravasation of intravenously injected Evans blue into the gastric wall and into gastric contents was used as an indicator of vascular permeability. India ink and monastral blue, which label damaged blood vessels, were used to demonstrate vascular injury morphologically. Intragastric instillation of 75% and 100% ethanol induced increased vascular permeability within 1-3 min and resulted in monastral blue labeling of vessels in 13% and 17%, respectively, of the glandular mucosa within 1 min. After 1 h of 100% ethanol exposure, the areal density of monastral blue-stained blood vessels did not increase compared with that seen at 1 min, but the areal density of grossly visible hemorrhagic lesions increased strikingly and approximated that of vessel staining. The hemorrhagic erosions consistently occurred in regions of glandular mucosa where vessels were stained with monastral blue. Pretreatment with prostaglandin F2 beta or cysteamine reduced ethanol-induced Evans blue extravasation and monastral blue staining of mucosal blood vessels but did not reduce histologic evidence of gastric surface cell damage in the glandular mucosa. As increased vascular permeability and morphologically detectable vascular lesions consistently preceded the development of grossly visible hemorrhagic erosions in the glandular mucosa, we suggest that vascular injury is an early pathogenetic factor in the development of ethanol-induced gastric hemorrhagic erosions. The data also indicate that the degree of vascular damage, unlike the injury to surface epithelial cells, is reduced by pretreatment with prostaglandin F2 beta or the sulfhydryl cysteamine.

Endotheline related duodenal vascular permeability increase may be a common element in the early phase of duodenal ulceration.

(Endotheline related) gastric vascular permeability increase was also observed in a stress induced gastric mucosal injury model.

Vascular permeability increase may be a common element in the early phase of mucosal injury.

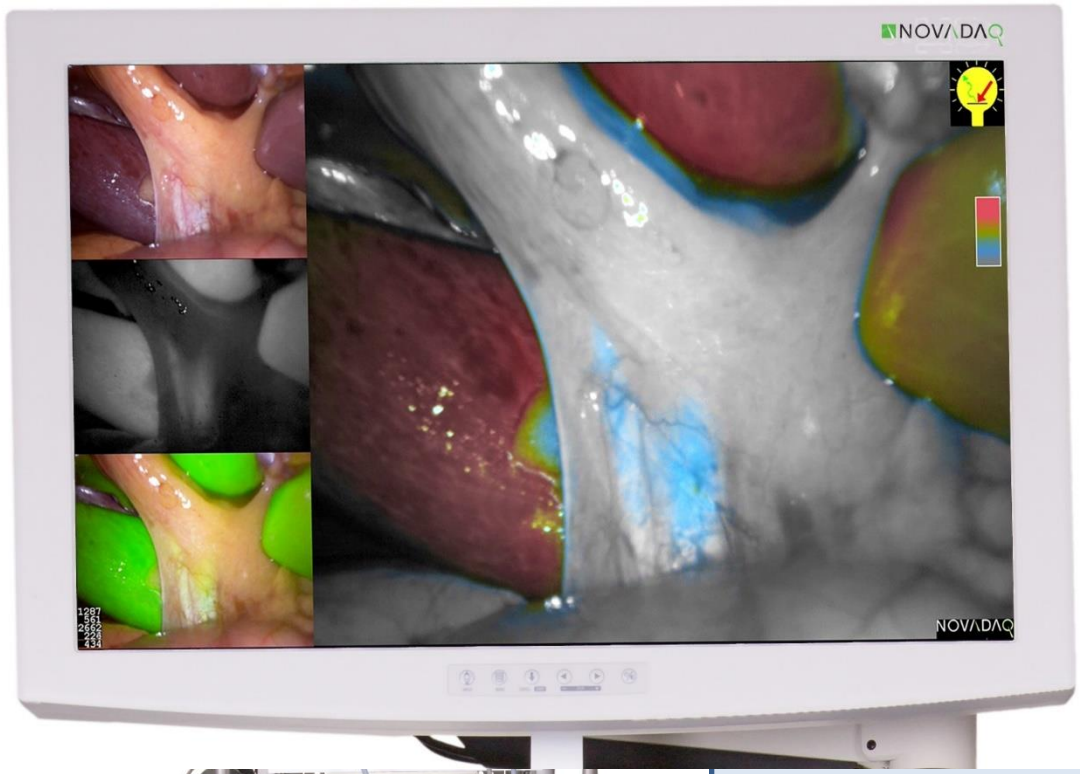

Effects of prostaglandin (PG) E1
2 hours after thermal injury

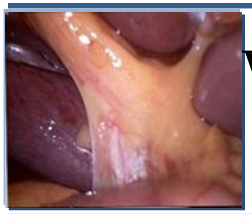
Indocyanine Green Fluorescence Guided Surgery

Masashi Yoshida, M.D., Ph.D, FACS

Visiting Professor,
Department of Surgical Research and Techniques,
Medical Faculty, Semmelweis University

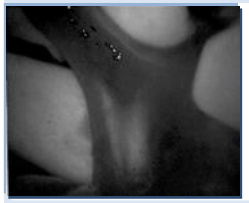
Professor,
Department of Surgery,
International University of Health and Welfare Hospital,
Tochigi, Japan





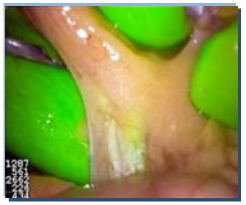
White light mode

Full color



Spy mode

Fluorescence



PINPOINT mode

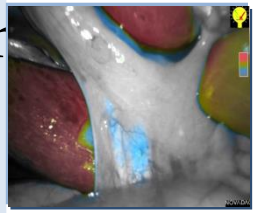
Full color

+

Fluorescence

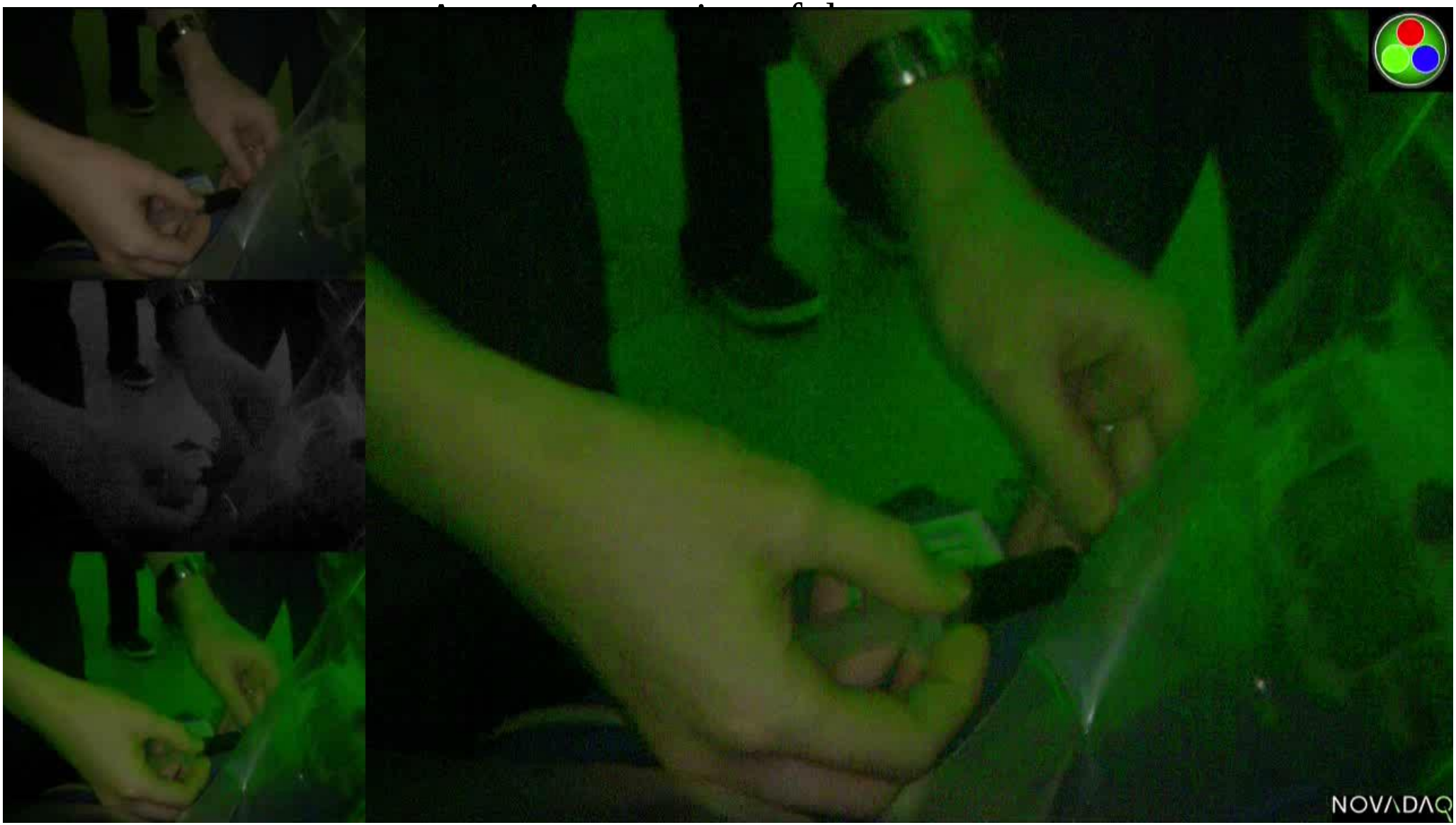
It was pr

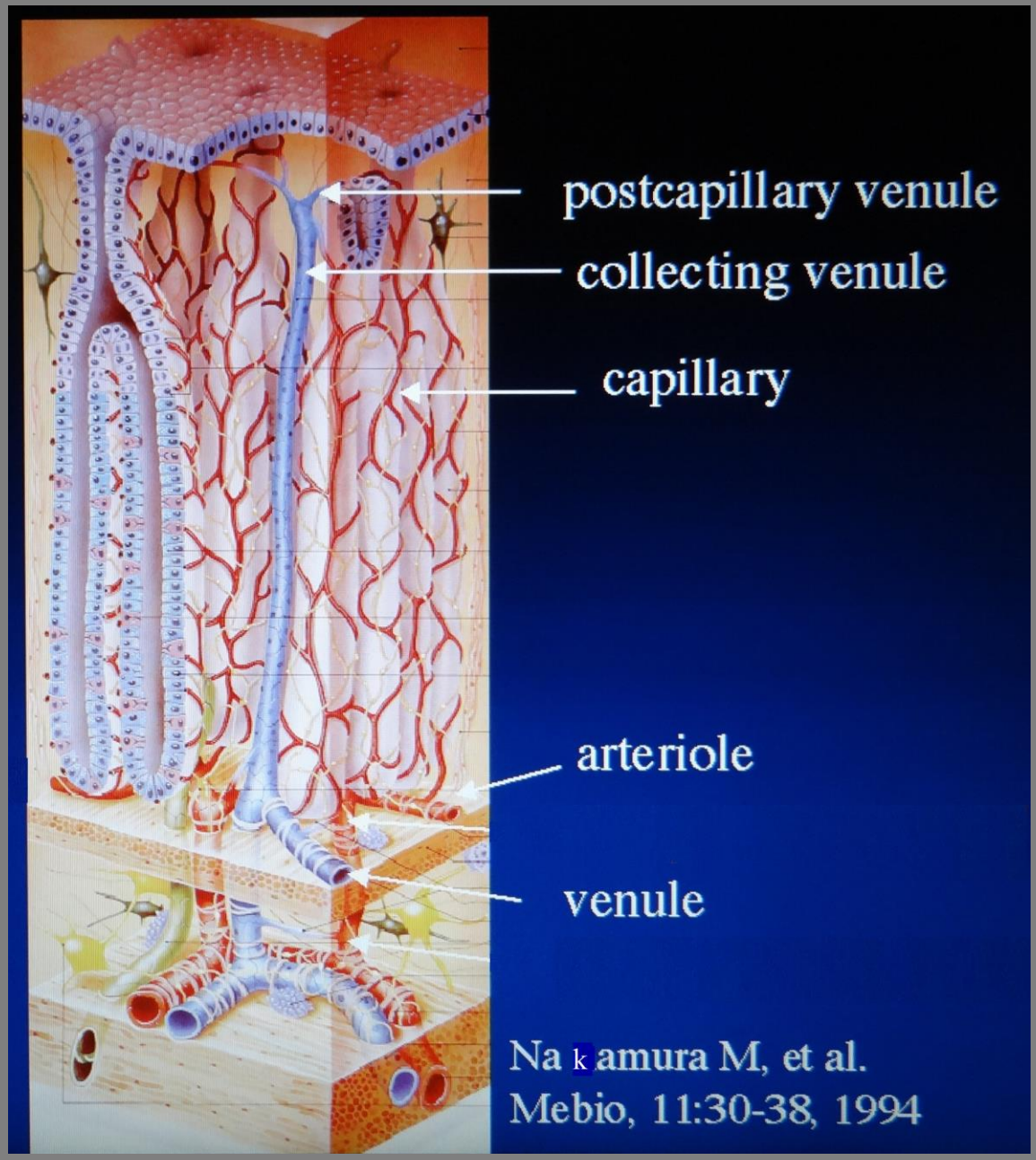
approved by



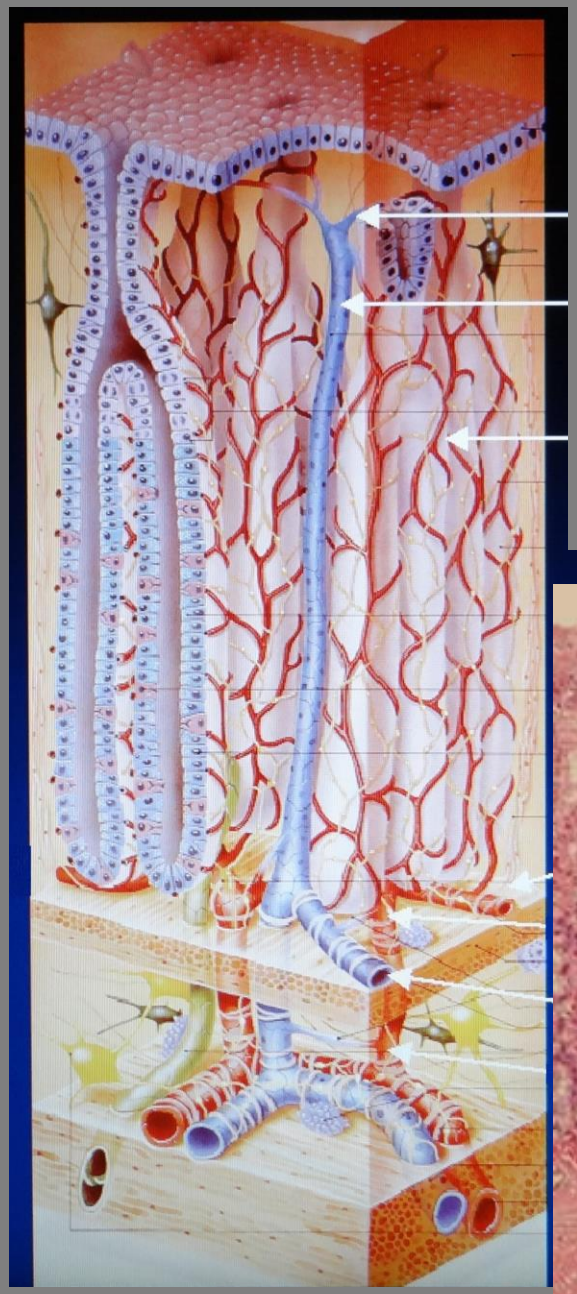
Colorized mode

To confirm blood flow



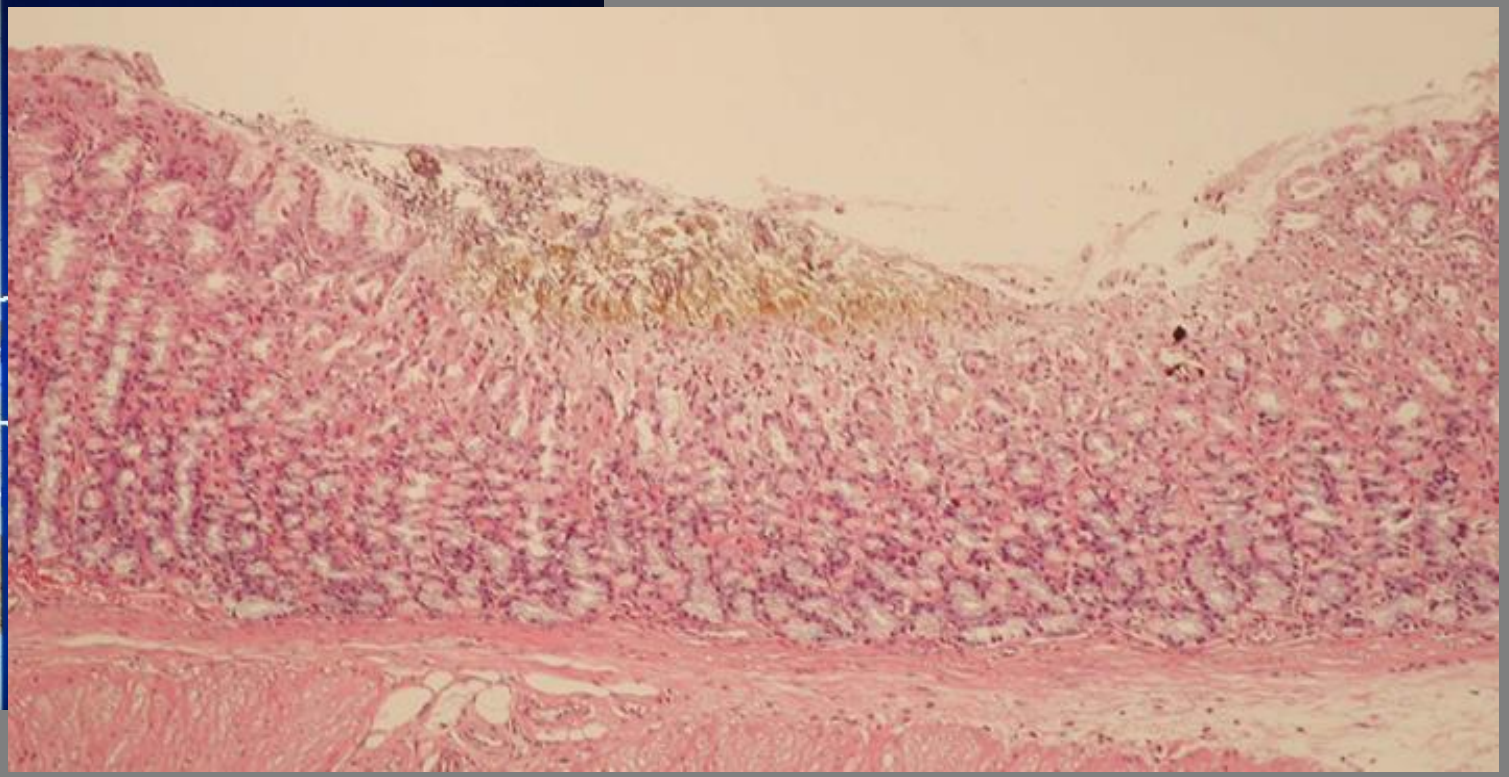


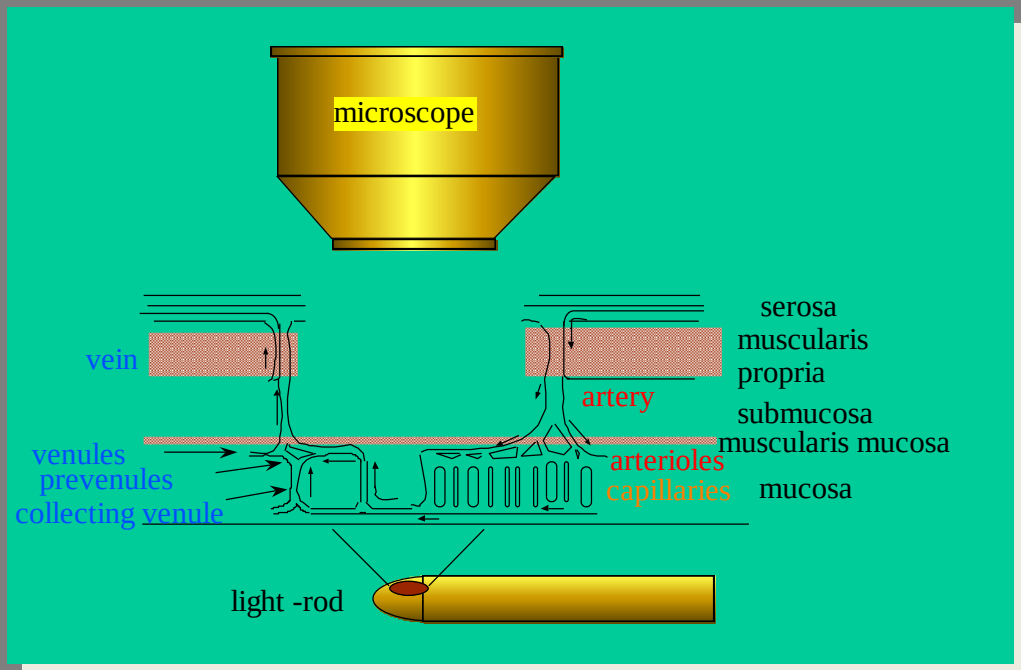
"The mucosal venules connected with the mucosal capillary network only at, or very close to, the luminal surface of the cast and passed through the mucosa without receiving further tributaries, i.e. all mucosal capillary blood must drain via vessels close to the stomach lumen ".
Gannon B, et al. J Anat 135:667-683, 1982.

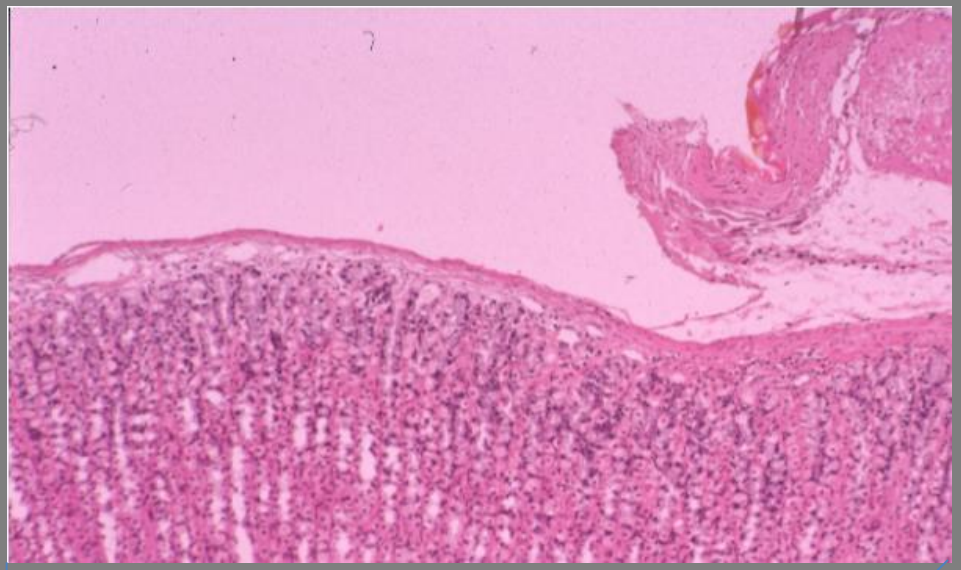


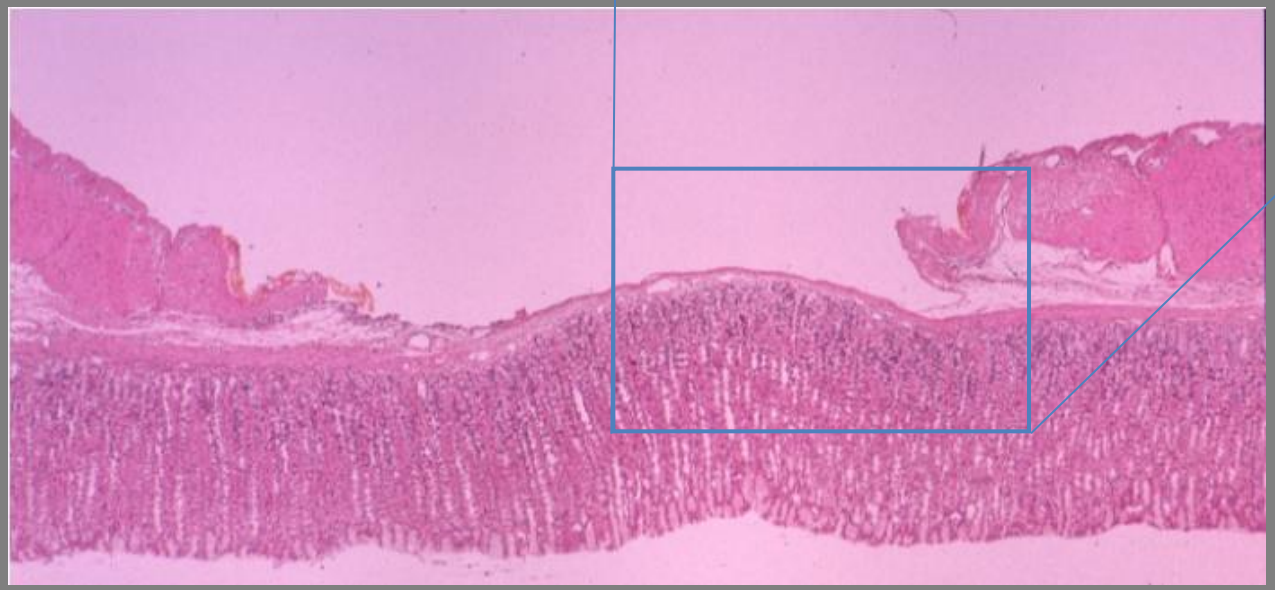
"The mucosal venules connected with the mucosal capillary network only at, or very close to, the luminal surface of the cast and passed through the mucosa without receiving further tributaries, i.e. all mucosal capillary blood must drain via vessels close to the stomach lumen ".

Gannon B, et al. J Anat 135:667-683, 1982.

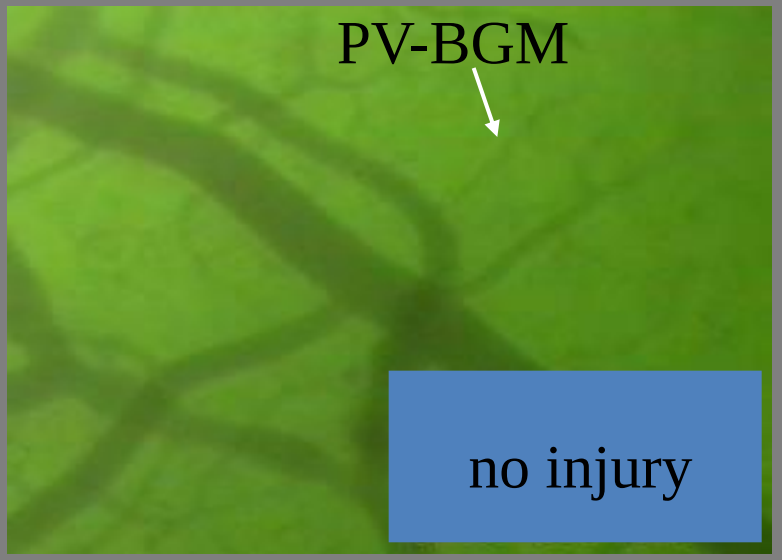


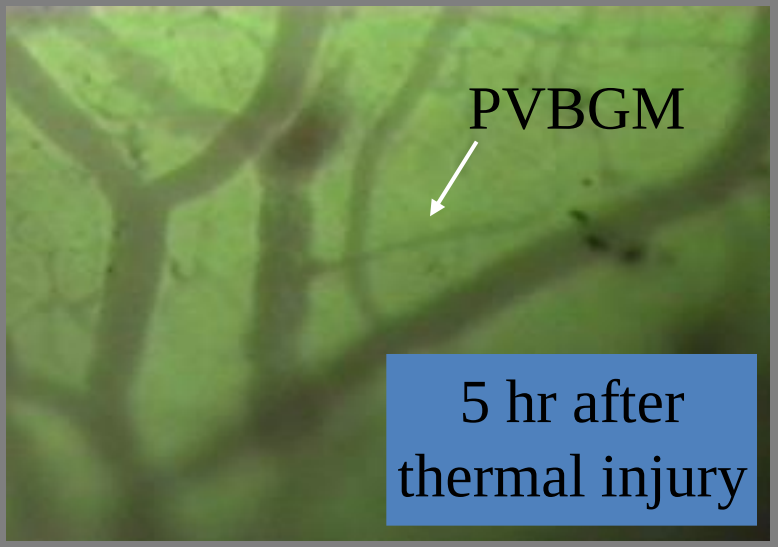

microscope
vein
artery
venules
prevenules
collecting venule
arterioles
capillaries
serosa
muscularis
propria
submucosa
muscularis mucosa
mucosa
light -rod

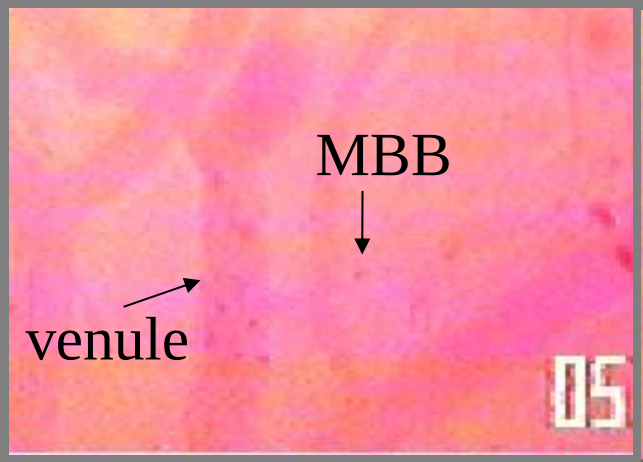


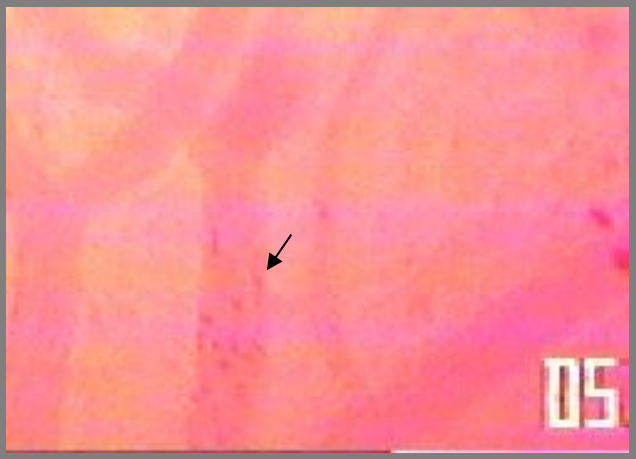


Postcapillary venule at the base of gastric mucosa (PV-BGM)

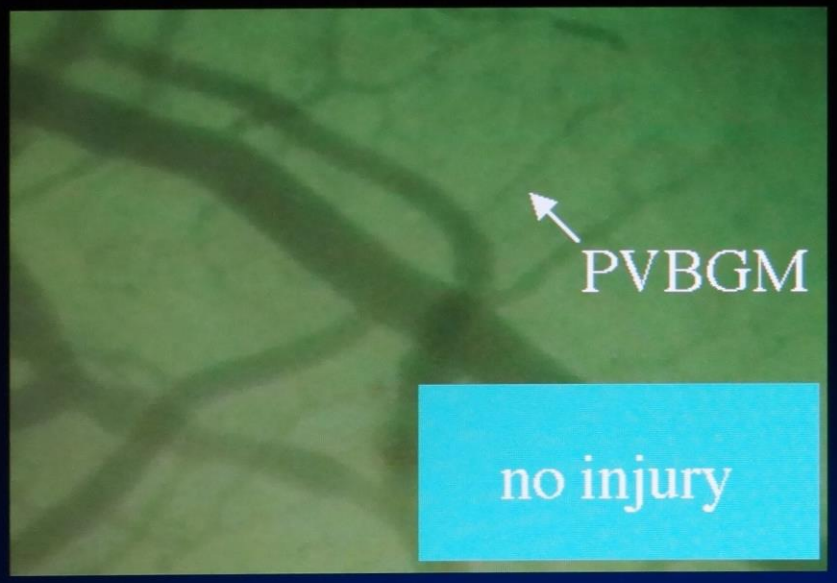


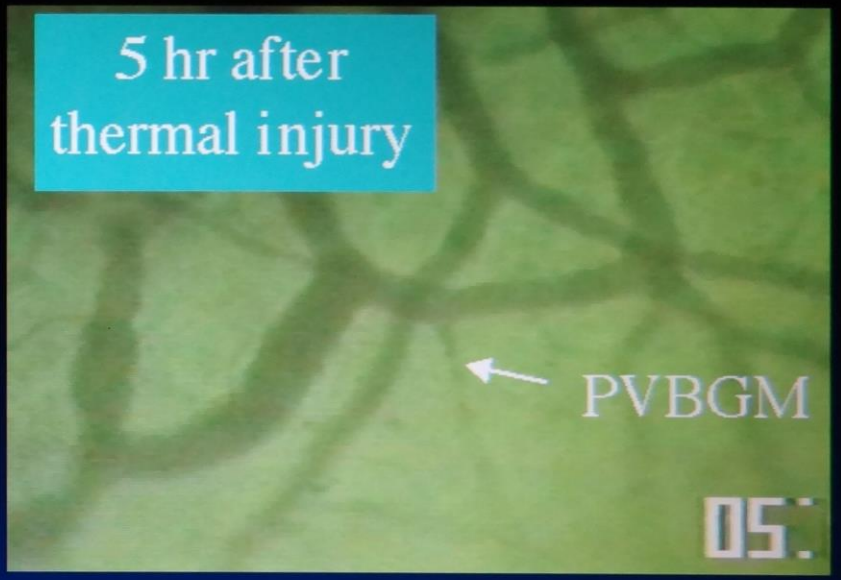


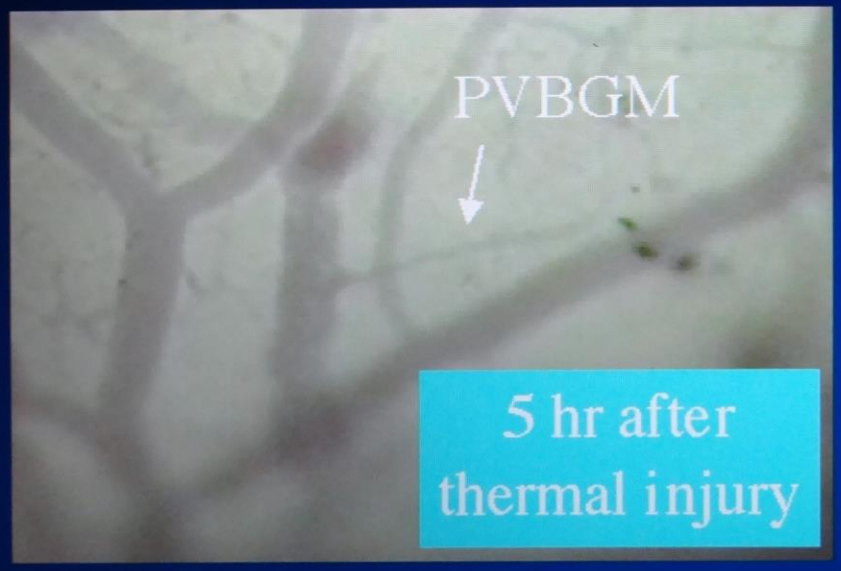


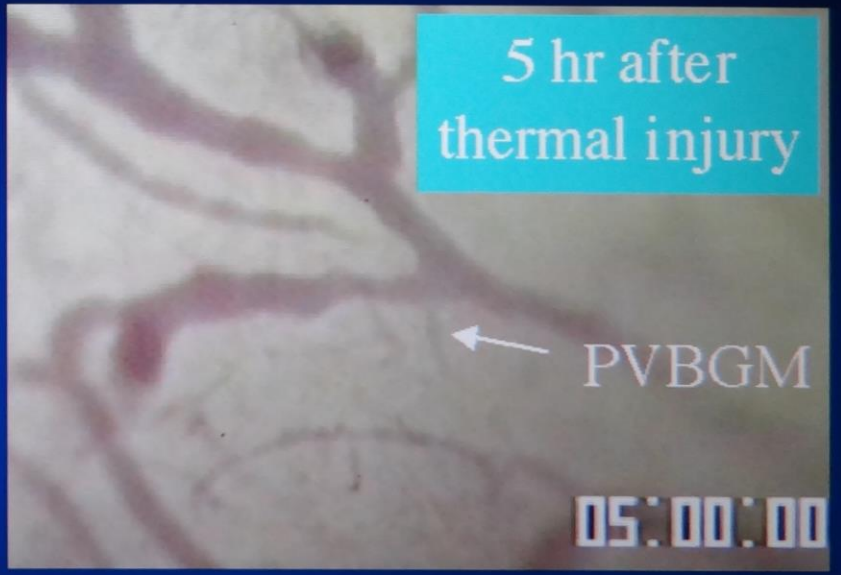


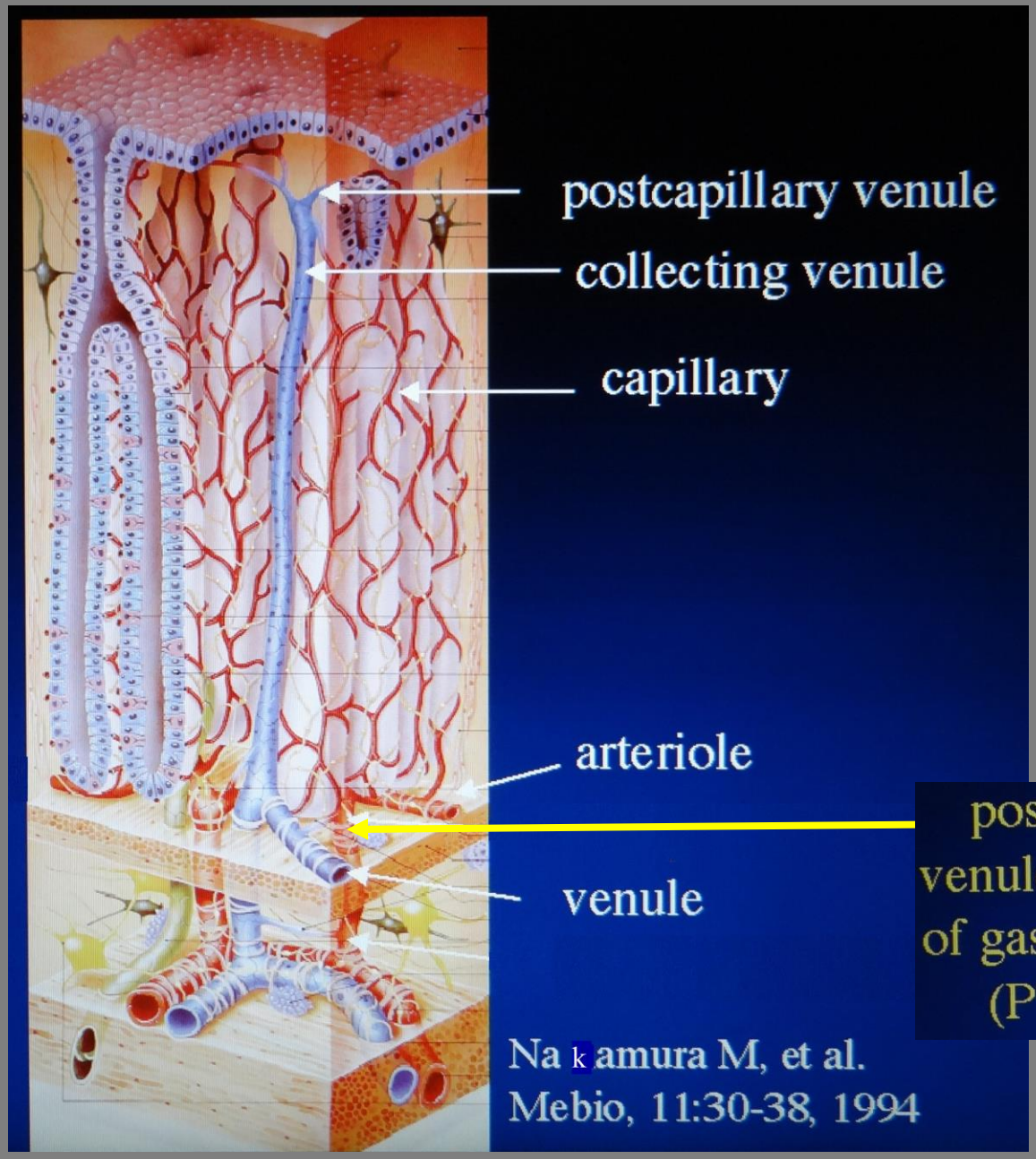
Postcapillary venule at the base of gastric mucosa (PVBGM)







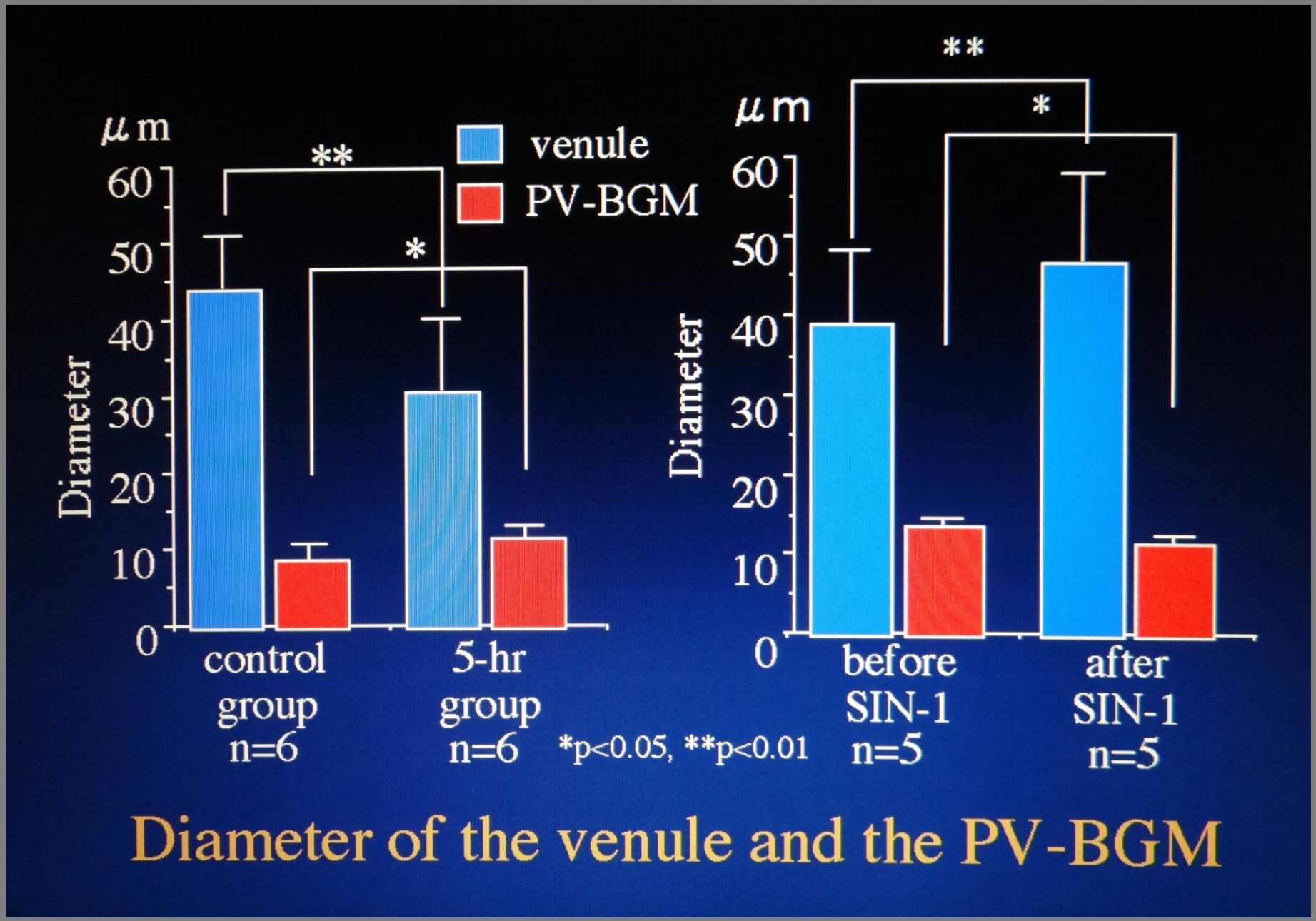




"The mucosal venules connected with the mucosal capillary network only at, or very close to, the luminal surface of the cast and passed through the mucosa without receiving further tributaries, i.e. all mucosal capillary blood must drain via vessels close to the stomach lumen ".
Gannon B, et al. J Anat 135:667-683, 1982.

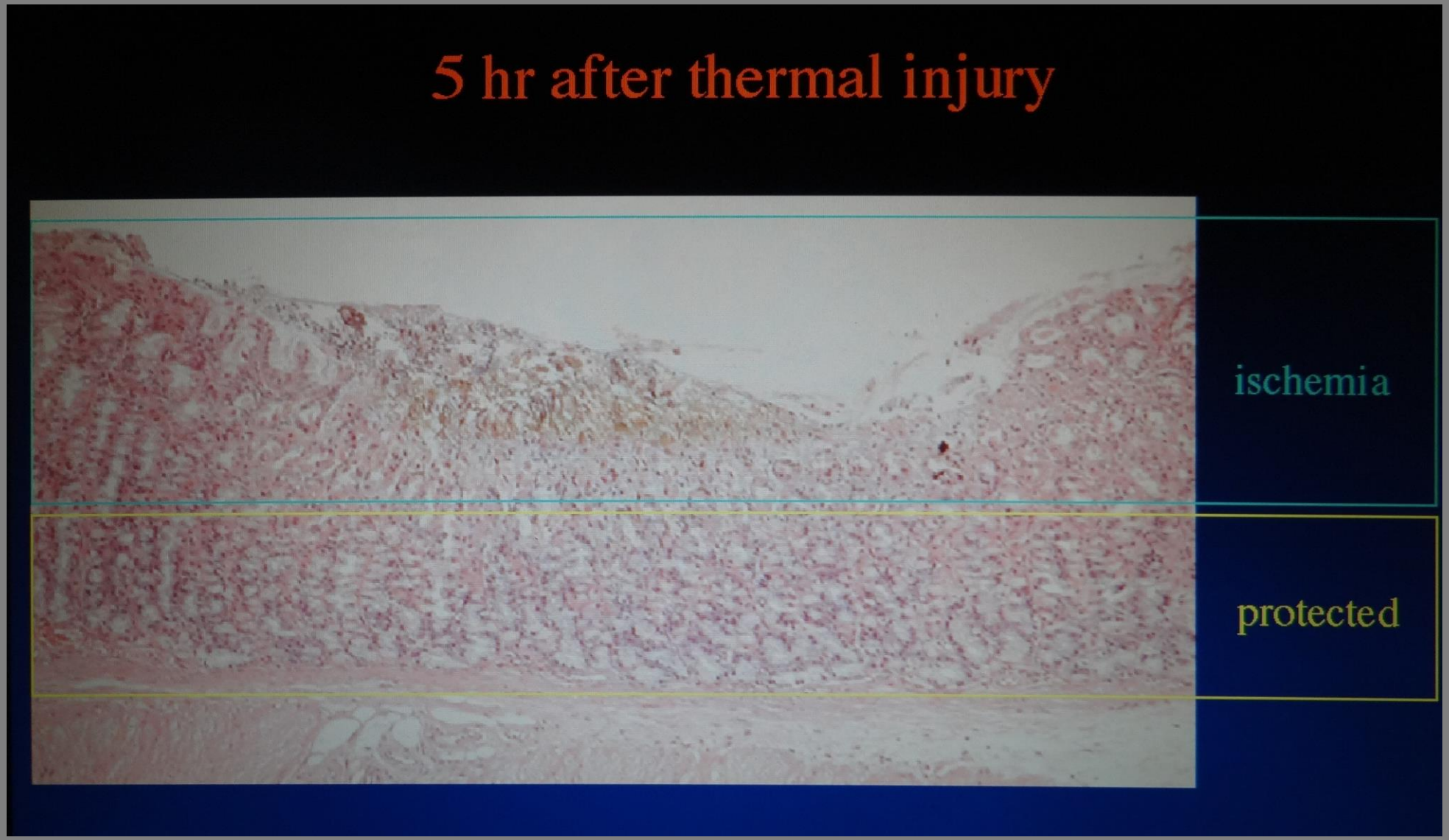
postcapillary venule at the base of gastric mucosa (PV-BGM)

A part of capillary blood can drain via vessels close to the base of the stomach.

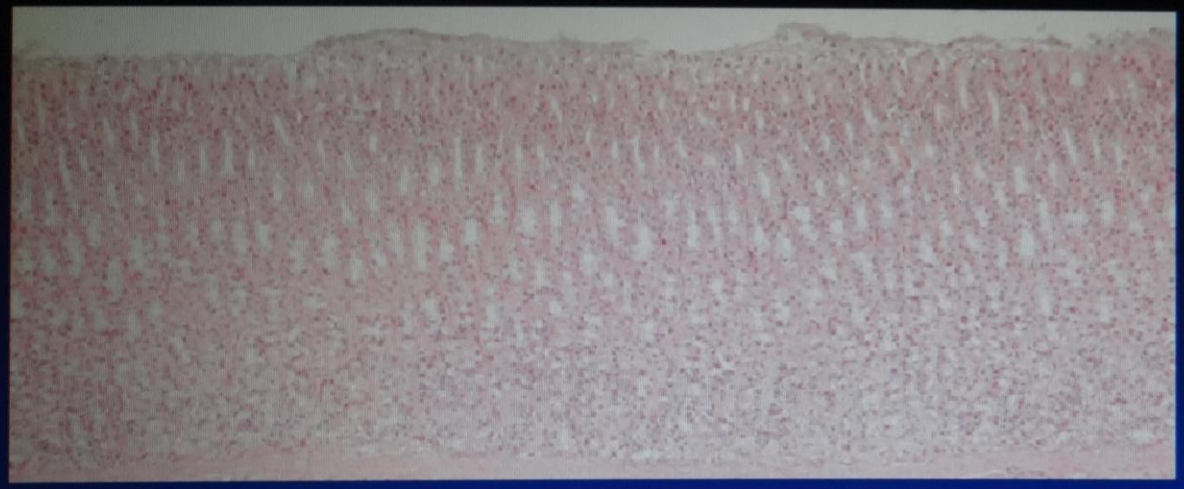


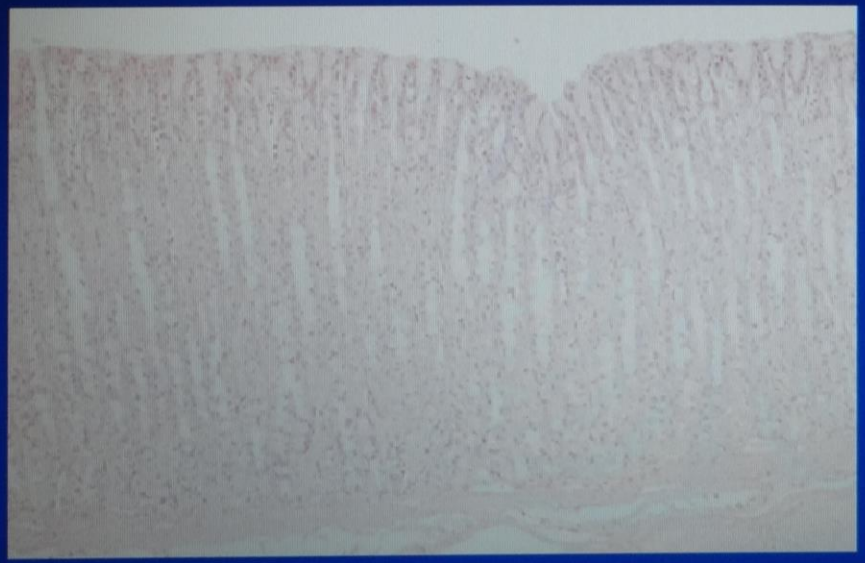
Diameter of the venule and the PV-BGM

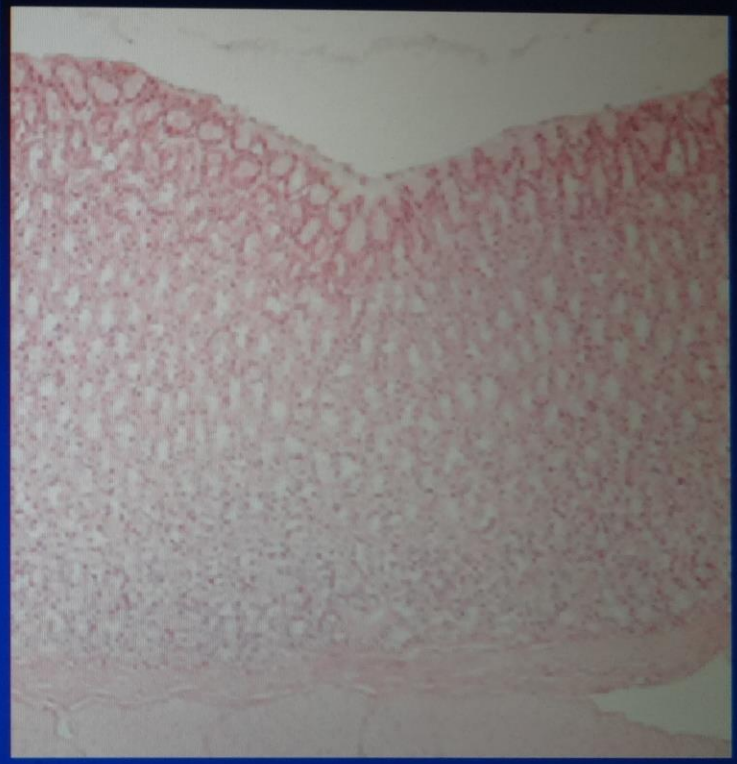
A possible defensive mechanism in the basal region of the gastric mucosa



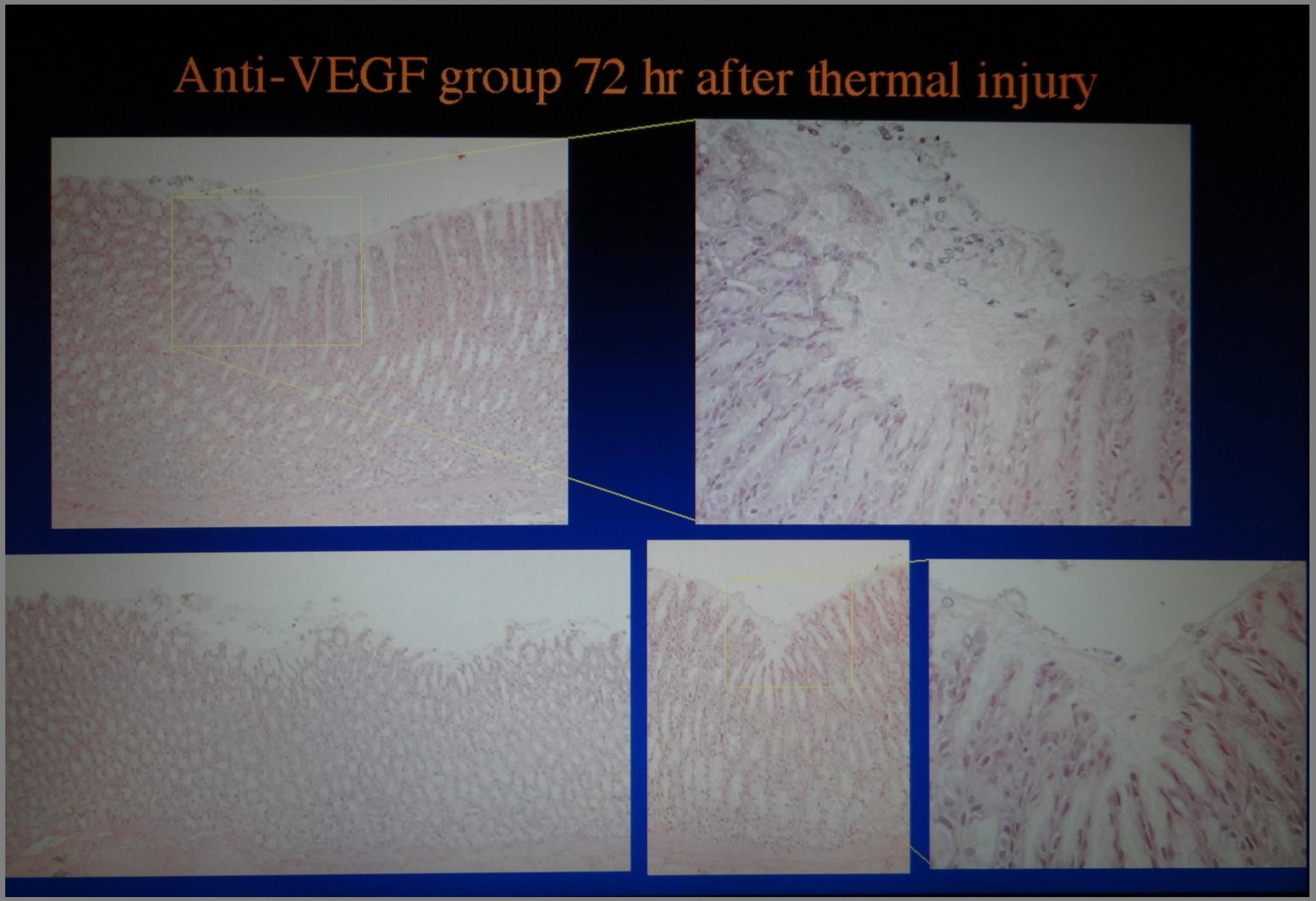
Saline group 72 hours after thermal injury



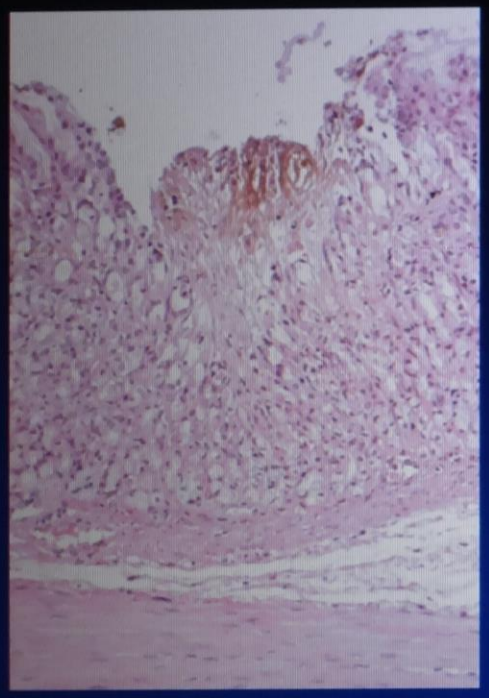




Anti-VEGF group 72 hr after thermal injury



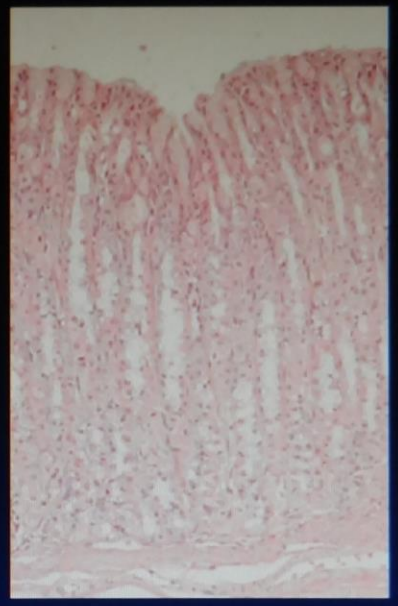
Effect of anti-VEGF antibody on healing of gastric erosions

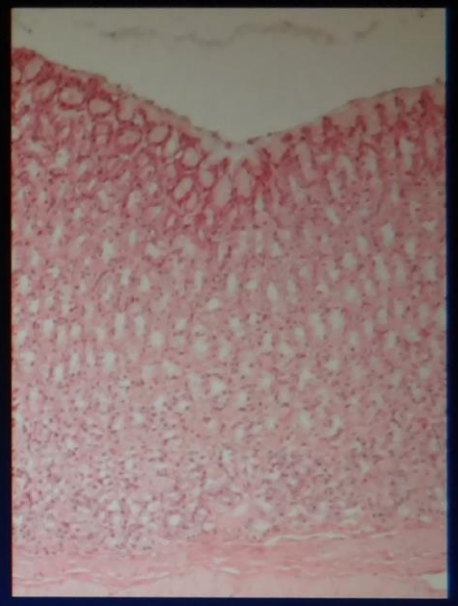


5 hr after thermal injury

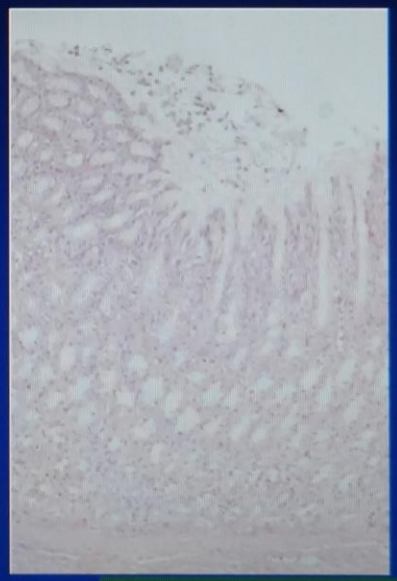
saline or normal goat IGG i.v.

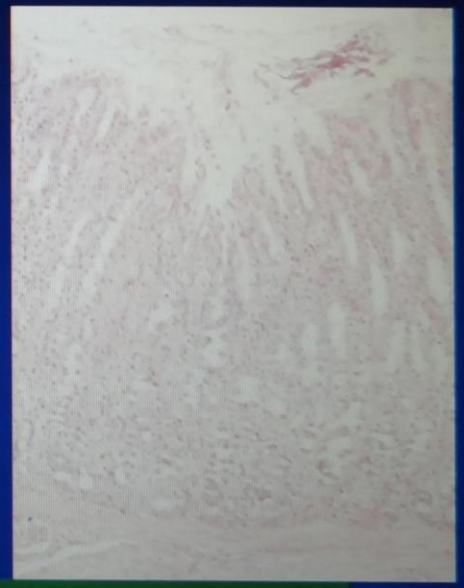
anti-VEGF antibody i.v.





erosion 2/6 exudative lesion 0/6





erosion 6/6# exudative lesion 5/6*

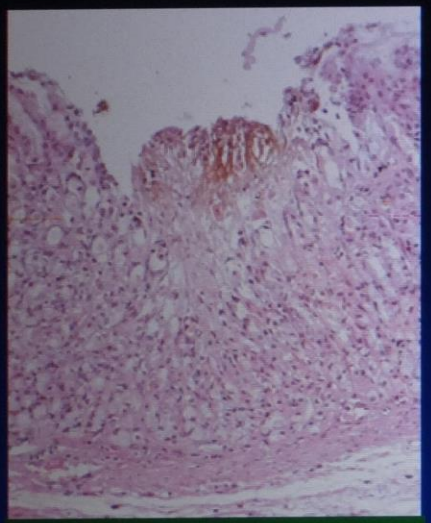
*p<0.05

#p=0.06

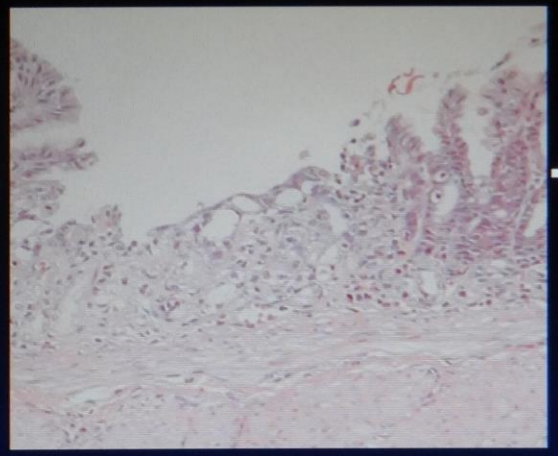
72 hr after thermal injury

Possible effect of anti-VEGF antibody on development of gastric ulcer

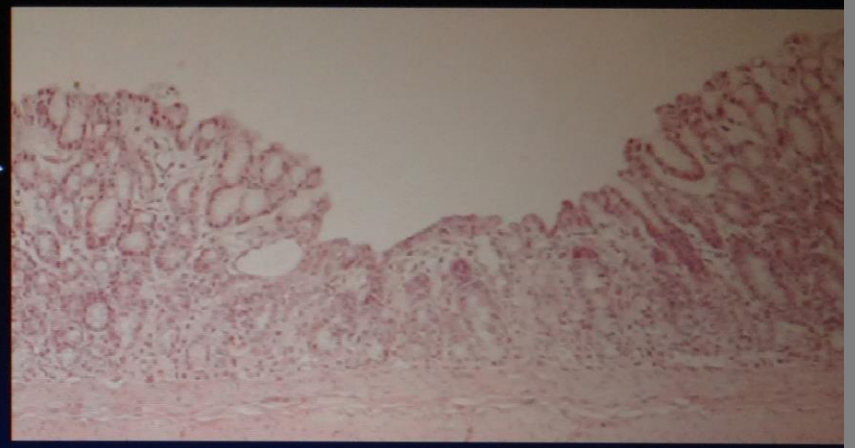
saline or normal goat IGG i.v.



5hr after thermal injury

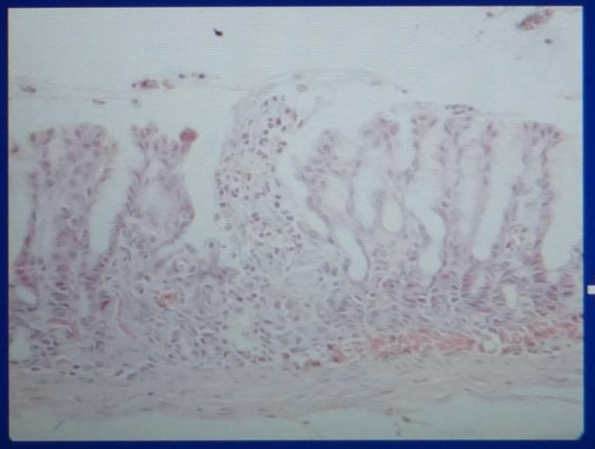


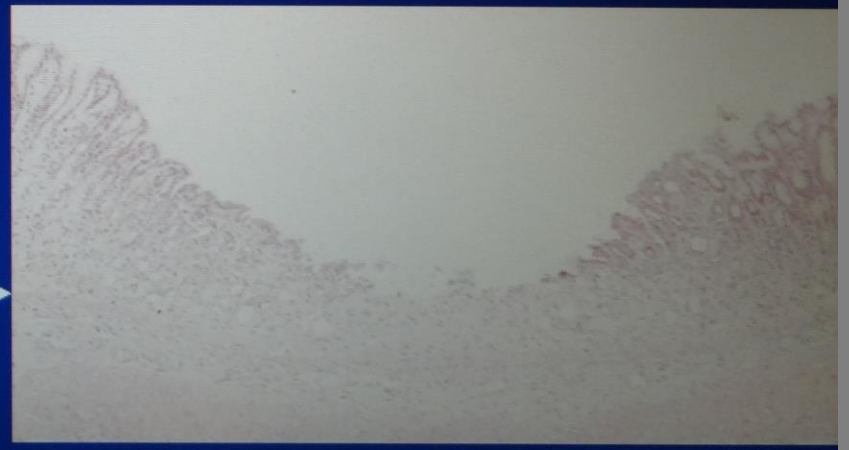
24 hr after thermal injury

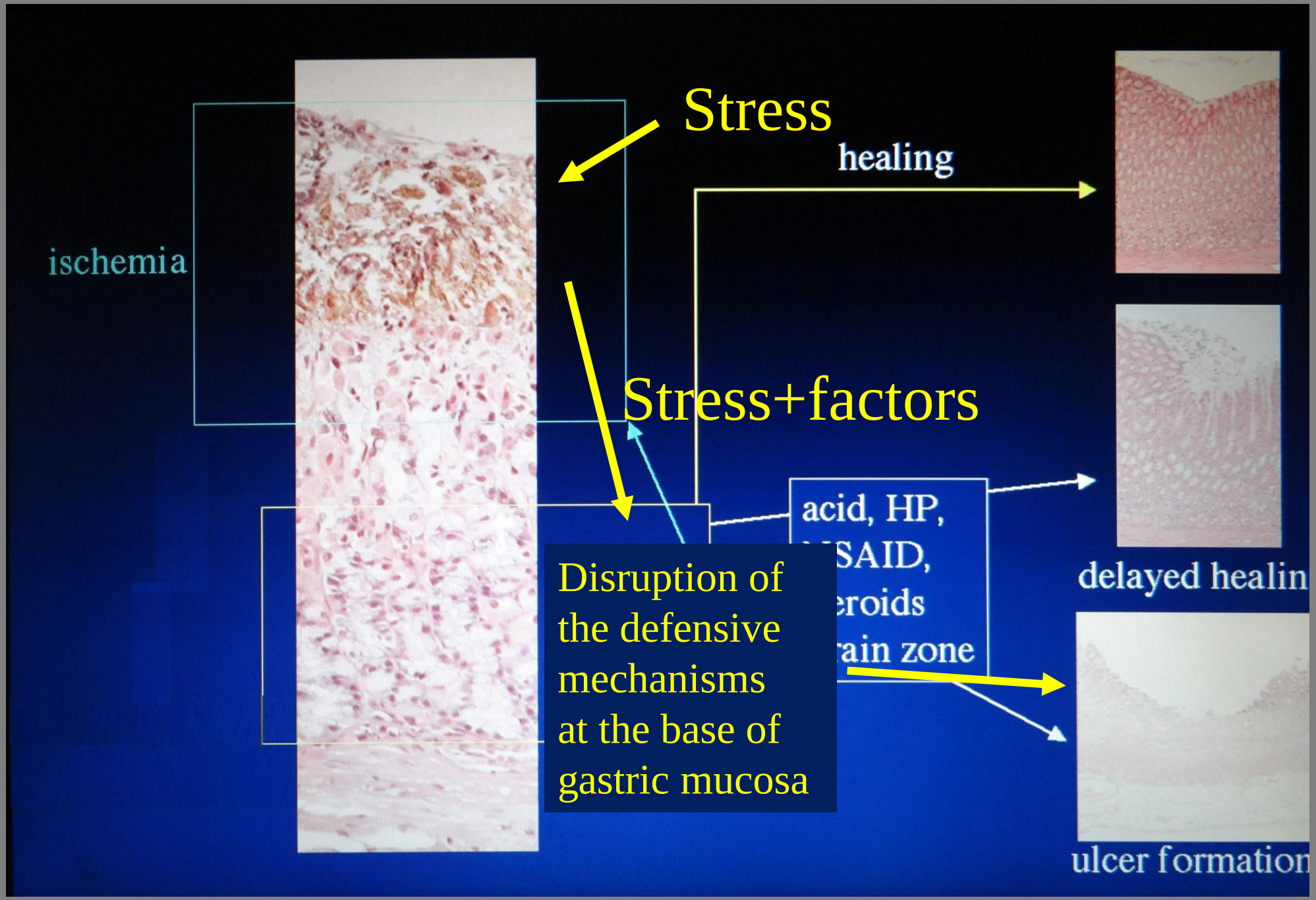


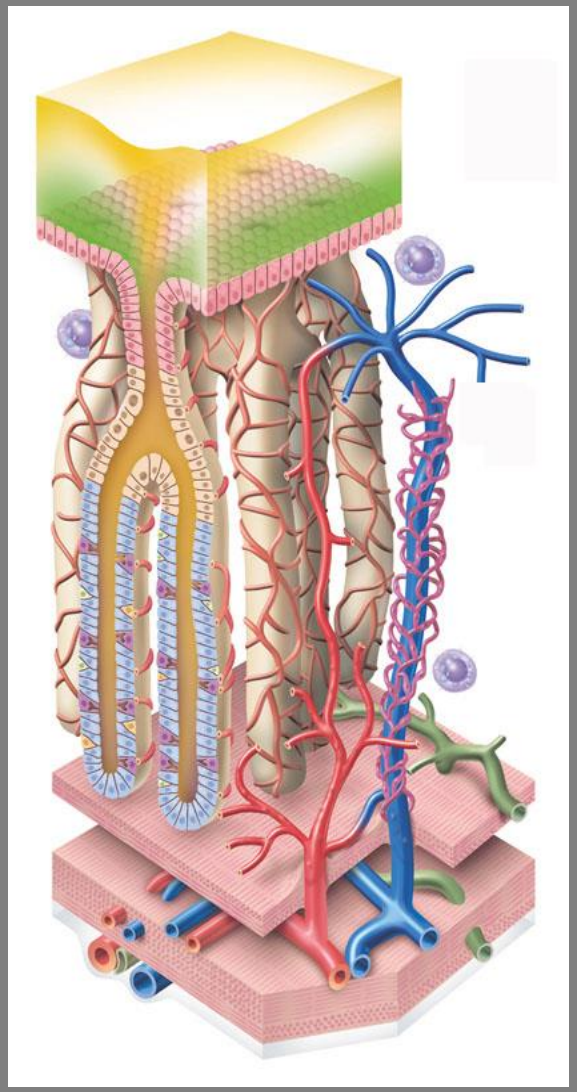
72 hr after thermal injury

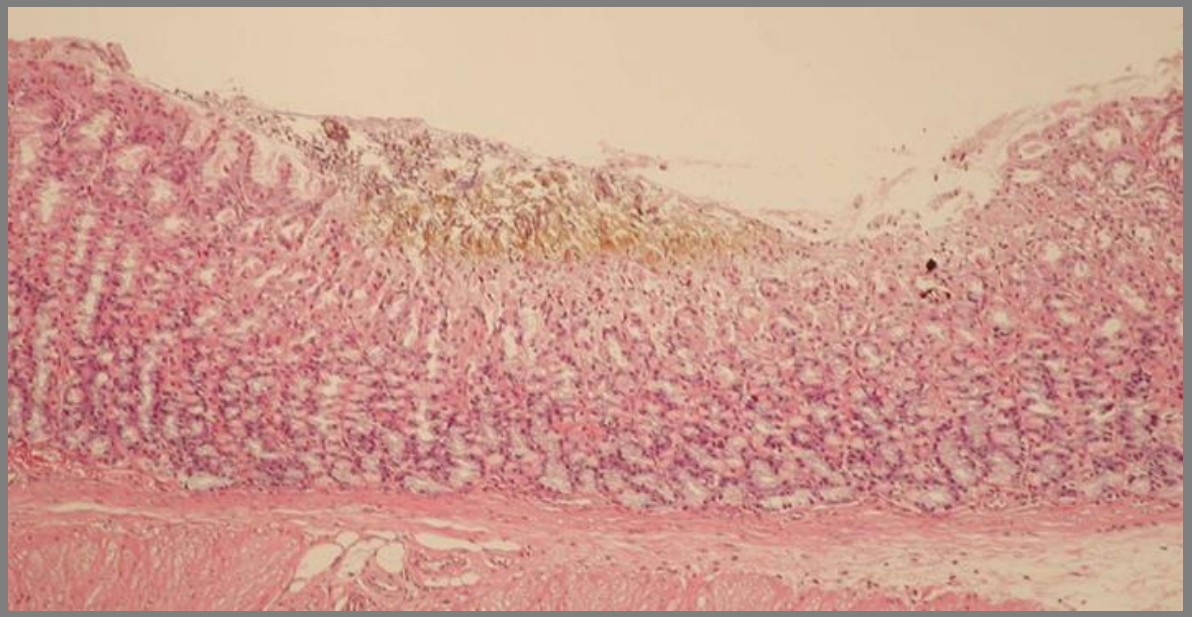
anti-VEGF antibody i.v.





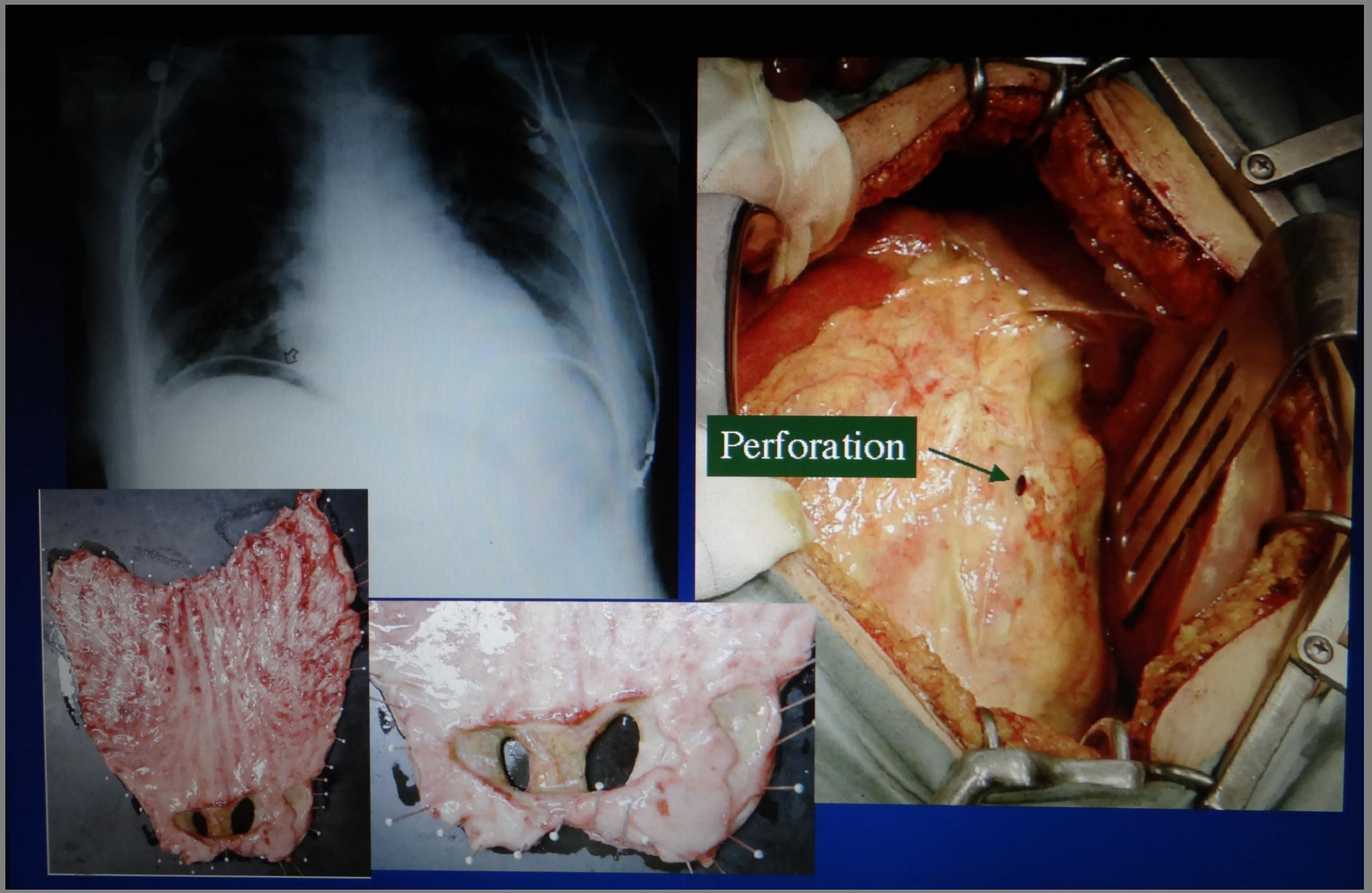

Stress
healing
ischemia
Stress+factors
acid, HP,
SAID,
eroids
ain zone
delayed healin
Disruption of
the defensive
mechanisms
at the base of
gastric mucosa
ulcer formation

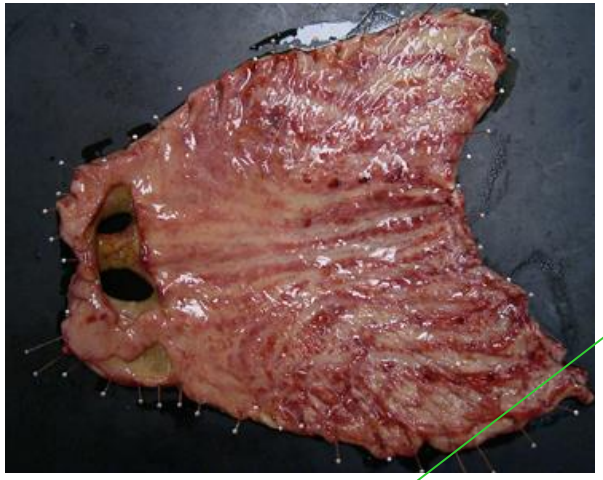


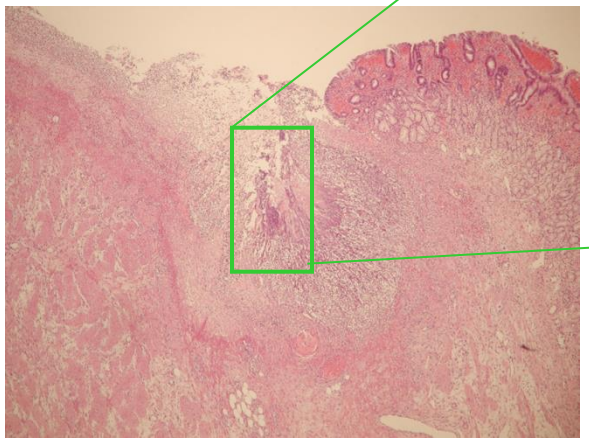


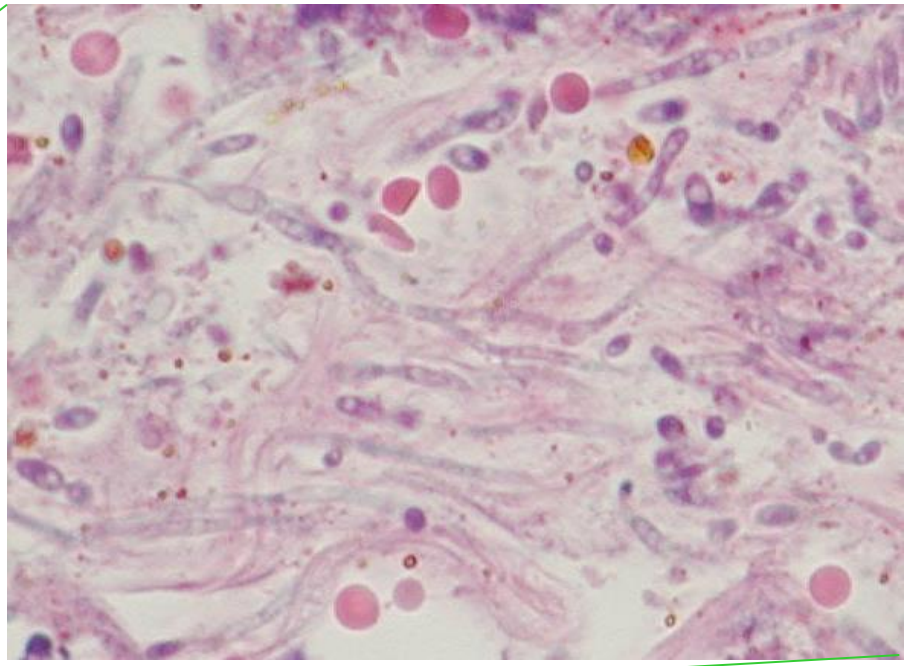
A possible defensive mechanism in the basal region of the gastric mucosa

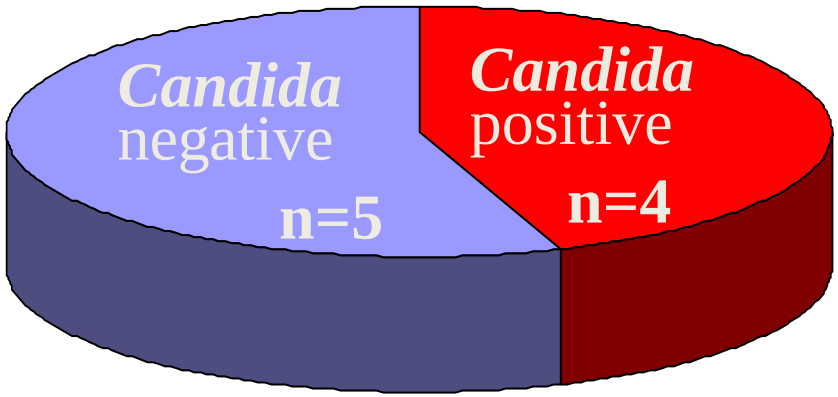
Presented by
Dr. Masashiko Nakamura


Perforation

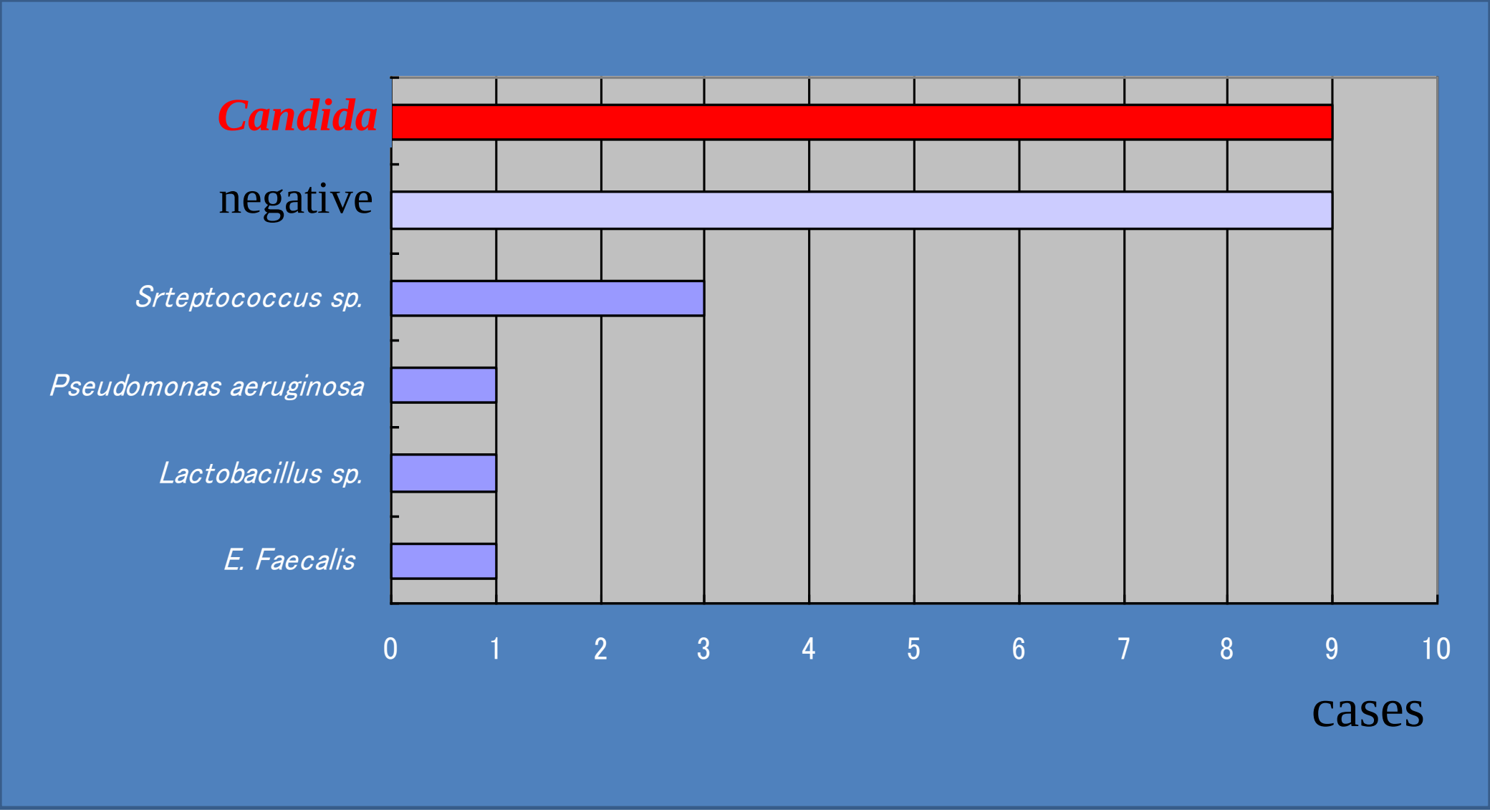








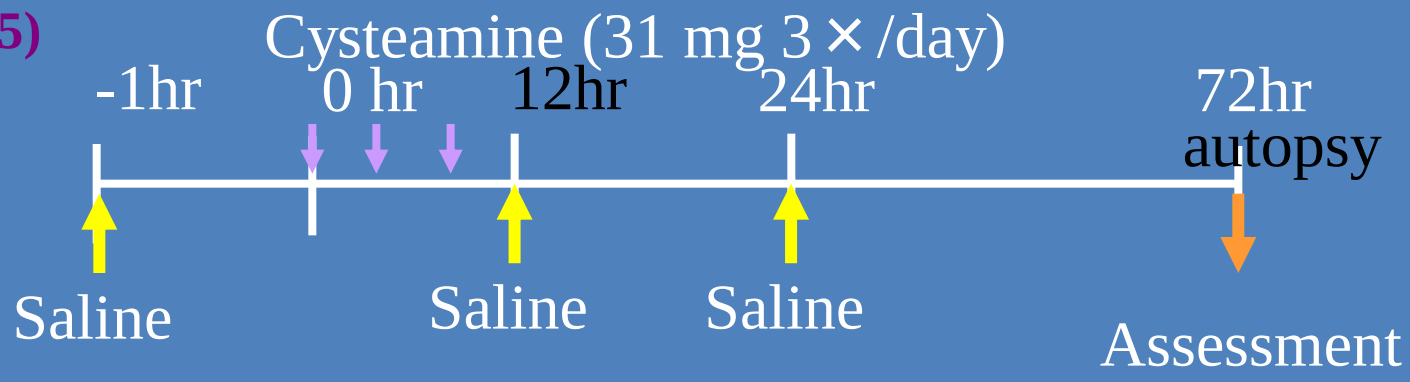
In the resected stomach, the hypha of *Candida* with massive granulocytes infiltration were observed at the base of ulcer microscopically.



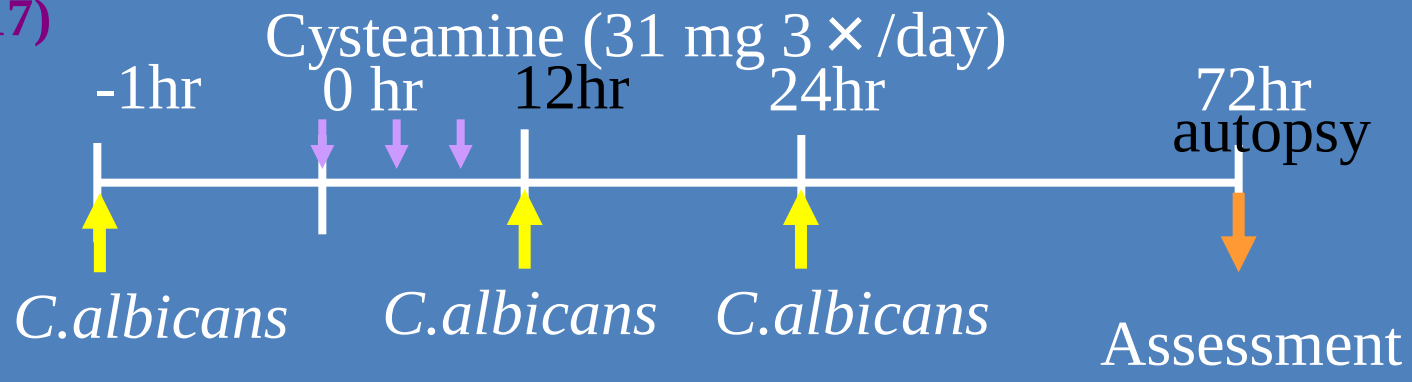
Biological culture isolated from the peritoneal fluid taken within 24 hours after onset of perforation

Experimental analysis: Method

Saline group (n=15)



***Candida* group (n=17)**



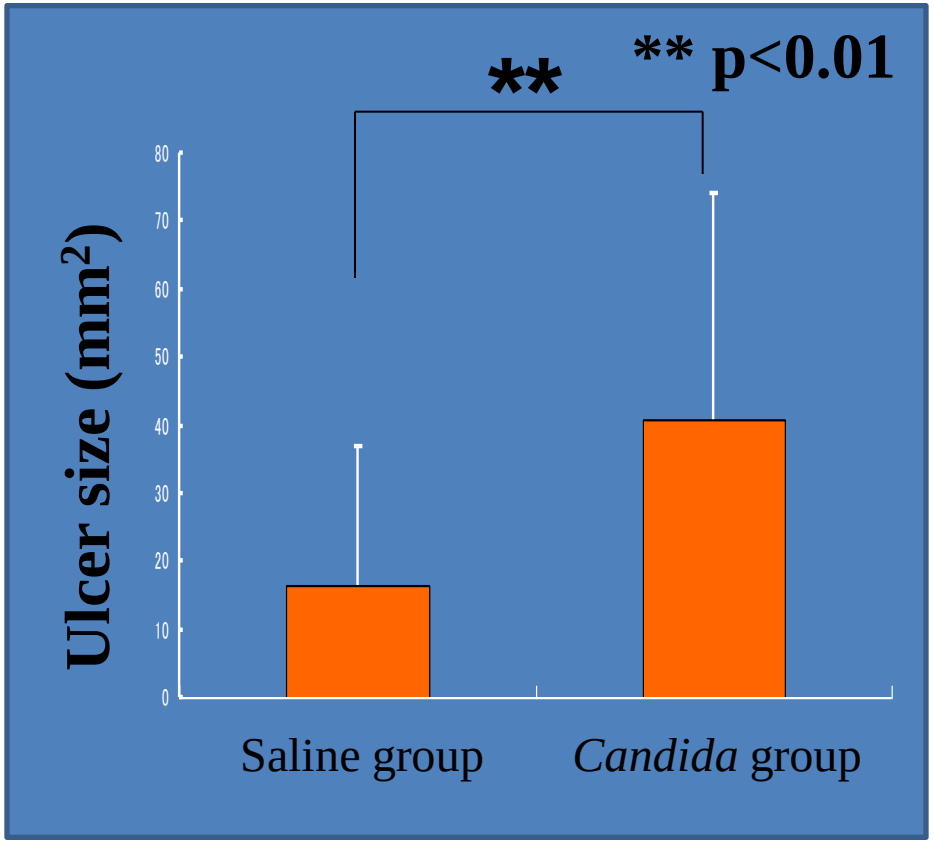
Cysteamine (31mg/100g) was administered thrice on Day 1 to Male Wistar rats in the *Candida* group (n=17) and the saline group (n=15).

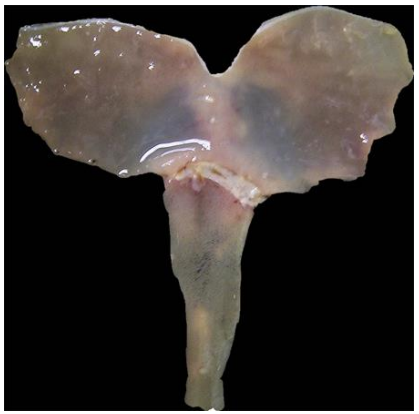
Candida albicans at a density of 10^8 in 0.5ml of saline was administered 1 hour before, 12 hours and 24 hours after the first administration of cysteamine in the *Candida* group.

Incidence of duodenal ulcer perforation

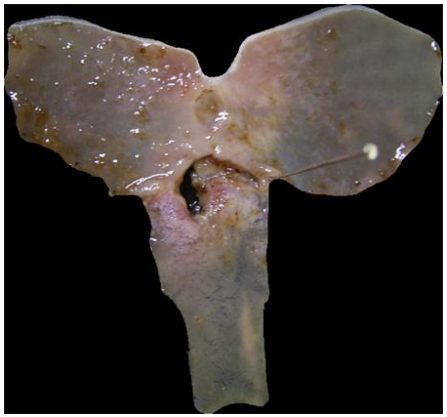
Fisher's exact test $p<0.01$

	Positive	Negative	rate
Saline	4	11	26.7%
Candida	16	1	94.1%





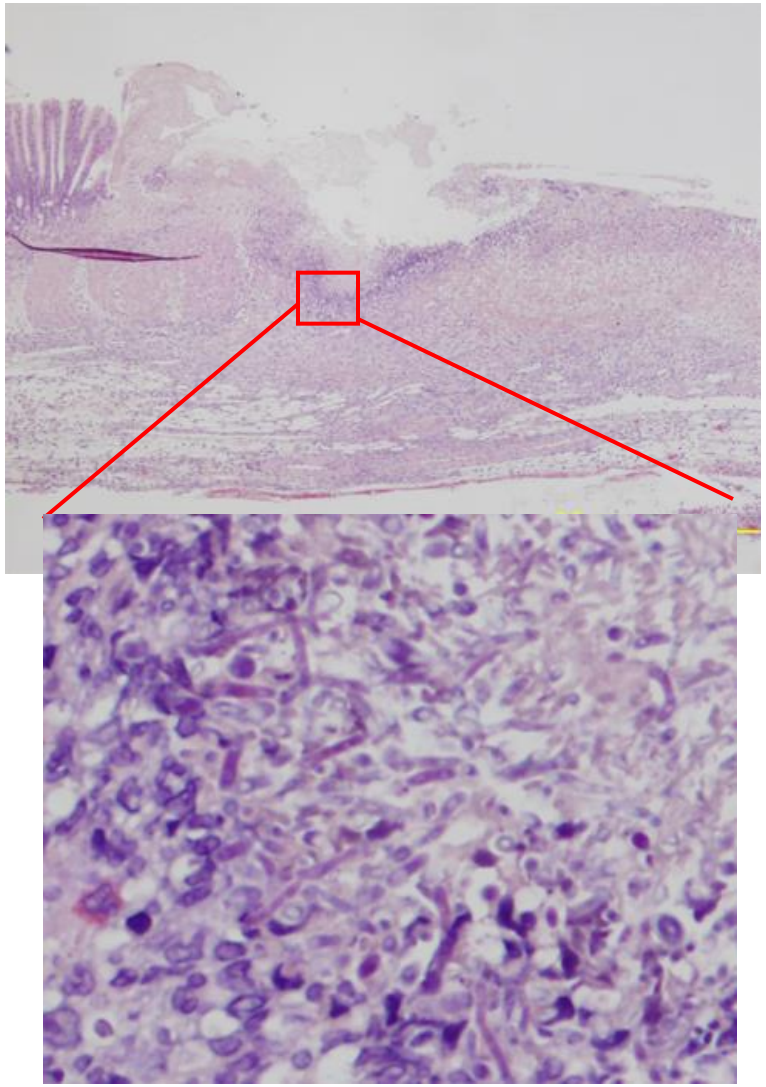
Saline group

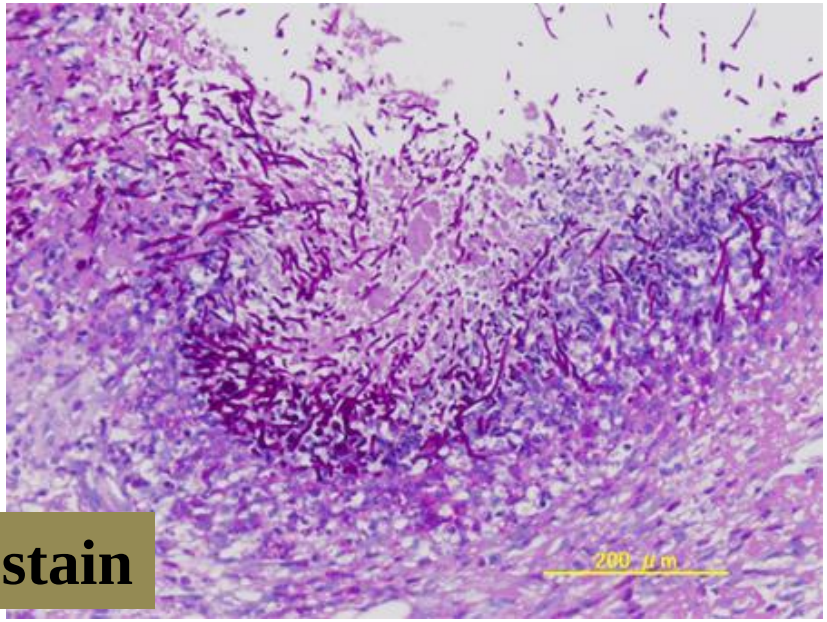


***Candida* group**

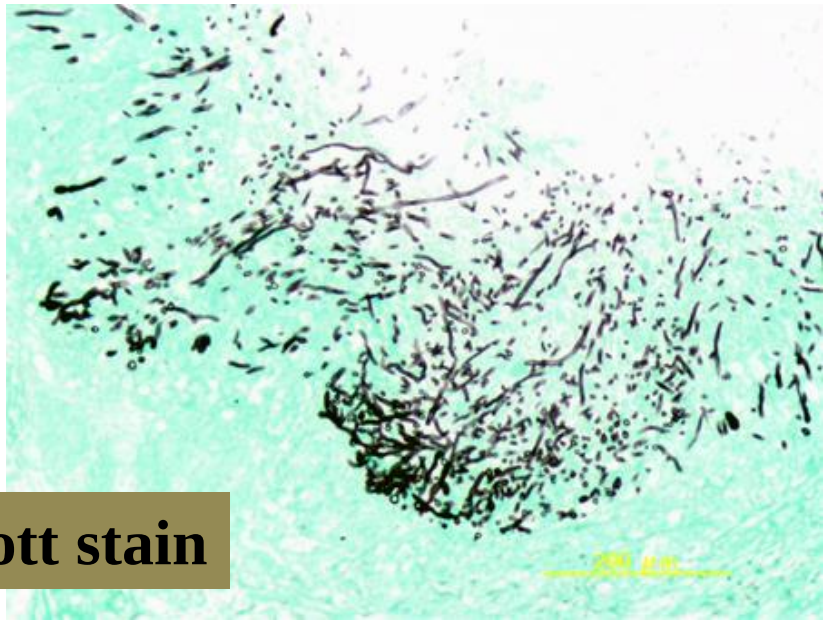
Pathological findings

H&E. stain



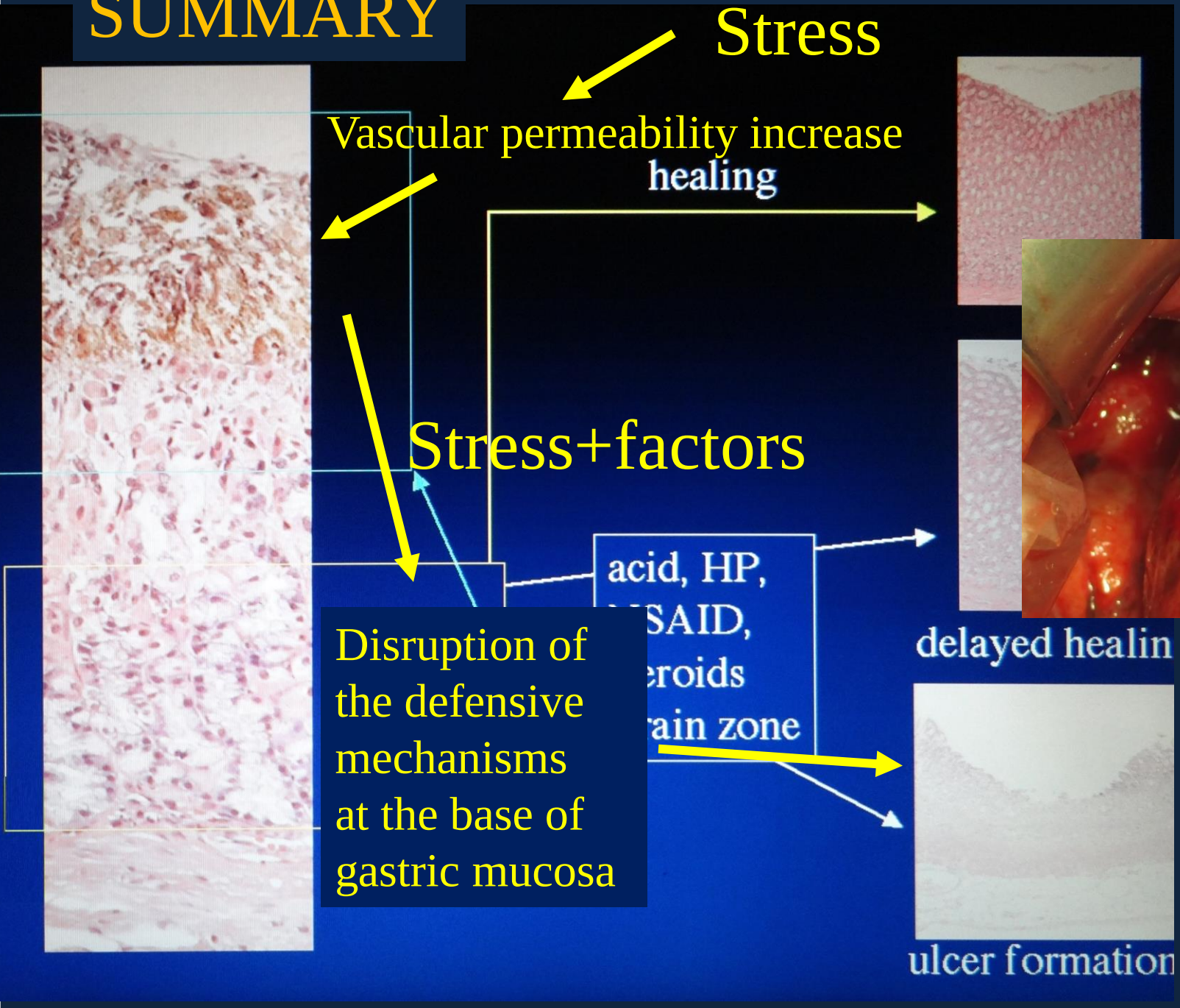


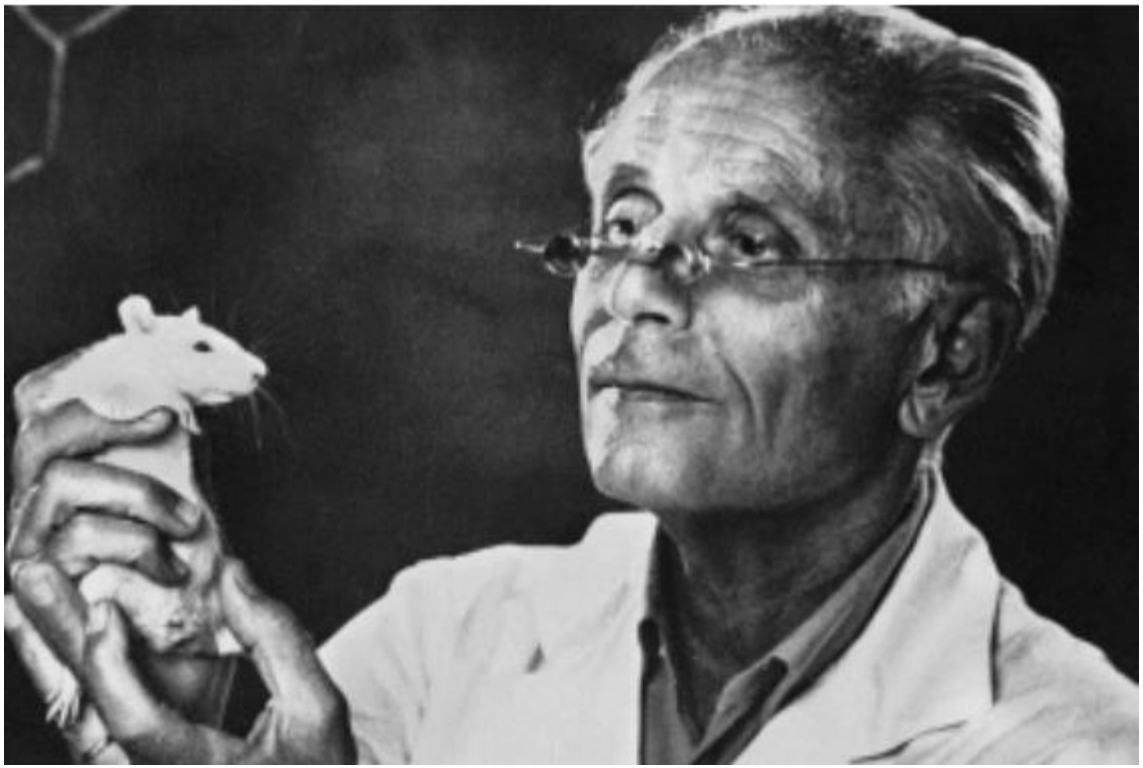
PAS stain



Grocott stain

SUMMARY


Stress
Vascular permeability increase
healing
Stress+factors
acid, HP,
SAID,
roids
ain zone
Disruption of
the defensive
mechanisms
at the base of
gastric mucosa
delayed healin
ulcer formation
aggravation
Candida



“Stress” is the crucial factor from perspectives of the surgeon in 2016, 80 years after the article of Hans Selye.