Pneumopéritoine et Cancer

M Canis

JL Pouly

G Mage **

B Rabischong

S Matsuzaki

R Botschorischvili

N Bourdel

AS Gremeau

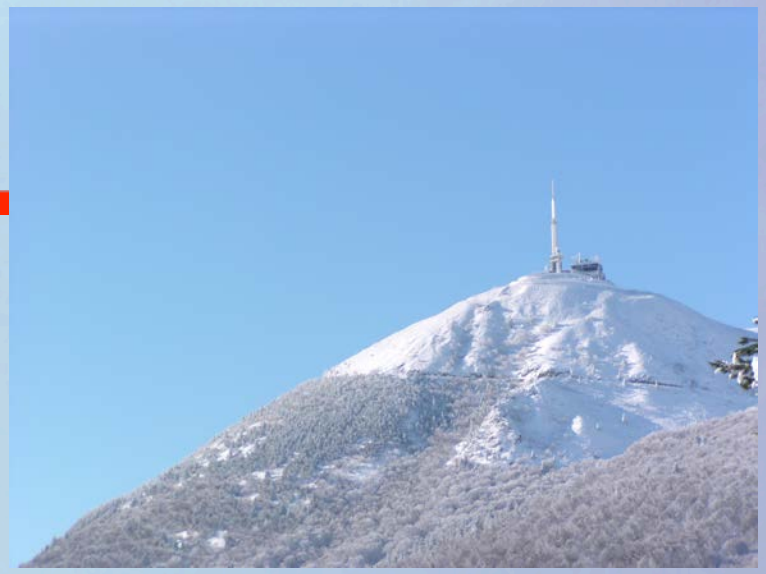
AG Kaemerlen

C Houlle

S Campagne

S Curinier

Dept Gyn Obst

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Tél : 33 (0)4 73 15 20 50 - Fax : 33 (0)4 73 15 20 79
@ : secretariat@cice.fr
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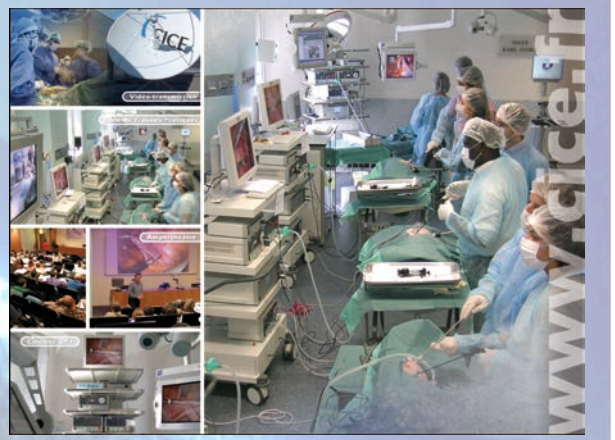
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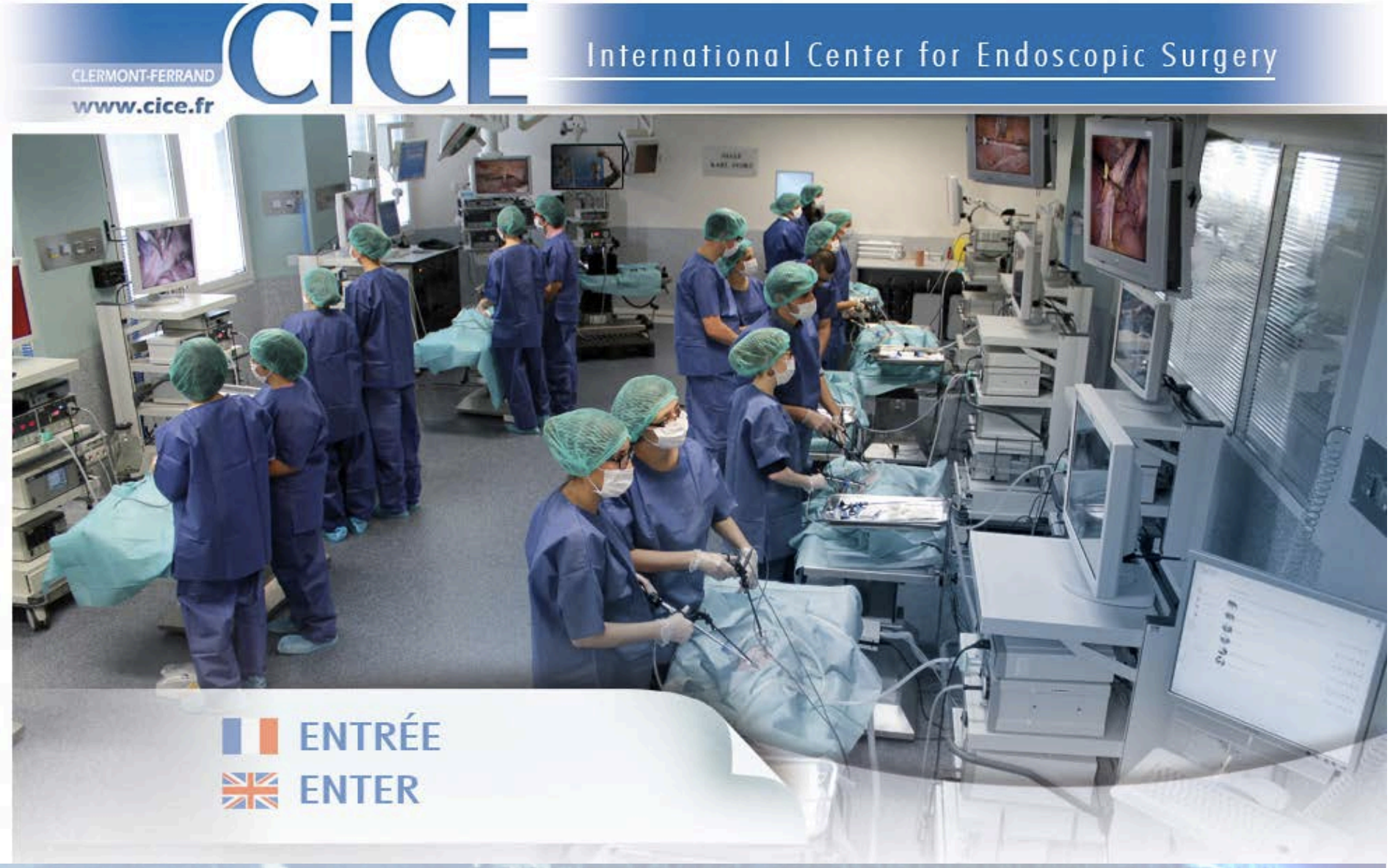
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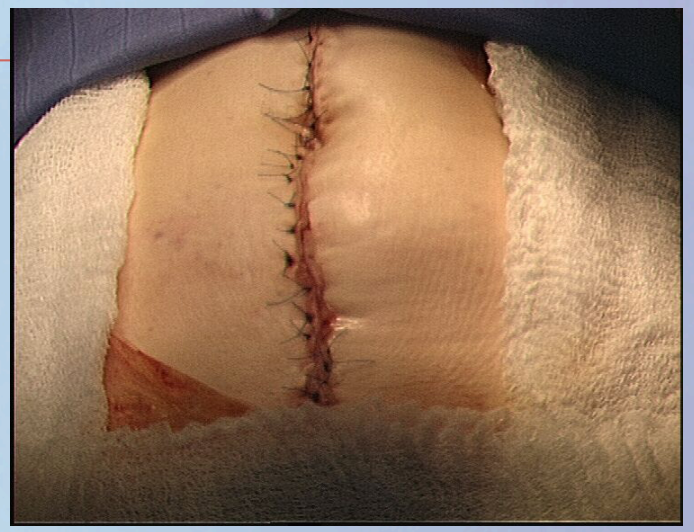
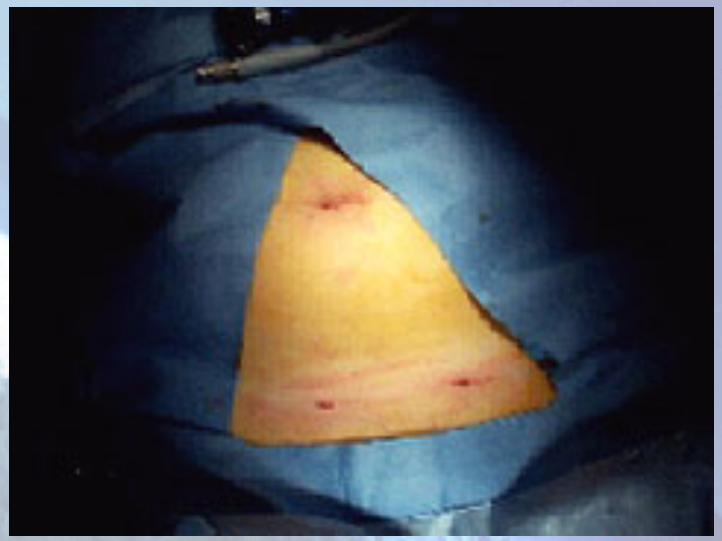
Dept Anesth.

Endoscopy: Revolution !

- Decreased
  - Scars
  - Trauma
  - Pain
  - Hospital stay
  - Costs





REVOLUTION ??

Mais !!

Adhesiolysis incidence ; USA 1988 = 1994

Ray et al., J Am Coll Surg 186: 1–9. 1998

Human Reproduction Vol.19, No.8 pp. 1877–1885, 2004
Advance Access publication June 3, 2004

DOI: 10.1093/humrep/deh321

Adhesion-related readmissions following gynaecological laparoscopy or laparotomy in Scotland: an epidemiological study of 24 046 patients

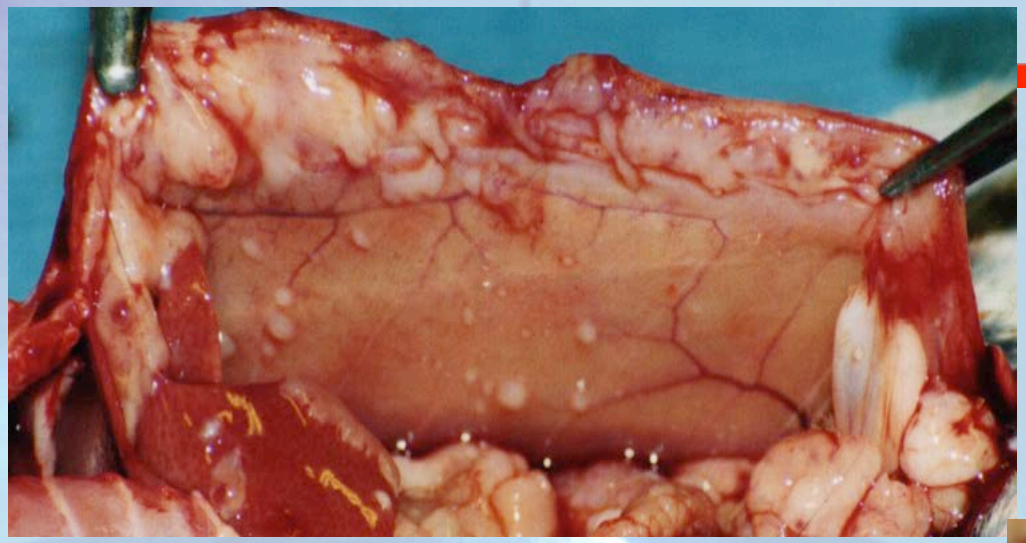
A.M.Lower[1,6], R.J.S.Hawthorn[2], D.Clark[3], J.H.Boyd[3], A.R.Finlayson[3], A.D.Knight[4] and A.M.Crowe[5] on behalf of the Surgical and Clinical Research (SCAR) Group

[1]Isis Fertility Centre, Colchester CO4 9YA, [2]Southern General NHS Trust, Glasgow G51 4TF, [3]Information and Statistics Division, Common Services Agency, Trinity Park House, Edinburgh EH5 3SQ [4]Evicom, Twickenham TW1 2AA, and [5]Corvus, Buxted TN22 4PB, UK

[6]To whom correspondence should be addressed. E-mail: adrian@lower.com

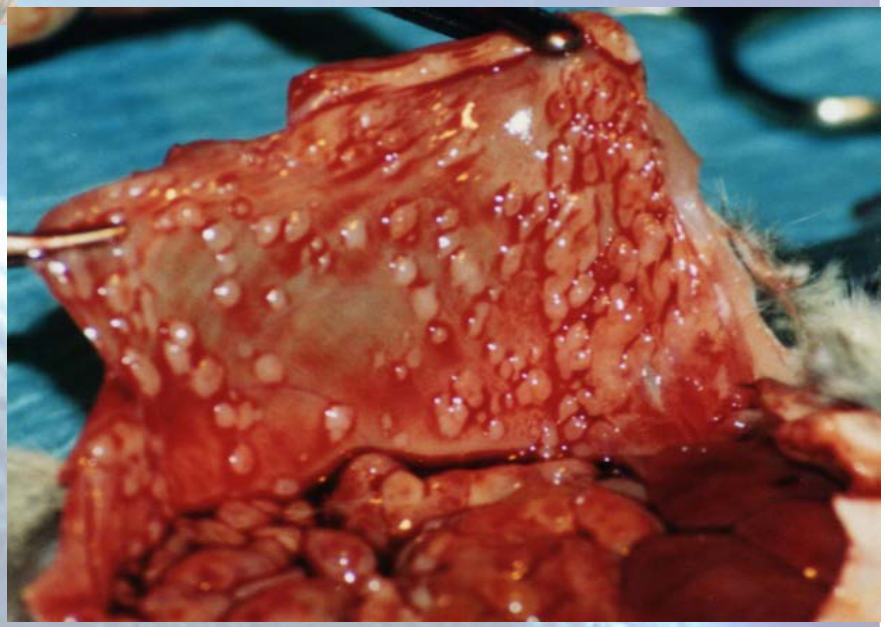
CONCLUSIONS: With the exception of laparoscopic sterilizations, open and laparoscopic gynaecological surgery are associated with comparable risks of adhesion-related readmissions.

But!!

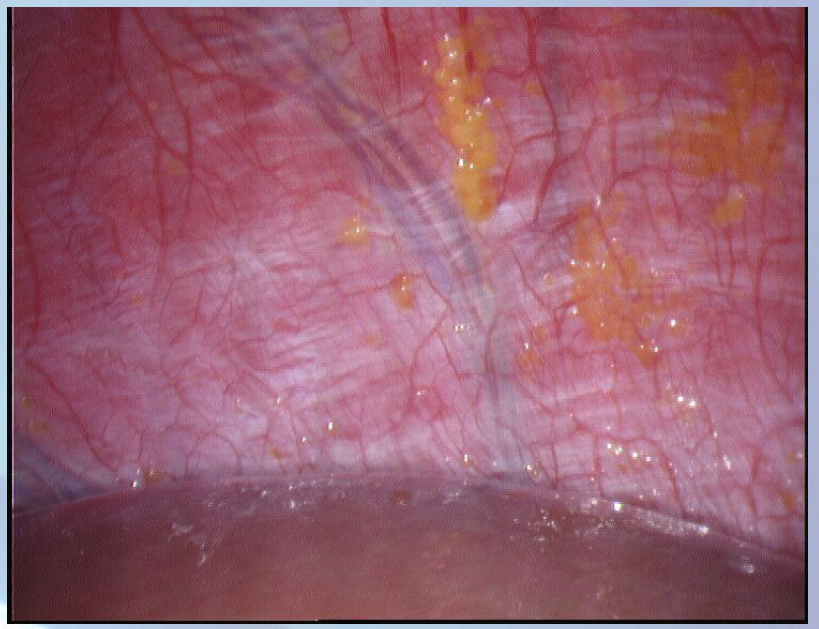


Laparotomy

Laparoscopy



Révolution ?



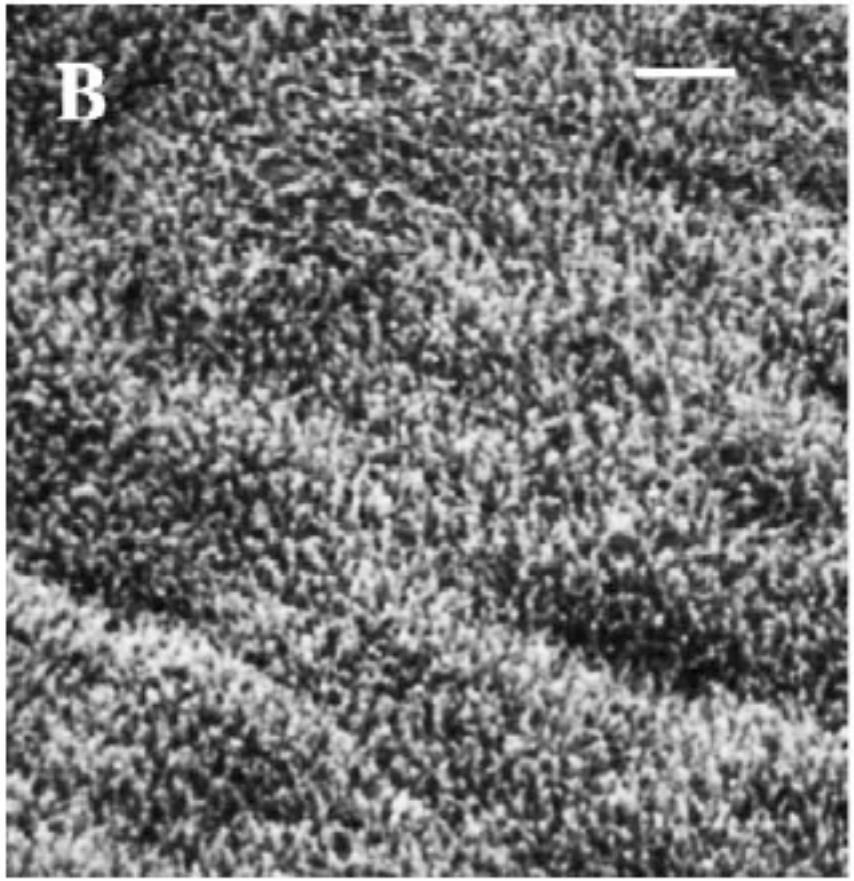
Open

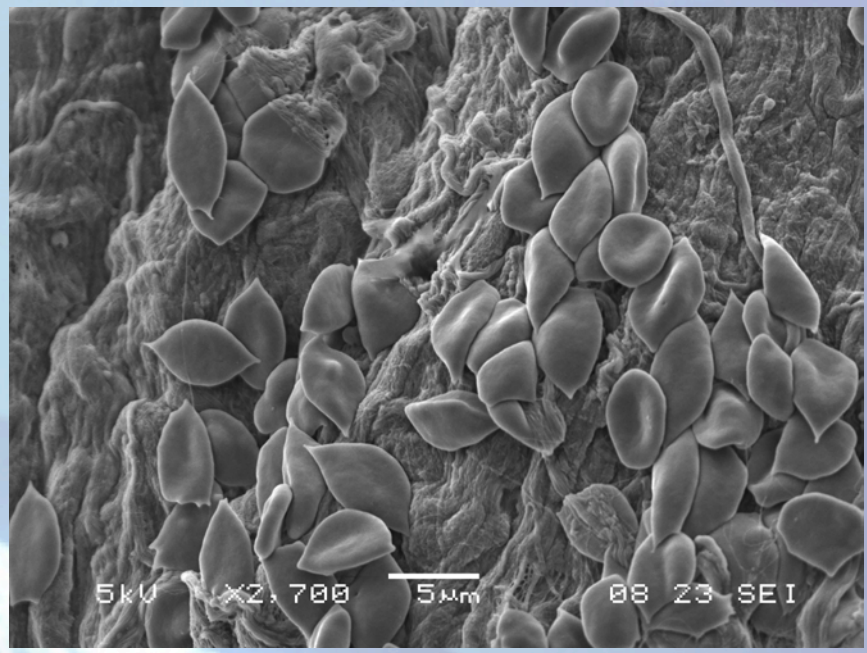
difficult to change

Closed

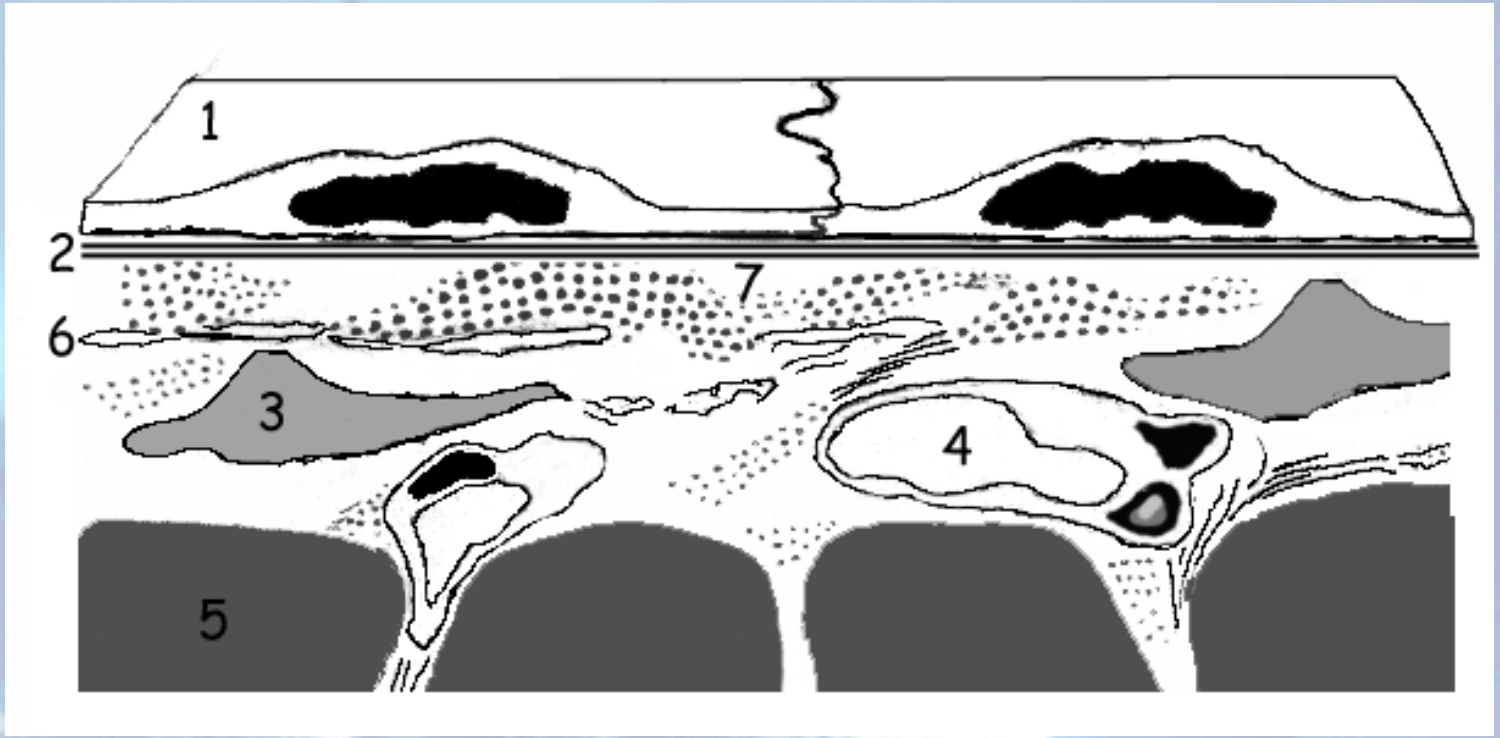
easy to adapt

Peritoneal Membrane





Peritoneal Histology



1: cellules mésothéliales, 2: membrane basale, 3: Fibroblaste,
4 : capillaires sanguins, 5: muscle, 6: fibres elastiques, 7 collagène

Which peritoneal surface area is important ?

- The anatomical area
- The area accounting for microvilli
- The area of peritoneal vessels (capillaries which is essential for exchanges)
- The volume of the inter cellular matrix

Peritoneal surface area

- It was recently measured in 10 non eviscerated cadavers

- The result was 14 323 ± 824 cm^2

Albanese et al Surgical and Radiologic Anatomy 2009

Peritoneal surface area

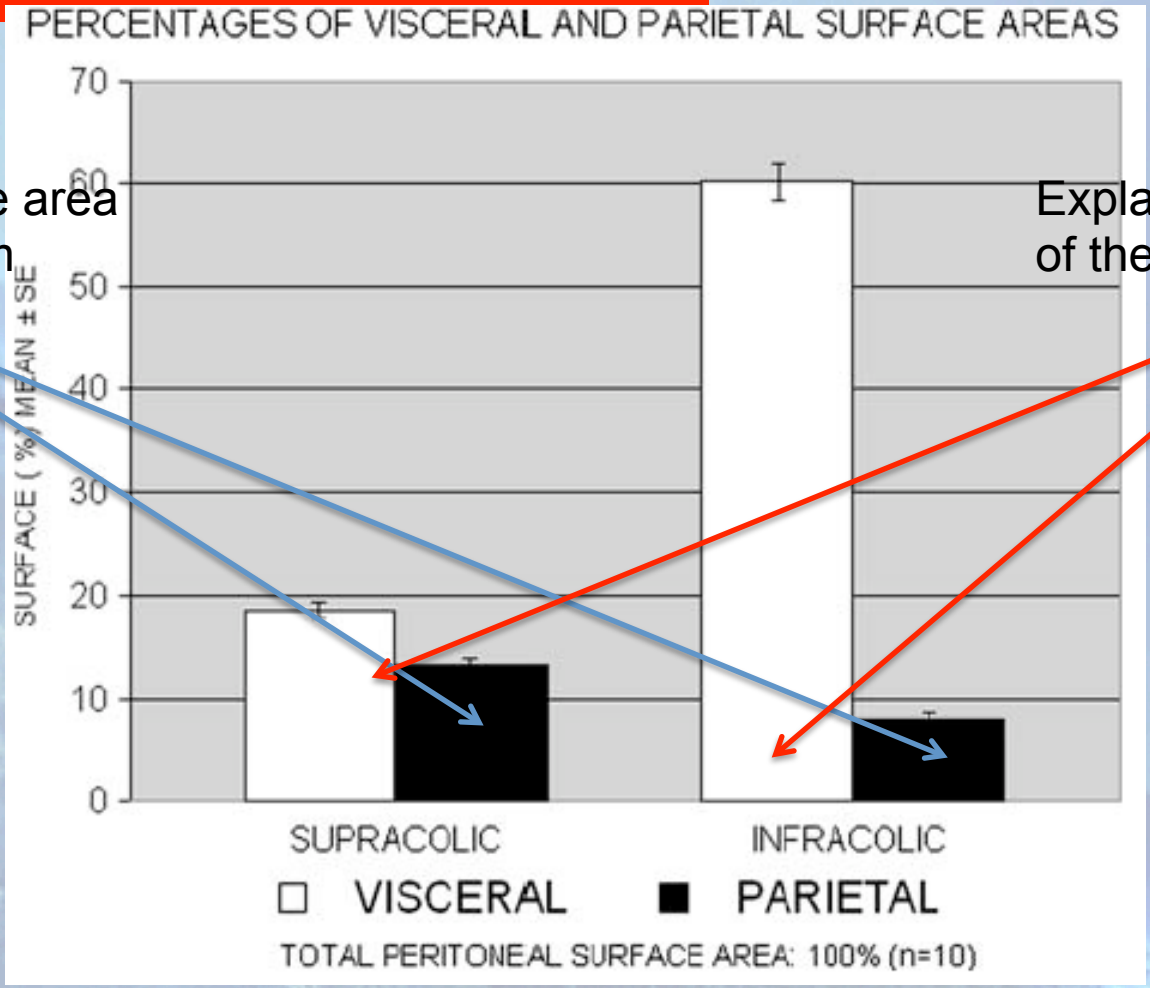
- Among 14 323 ± 824 cm^2
  - The visceral peritoneum represented
    - 81.89 % ± 0.99%
  - and the parietal peritoneum
    - 18.11% ± 0.99 %

Albanese et al Surgical and Radiologic Anatomy 2009

Peritoneal surface area

Explained by the area of the diaphragm

Explained by the area of the mesentery



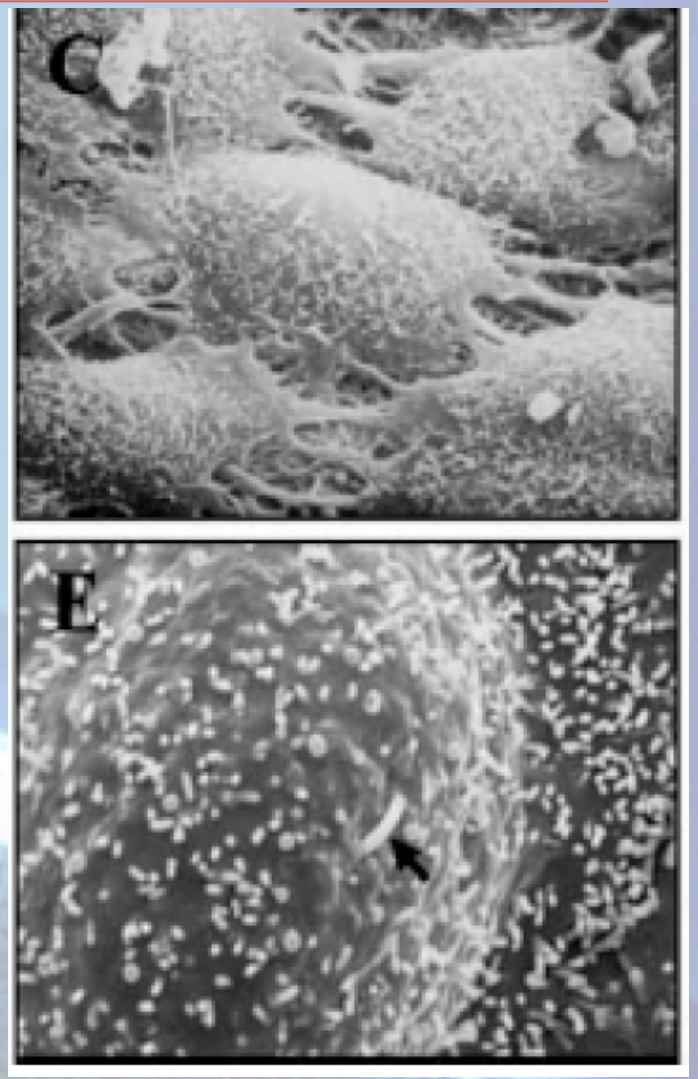
Albanese et al Surgical and Radiologic Anatomy 2009

Peritoneal surface area

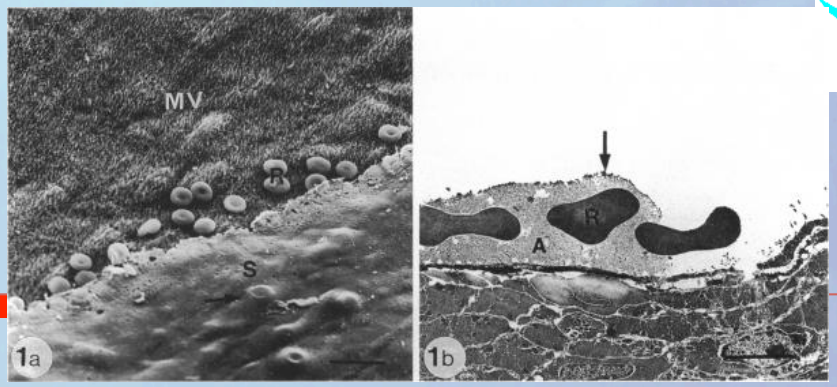
- 1 – Microscopic peritoneal surface area: ie accounting for microvilli

Microvilli

- The luminal surface of mesothelial cells has numerous microvilli, which vary in length, density and shape
- These microvilli increase the mesothelial surface area up to 40m^2
- Microvilli protect the delicate mesothelial surface from frictional injury by entrapping water, serous exudates, and phospholids which act as lubricants for the cells.



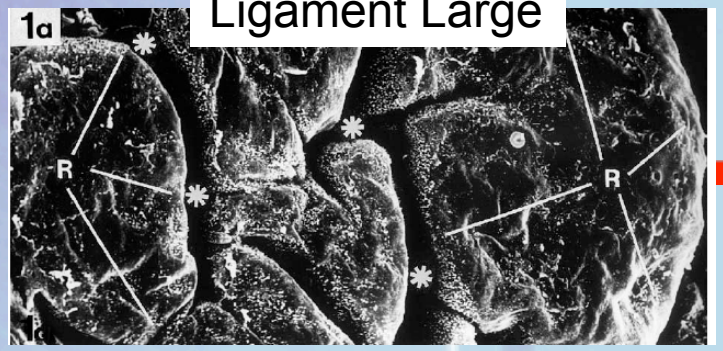
Microvilli



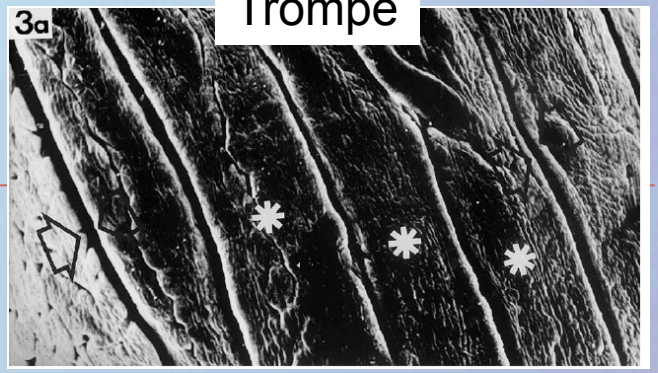
- The density of microvilli dépends on the area studied
  - - 230 /µ on the bladder
  - - 540 /µ on the spleen
  - Sometimes absent on the parietal and the diaphragmatic peritoneum (Di Paolo 2000)

- Most importantly ultrastructural changes on the surface of the cells clearly demonstrate that microvilli are dynamic structures.

Ligament Large

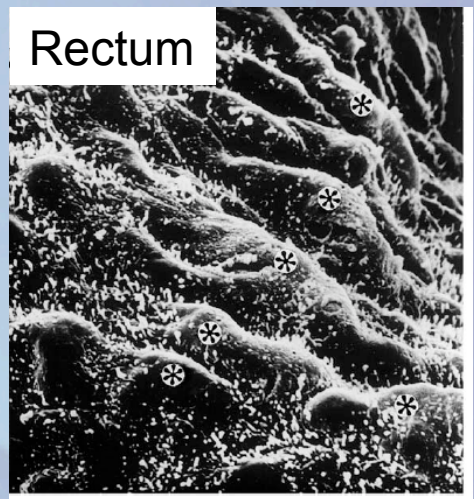


Trompe

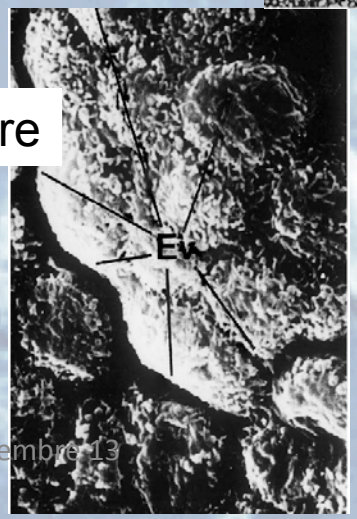


Utérus

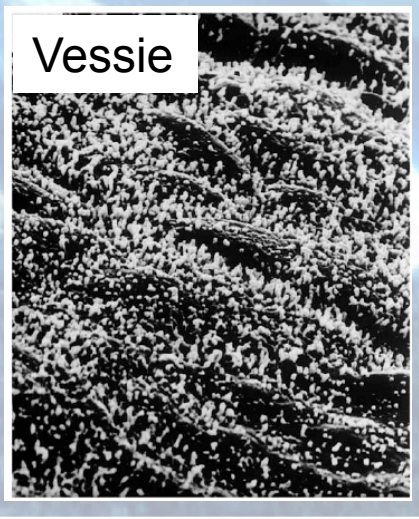
Rectum



Ovaire



Vessie



Michailova 2004, 2006

Functions of mesothelial cells

- The primary role of the mesothelium is
  - to maintain serosal integrity and function.
  - provide a protective barrier against abrasion and invading pathogens
  - secrete surfactant, proteoglycans and glycosaminoglycans to provide a slippery, non-adhesive surface to allow intracoelomic movements.
  - Major source of Plasminogen activators in serosal fluid which is important in fibrinolysis and the prevention of adhesions
  - secrete hyaluronan and other glycosaminoglycans which may prevent tumour cell adhesion.

  - They facilitate transport of fluid and cells across the serosal cavities,
  - present antigen to T cells
  - secreting cytokines, growth factors, ECM, proteases and other inflammatory mediators participate in the induction and resolution of inflammation and tissue repair.

2 main morphologic types of cells

	Epidermoid	Cubic
•Nuclear	Ovoid	Large
•Mitochondria	rare	Numerous
•REG	+	+++
•Golgi	+	+++
•Microtubules	+	+
•Microfilaments	+	+++

Peritoneal Mesothelium of the Genital Tract

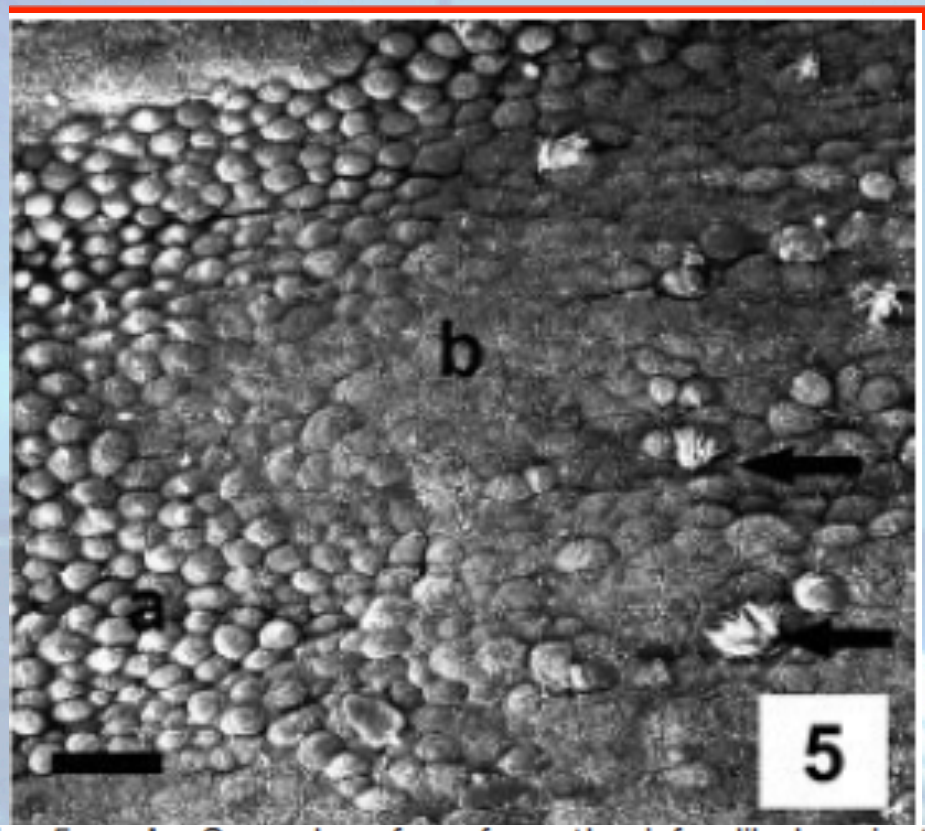


Fig. 5. **a,b:** Serosal surface from the infundibulum in transitional area between the oviductal epithelium (a) and the mesothelium (b). Observe that the transition between the mucosa and serosa was gradual, with oviductal ciliated cells penetrating between mesothelial cells (arrows). Scale bar = 20 μm.

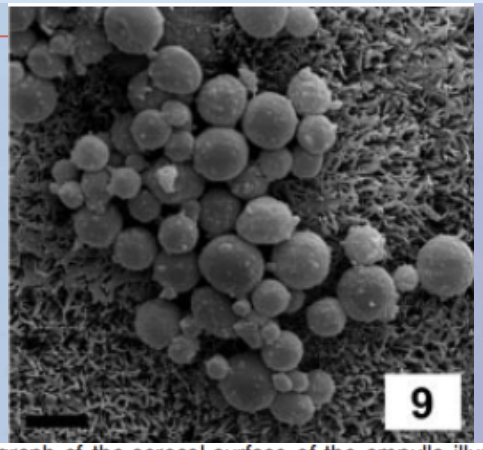
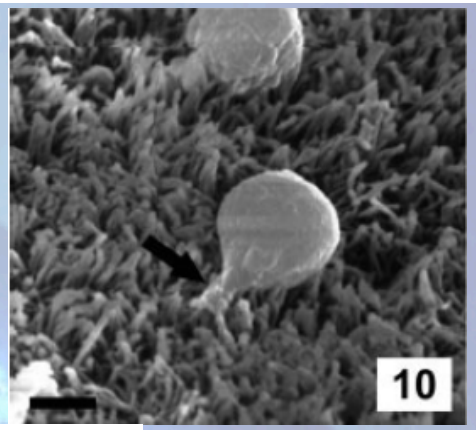


Fig. 9. This micrograph of the serosal surface of the ampulla illustrates the accumulation of bulbous processes observed in some samples. Scale bar = 5 μm.



YÁNIZ ET AL.

Anat Rec, 290:831–837, 2007.

Rosario

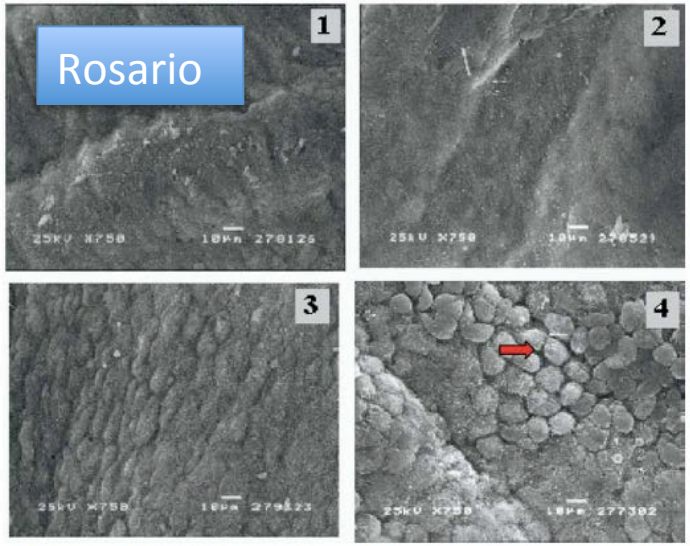


FIG. 1. Fragment of peritoneum after 2 h of procedure (original magnification 750×). Control group (1); laparotomy group showing absence of clear cell limits (2); air pneumoperitoneum group. Fusiform mesothelial cells and absence of intercellular clefts can be seen (3); CO_2 pneumoperitoneum group with spherical shape cells and intercellular clefts (arrow) (4). (Color version of figure is available online.)

Volz J.

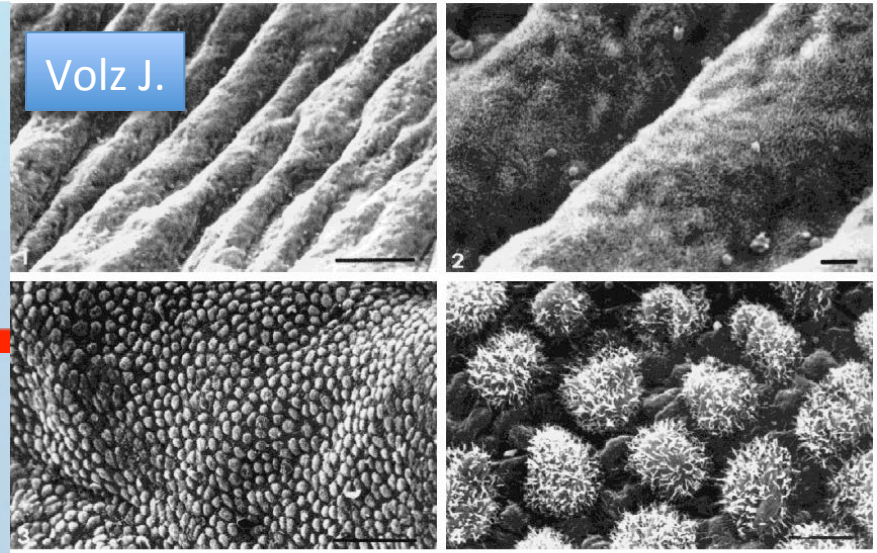


Fig. 1. Untreated animal. The normal peritoneum with intact mesothelial surface and indistinct cell borders. Magnification ×170.

Fig. 2. Untreated animal, a closer look at Fig. 1. The normal peritoneum is covered by a sheet of flat mesothelial cells densely strewn with microvilli. No intercellular clefts and no open basallamina can be detected. Magnification ×710.

Fig. 3. Mesothelium 2 h after CO_2 application. The dimensions of the CO_2 application on to the mesothelial lining are clearly visible. It must be noted that the magnification of this figure is the same as in Fig. 1. Magnification ×170.

Fig. 4. Mesothelium 2 h after CO_2 application. The mesothelial cells have partially retracted, strongly bulged up, and appear nearly spherical. Intercellular clefts and the underlying basal lamina are clearly visible. Magnification ×1,310.

Suematsu

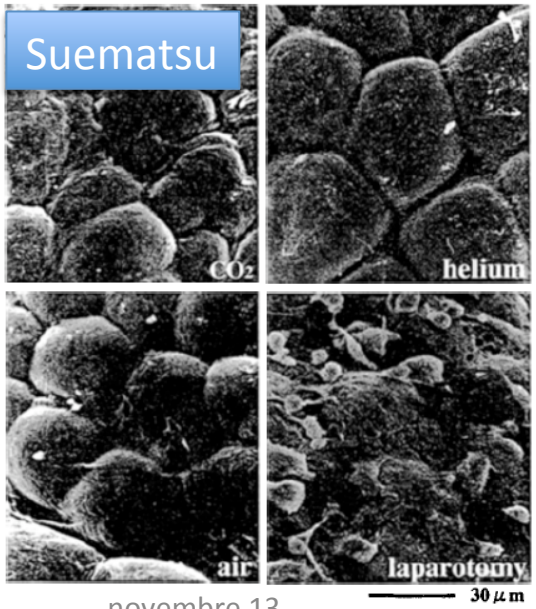


Fig. 3. At 24 h, after CO_2 pneumoperitoneum, bulging up of the mesothelial cells was decreased, but intercellular clefts were evident. At 24 h after laparotomy, detachment of the mesothelial cells persisted and attachment of macrophages was found. (Original magnification, ×1000)

Morphology of the rat peritoneum after carbon dioxide and helium pneumoperitoneum

A scanning electron microscopic study

J. Ordemann,[1] J. Jakob,[1] C. Braumann,[1] M. Kilian,[1] S. Bachmann,[2] C. A. Jacobi[1]

Conclusions: The study demonstrated that the morphologic integrity of the rat peritoneum is not disturbed when CO2 or helium is used for insufflation combined with the intraperitoneal injection of carcinoma cells. Pneumoperitoneum therefore probably is not the condition causing peritoneal changes that favor intraperitoneal tumor growth.

Surg Endosc (2011) 25:619–627
DOI 10.1007/s00464-010-1235-3

Application of stereology to study the effects of pneumoperitoneum on peritoneum

Jiang Du · Pei-wu Yu · Bo Tang

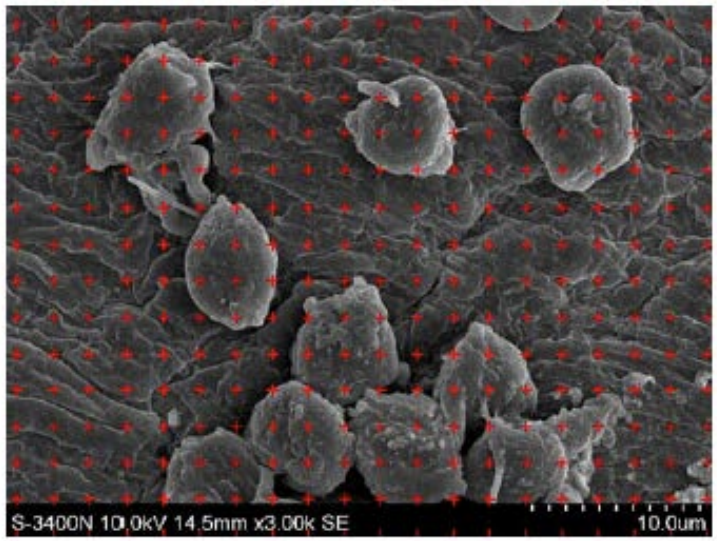


Fig. 2 The number of points hitting the basal lamina is counted

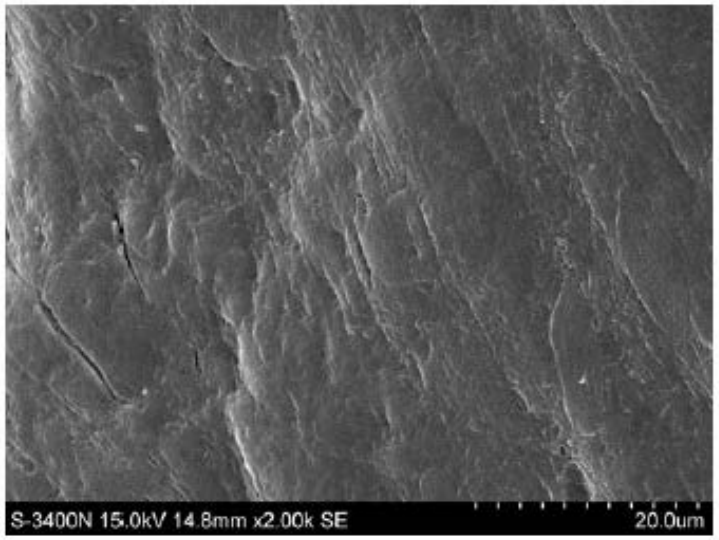


Fig. 4 In the control group, the peritoneum is covered by a sheet of flat mesothelial cells densely covered with microvilli. No intercellular clefts and no exposed basal lamina can be detected (magnification ×3,000)

5 animals in each group

Groupe	Pressure mm Hg	Time (h)	Gas flow (l/min)	Area of basal lamina exposed (fraction)	Diameter of mesothelial cells
Control	0	1	0	0	
C02 1h	5	1	1.0	0.076 ± 0.002	5.652 ± 0.040
C02 2h	5	2	1.0	0.197 ± 0.003	4.539 ± 0.029
CO2 3h	5	3	1.0	0.752 ± 0.004	4.590 ± 0.044
He 1h	5	1	1.0	0.074 ± 0.001	5.708 ± 0.104
He 2h	5	2	1.0	0.195 ± 0.003	4.528 ± 0.048
He 3h	5	3	1.0	0.751 ± 0.004	4.566 ± 0.043
CO2 8mm	8	1	1.0	0.281 ± 0.008	5.358 ± 0.066
CO2 2l/mn	5	1	2.0	0.276 ± 0.009	6.036 ± 0.043
CO2 3l/mn	5	1	3.0	0.362 ± 0.003	6.268 ± 0.061

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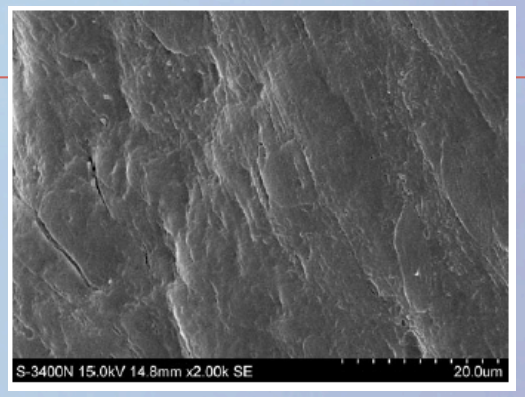
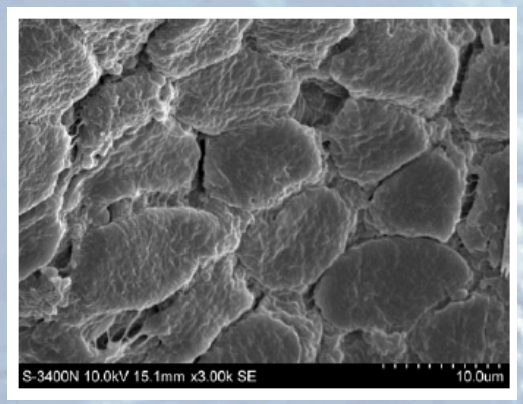
Time

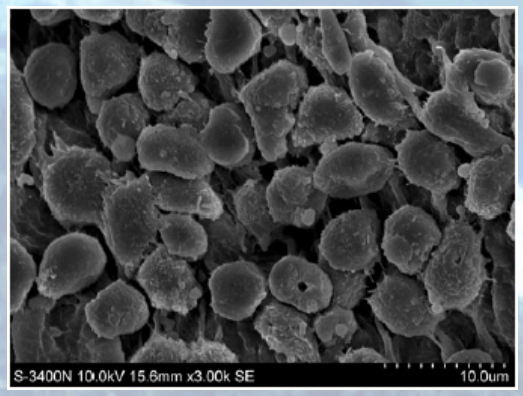
Control



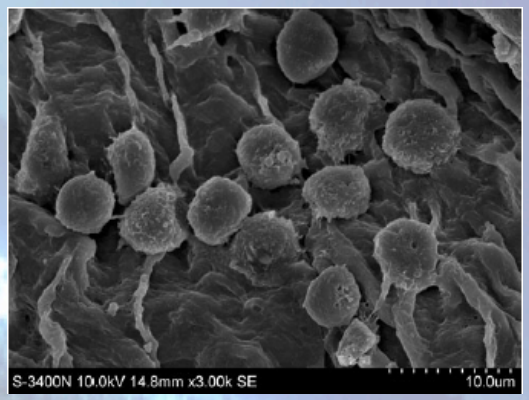
C02 1 heure



C02 2 heures



C02 3 heures



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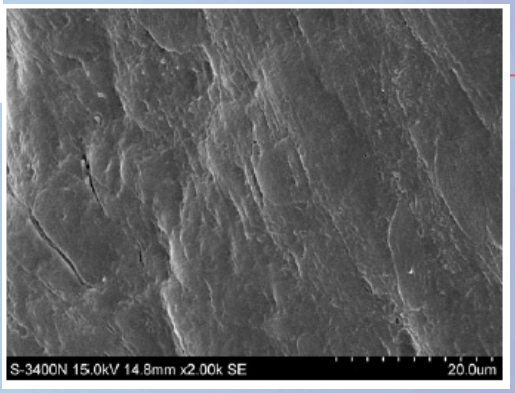
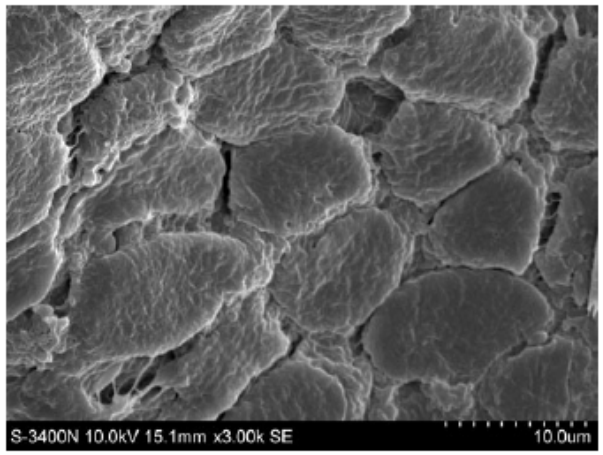
Control



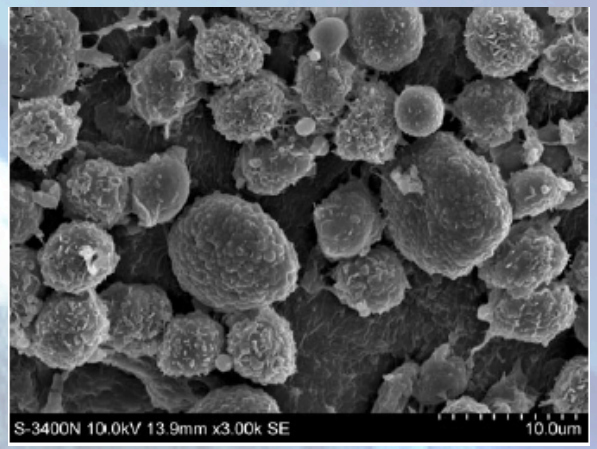
Pressure

C02 1 heure



5 mmHg

C02 1 heure



8 mmHg

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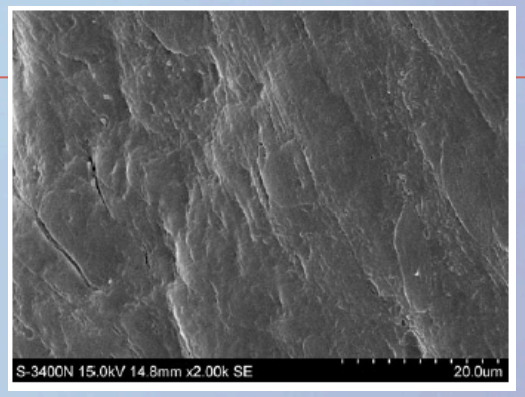
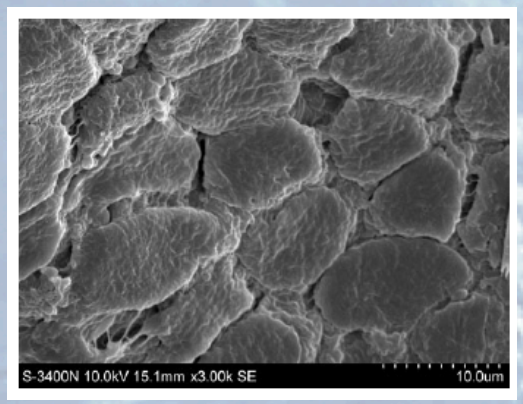
Flow

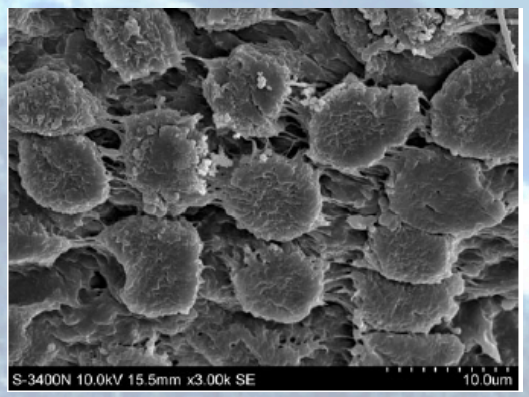
Control



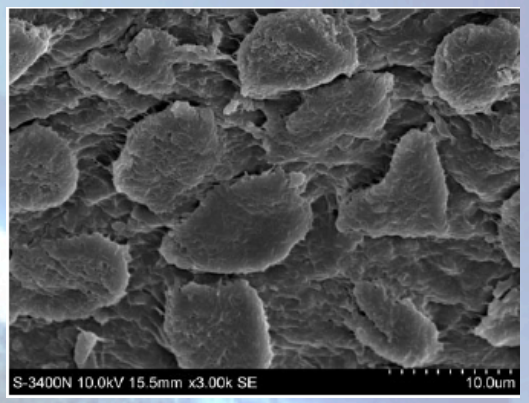
C02 1 heure



C02 1 heure
2 liters / minute



C02 1 heure
3 liters / minute



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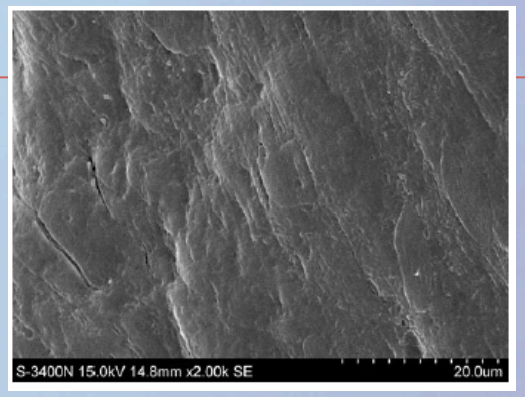
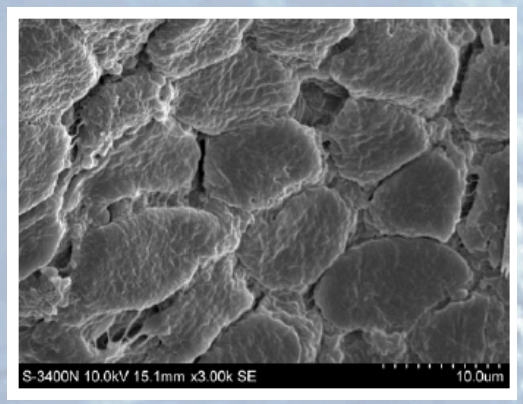
Flow

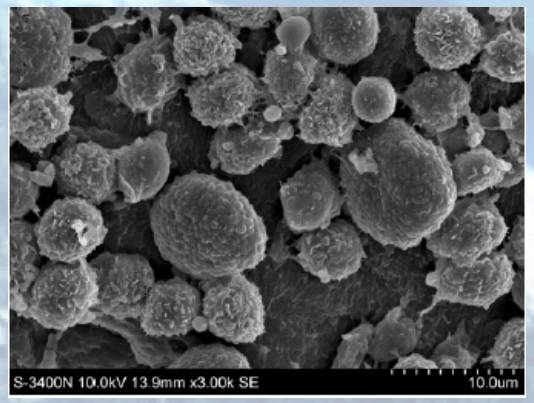
Control



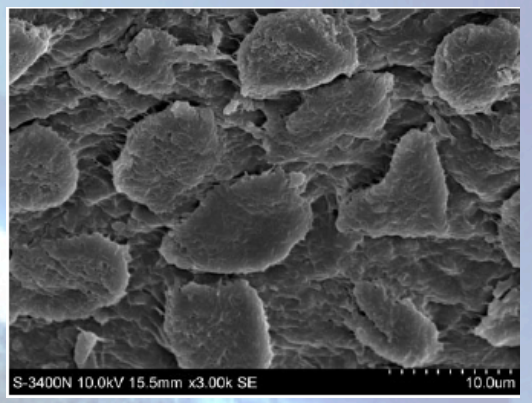
C02 1 heure



C02 1 heure



C02 1 heure
3 liters / minute



8 mmHg

The model is essential !!

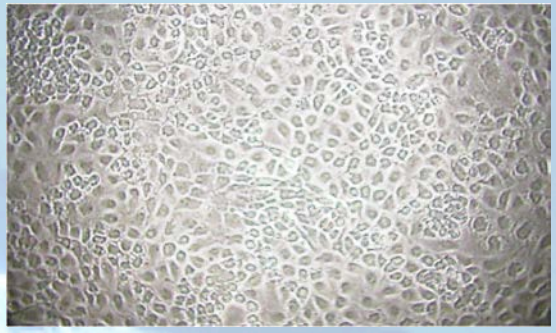
Animal Model

- Anesthesia
- Ventilation
- Pressure
- Surgical model
- Cancer model

Methods

ID 8, Mouse epithelial ovarian cancer cell line

Dr. K. Roby, University of Kansas Medical Center (Carcinogenesis 2000)



1 x10^6 cells

intraperitonéal

Immunocompetents C57BL/J6 8 weeks, mice,

Animals and methods

- Indu
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  - (
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- Ar
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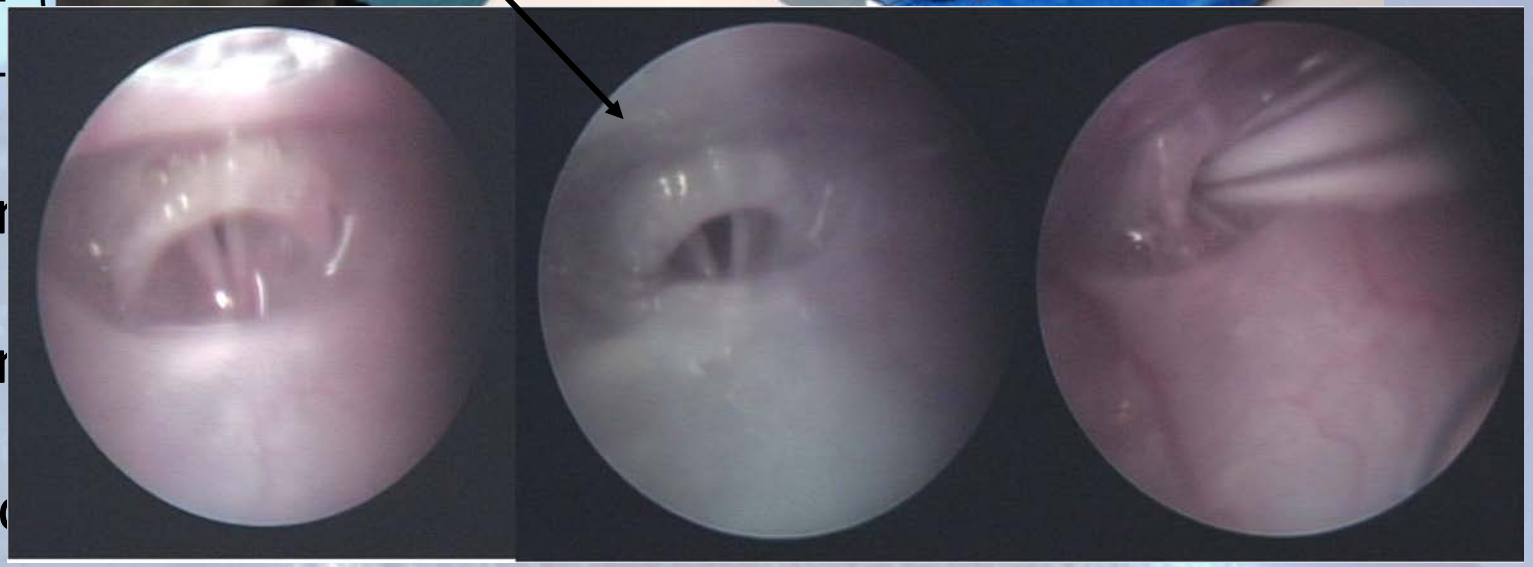
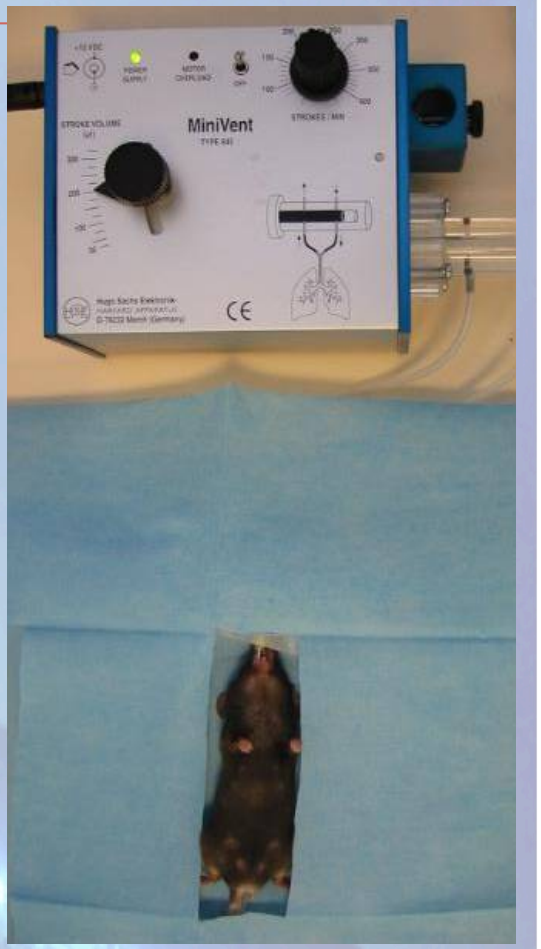


Animals and methods

- Mechanical ventilator
- Adapted to the type of surgery:
  - Tidal volume (200 μl)
  - Strokes per minute (250: laparoscopy; 220 laparotomy, control)
- Values delimited in a preliminary study to obtain PCO_2 : 25-35 mmHg and pH : 7.3-7.4



Animals and methods

- CO_2 pneumoperitoneum, two catheters: one for insufflation, one connected to a water valve
- Laparotomy: 3 cm abdominal incision
- After 1 hour: Carotid blood sample were analysed to obtain PaO_2, $PaCO_2$ and pH

Arterial blood gas analysis

In Mice without intubation

	Control (Anesthesia) (n=5)	CO2 Pneumoperitoneum 2mmHg (n=5)	CO2 Pneumoperitoneum 8 mmHg (n=5)	Laparotomy (n=5)
PaO2 (mmHg)	101.3 ± 5.2	107.2 ± 2.0	70.2 ± 17.7	101.6 ± 3.2
PaCO2 (mmHg)	36.2 ± 3.5	41.7 ± 2.3	61.8± 4.25	30.9 ± 3.6
pH	7.374 ± 0.041	7.260 ± 0.012	7.155± 0.027	7.350 ± 0.032

Data are mean ± SEM

Normal value of PaCO2 in mice: 25-35mmHg

Arterial blood gas analysis

In Mice with intubation

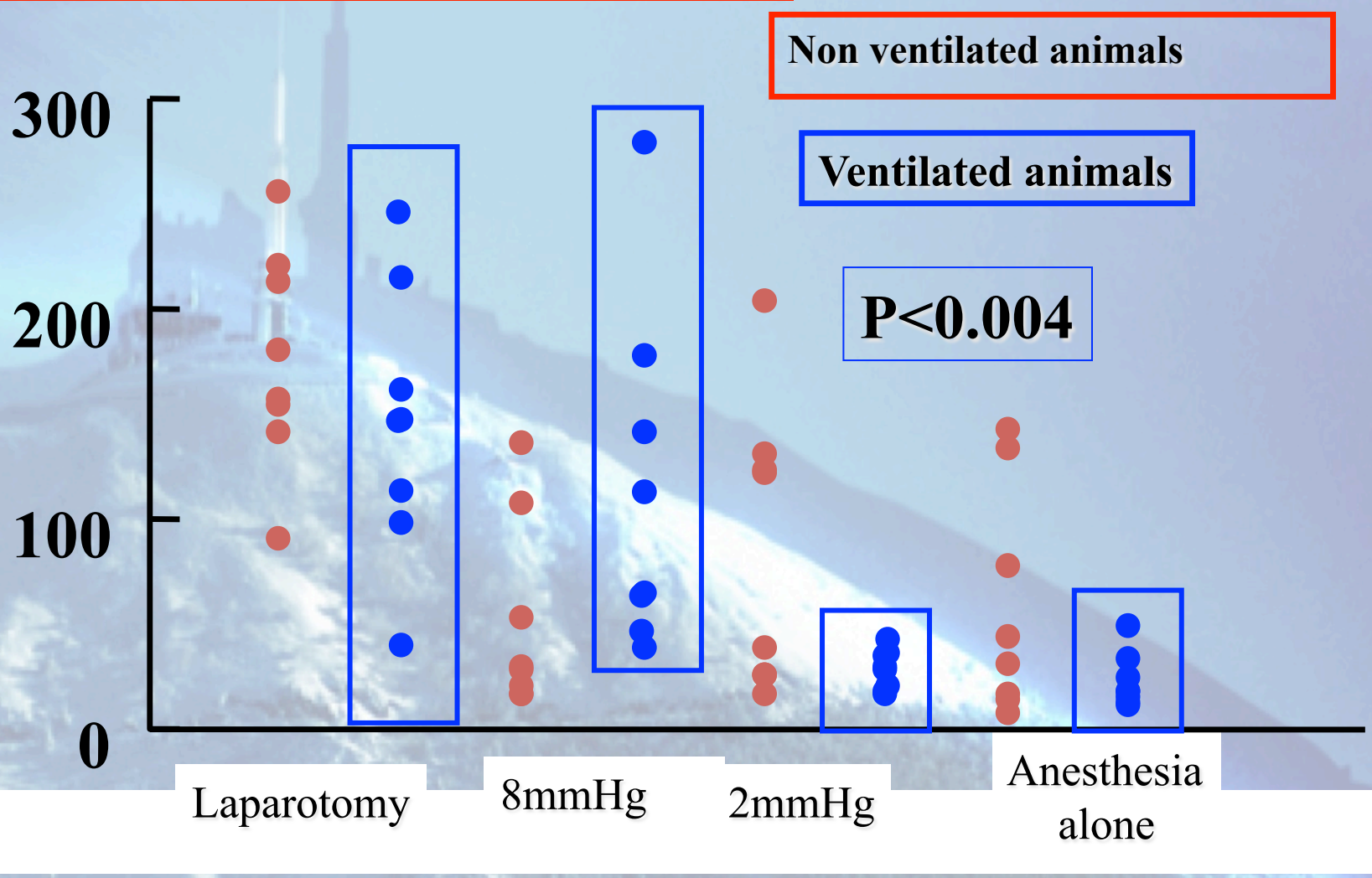
Tidal volume : 200 µL
250 strokes/mn (laparoscopy) ou 220 /mn (laparotomy, anesthesia)

	Control (Anesthesia) (n=5)	CO2 Pneumoperitoneum 2mmHg (n=5)	CO2 Pneumoperitoneum 8 mmHg (n=5)	Laparotomy (n=5)
PaO2 (mmHg)	106.6 ± 4.2	106.0 ± 3.2	112.2 ± 3.6	105.4 ± 4.4
PaCO2 (mmHg)	26.8 ± 2.9	34.2 ± 2.2	32.2 ± 3.6	28.5 ± 1.9
pH	7.379 ± 0.037	7.342 ± 0.023	7.269 ± 0.041	7.376 ± 0.022

Data are mean ± SEM

Normal value of PaCO2 in mice: 25-35mmHg

Results: Peritoneum Dissemination score



Conclusions

- An adapted pressure must be used (further hemodynamics studies are necessary)
- In studies with no CRS, effect of pneumopertioneum might be reconsidered
- CRS is required for operative and post-operative studies in animals

Humidification ??

- Meta analysis are in favour of humidification

  - Sajid MS, Mallick AS, Rimpel J, Bokari SA, Cheek E, Baig MK. Effect of heated and humidified carbon dioxide on patients after laparoscopic procedures: a meta-analysis. Surg Laparosc Endosc Percutan Tech. 2008 Dec;18(6):539-46. Review.

  - Sammour T, Kahokehr A, Hill AG. Meta-analysis of the effect of warm humidified insufflation on pain after laparoscopy. Br J Surg. 2008 Aug;95(8):950-6. Review

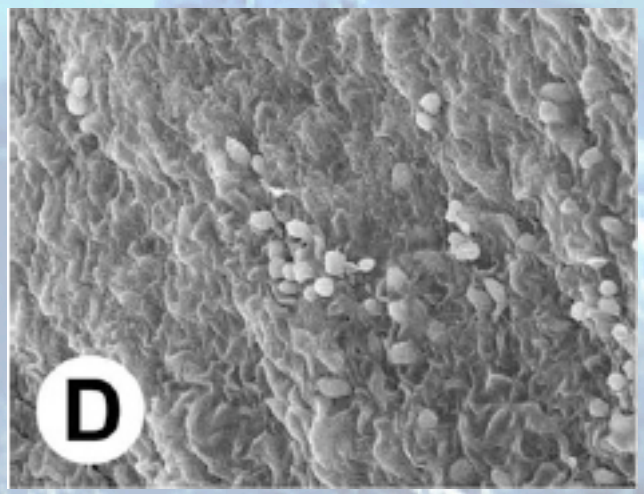
Heated and Humidified CO_2 Prevents Hypothermia, Peritoneal Injury, and Intra-Abdominal Adhesions During Prolonged Laparoscopic Insufflations

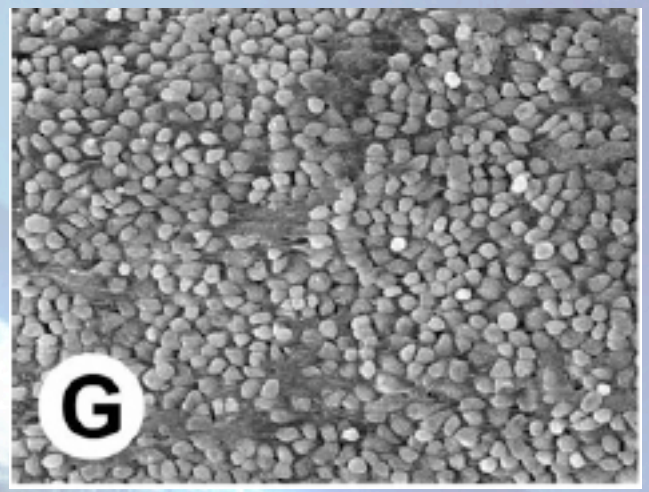
Yuanfei Peng, Ph.D.,* Minhua Zheng, M.D., Ph.D.,*,[1] Qing Ye, Ph.D.,* Xuehua Chen, Ph.D.,†
Beiqing Yu, Ph.D.,† and Bingya Liu, M.D., Ph.D.†

*Department of General Surgery, Shanghai Minimally Invasive Surgery Center, †Institute of Digestive Surgery, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Submitted for publication September 19, 2007

- *Conclusions. Heated-humidified CO2 insufflation* results in significantly less hypothermia, less peritoneal damage, and decreased adhesion formation as compared with cold-dry CO2 insufflation.





6 hours after 3 hours of dry CO2

6 hours after 3 hours of humidified CO2

Mesothelial stem cells ?!

Potentiel fibroblastique

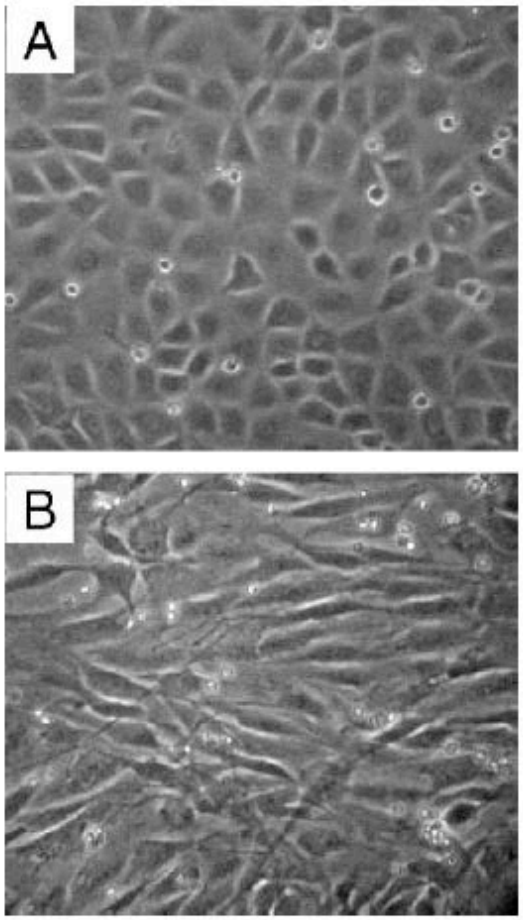


Fig. 3. Primary cultures of human pericardial mesothelial cells representing (A) epithelioid and (B) fibroblastic phenotypes, at different passage numbers of the same cell preparation. Micrographs courtesy of Jason Tee.

Epithelioid , cytokeratine

Several passages
EGF
PDGF
IL1ß

Fibroblastique , vimentine

Stem cells ?

Table. Potential use of mesothelial cells

- Prevention and treatment of peritoneal adhesions resulting from surgical procedures
- Treatment of abdominal hernias
- Peritoneal restoration in patients receiving long term peritoneal dialysis
- Prevention of ischemic damage of myocardium after myocardial infarction
- Damaged nerves regeneration
- With appropriate modification, producing proteins by genetic recombination

Dog peritoneal and pleural cavities as bioreactors to grow autologous vascular grafts

Wai-Leng Chue, MBBS,[a] Gordon R. Campbell, PhD,[a] Noel Caplice, MBBS, PhD,[b] Amjid Muhammed, BSc,[a] Celia L. Berry, BSc,[a] Anita C. Thomas, MSc,[a] Michael B. Bennett, PhD,[c] and Julie H. Campbell, PhD,[a] *Brisbane, Australia; and Rochester, Minn*

Objective: The purpose of this study was to grow "artificial blood vessels" for autologous transplantation as arterial interposition grafts in a large animal model (dog).
Method and results: Tubing up to 250 mm long, either bare or wrapped in biodegradable polyglycolic acid (Dexon) or nonbiodegradable polypropylene (Prolene) mesh, was inserted in the peritoneal or pleural cavity of dogs, using minimally invasive techniques, and tethered at one end to the wall with a loose suture. After 3 weeks the tubes and their tissue capsules were harvested, and the inert tubing was discarded. The wall of living tissue was uniformly 1-1.5 mm thick throughout its length, and consisted of multiple layers of myofibroblasts and matrix overlaid with a single layer of mesothelium. The myofibroblasts stained for α-smooth muscle actin, vimentin, and desmin. The bursting strength of tissue tubes with no biodegradable mesh scaffolds was in excess of 2500 mm Hg, and the suture holding strength was 11.5 N, both similar to that in dog carotid and femoral arteries. Eleven tissue tubes were transplanted as interposition grafts into the femoral artery of the same dog in which they were grown, and were harvested after 3 to 6.5 months. Eight remained patent during this time. At harvest, their lumens were lined with endothelium-like cells, and wall cells stained for α-actin, smooth muscle myosin, desmin and smoothelin; there was also a thick "adventitia" containing vasa vasorum.
Conclusion: Peritoneal and pleural cavities of large animals can function as bioreactors to grow myofibroblast tubes for use as autologous vascular grafts. (J Vasc Surg 2004;39:859-67.)

Phagocytosis of dying tumor cells by human peritoneal mesothelial cells

Britta Janina Wagner[1,2], Dennis Lindau[1], Dagmar Ripper[3], York-Dieter Stierhof[3], Jörg Glatzle[2], Maria Witte[2], Henning Beck[4,5], Hildegard Keppeler[6], Kirsten Lauber[6,7,*], Hans-Georg Rammensee[1] and Alfred Königsrainer[2]

Our data strongly suggest that HMCs contribute to dying cell removal in the peritoneum, and future studies will elucidate in what manner this influences tumor cell dissemination and the antitumor immune response.

Accepted 17 January 2011
Journal of Cell Science 124, 1644-1654

doi:10.1242/jcs.078907

The mesothelium contributes to:

- The initial response of the peritoneum to infection
- The amplification of this response
- The recruitment of leucocytes
- The control and the resolution of inflammation
- The control of peritoneal fibrinolysis
- The control of peritoneal homeostasis and maintenance of peritoneal membrane structure and function.

Topley et al

Stoma

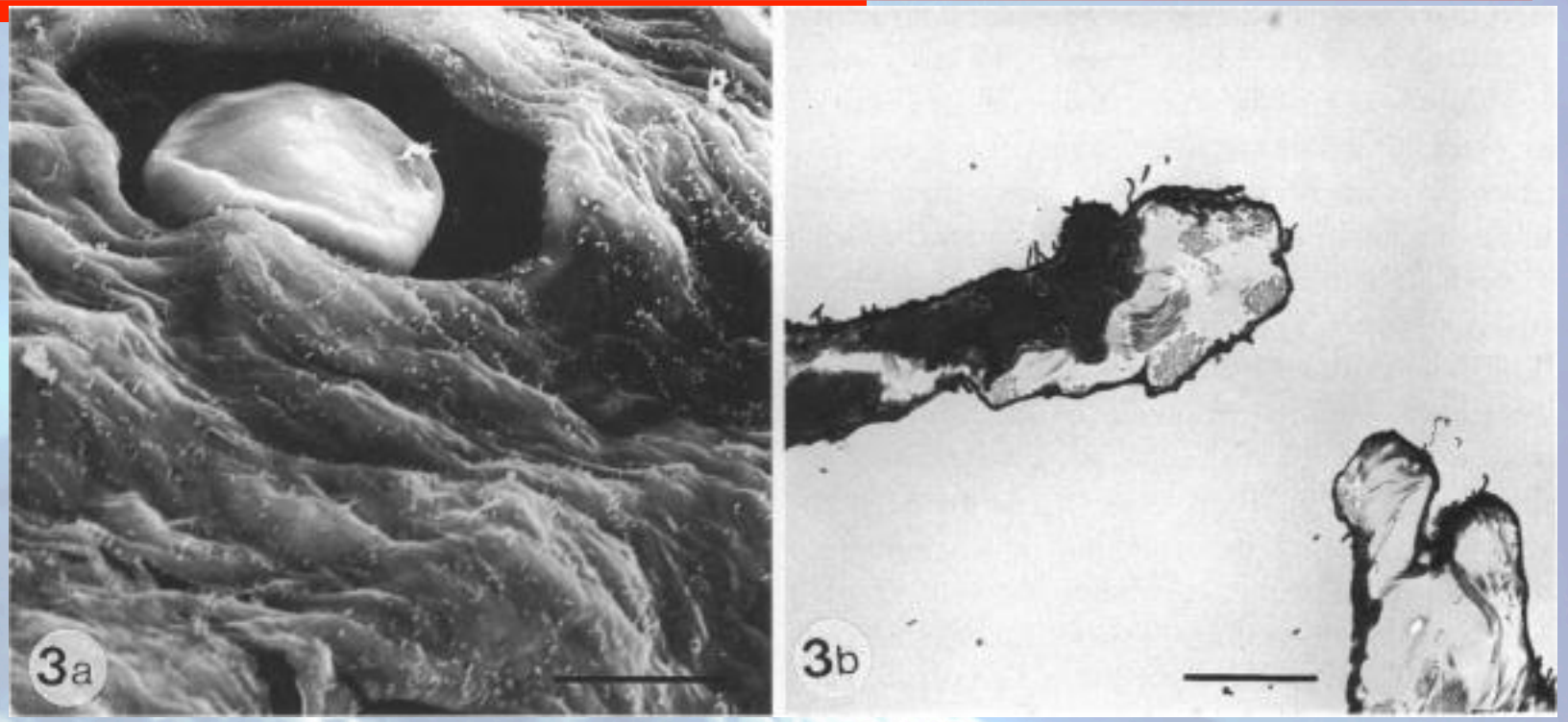


Fig. 3. (*a*) Scanning electron micrograph of mesentery. Two stomata can be seen in the micrograph, one of them containing a red blood cell. The microvilli extend on to the margins of the stomata. Bar, 10 µm. (*b*) Transmission electron micrograph of the specimen shown in (*a*) sectioned through a mesenteric stoma. The mesothelial cells on either side of the stoma form the margins of the opening. The mesenteric microvilli are fewer in number (cf. Fig. 2*a*) than in the serosa. Bar, 5 µm.

R. R. ETTARH[1] AND K. E. CARR[2]

Les stomas diaphragmatiques

- Situés à la jonction de 3 à 5 cellules mésothéliales
- Plus fréquents sur la coupole diaphramatique droite
- Leur diamètre varie de 4 à 10 microns mais varie en fonction des circonstances (tension du diaphragme, pression intrapéritonéale, circonstances pathologiques) en raison de la présence de filaments contractiles dans les cellules mésothéliales
- Ces stomas mettent en communication la cavite péritonéale avec le système lymphatique, les membranes basales du mésothélium et de l'endothelium lymphatique sont discontinues à ce niveau.
- Les lacunes lymphatiques communiquent avec les lymphatiques sous-pleuraux
- Des bactéries injectées dans le péritoine de chien sont retrouvées dans le canal thoracique moins de 6 minutes après l'injection.

- Ces stomas sont des structures dynamiques dont le diamètre varie en fonction des circonstances de 4 à 10µ

Diaphragmatic stoma

- Dynamic structures +++++++
- Their diameter may change from 4 to 10 microns but depens on the circumstancies as there are a lot of actin microfilament inside mesothelial cells.
- The diameter also changes in intraperitoneal disease.
- The study by Tsilibary and Wissig (1983) demonstrated that whether the lymphatic stomata of diaphragmatic peritoneum was open or close depended on respiratory movement. During inspiration, the diaphragmatic muscles contract, the number of open lymphatic stomata was decreased. On the contrary, during expiration, the diaphragmatic muscles relaxed, the number of open lymphatic stomata was increased.
- The increase of intraabdominal pressure leads to increased number of open lymphatic stomata.
- The diameter of stoma of the pericardium is increased by VEGF and angiotensin
- The diameter of peritoneal stoma of the ovarian bursa is ifluenced by pregnancy.

Lymphatiques du diaphragme

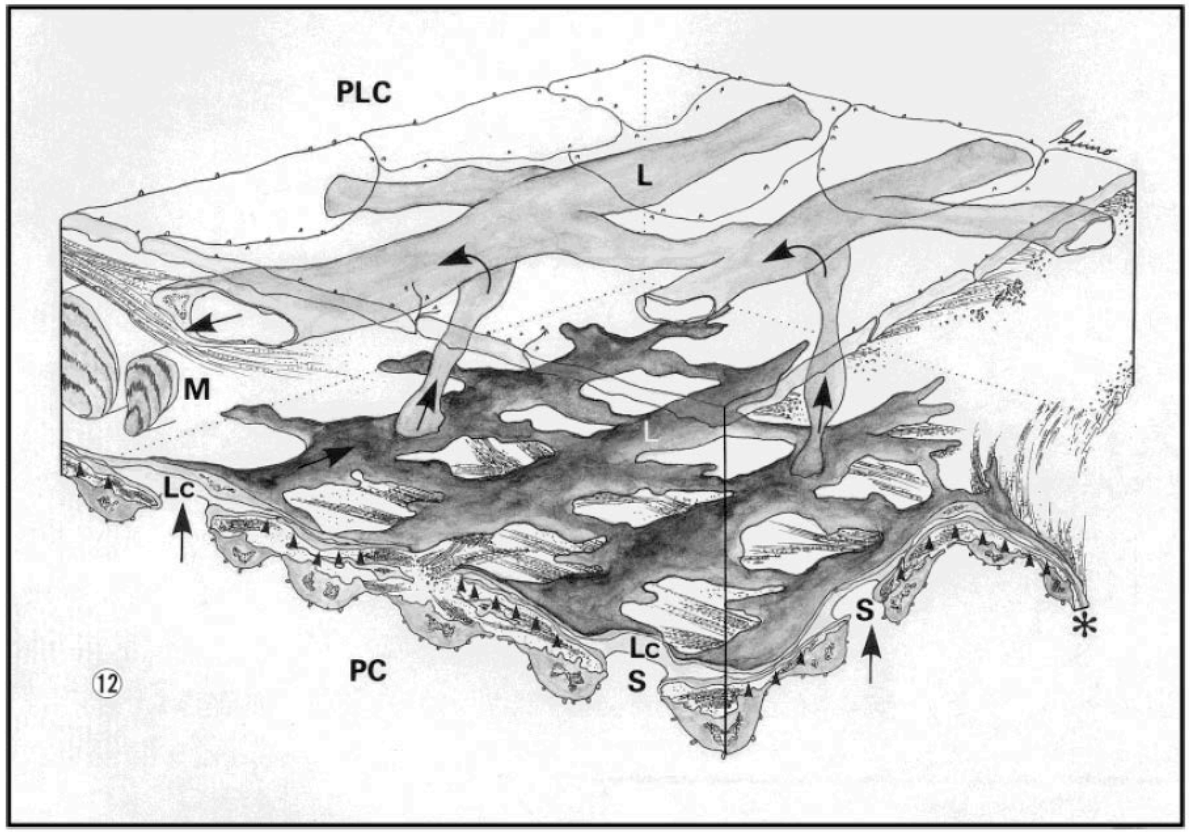
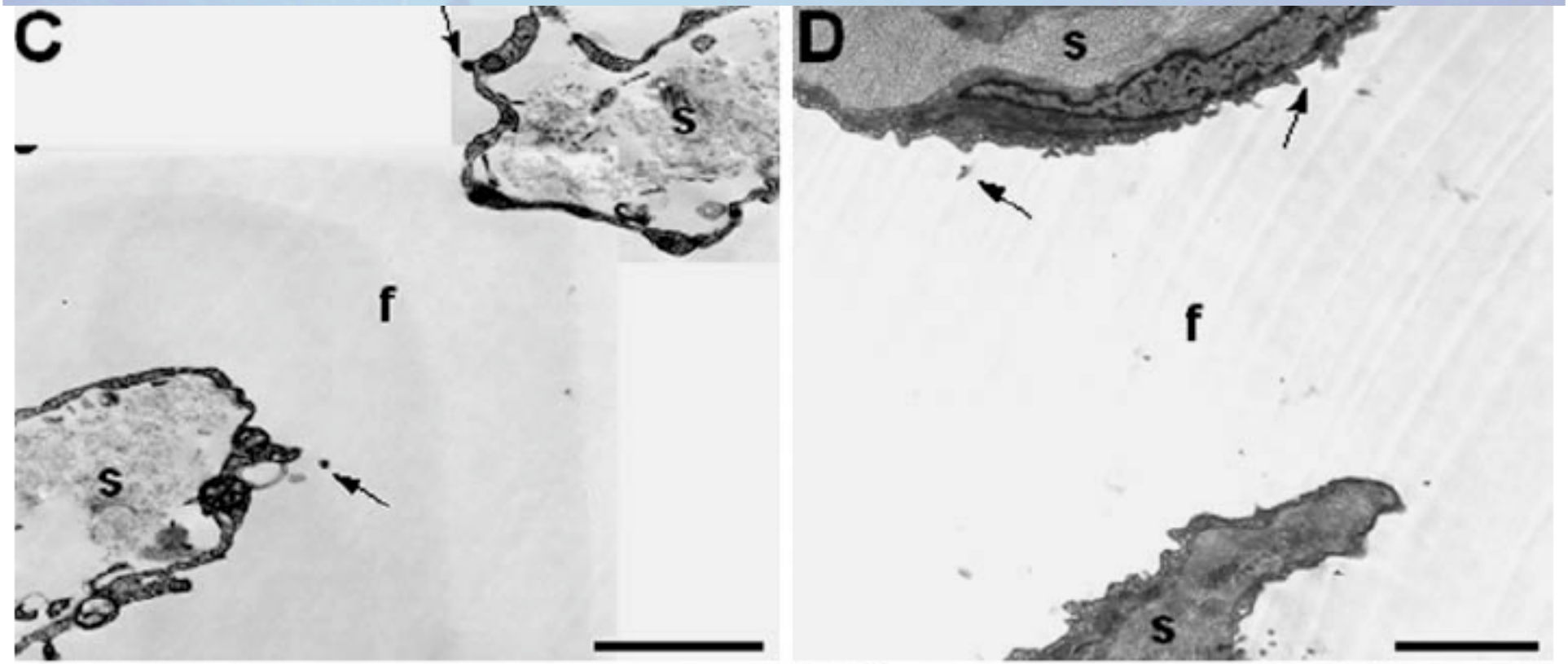


Fig. 12. Three-dimensional diagram to illustrate the lymphatic sieve of the mouse diaphragm. The arrows indicate the flow of lymph through the sieve. Note that the subperitoneal lymphatic vessels are extremely flat (arrowheads) for the most part. Each lumen appears as a narrow channel (= vadum) in ultrathin sections. In some regions, the lymphatic lumen is spacious and forms a lacuna. The lacunae in the peritoneal lymphatic vessels are usually not as spacious as the lymphatic lumen of pleural lymphatic vessels. Asterisk: stripping of the peritoneal mesothelium attached to the lymphatic vessels.

Omentum



SEM of translucent region of murine (c) and human (d) omentum showing numerous fenestrations (f).

Gerber SA, Rybalko VY, Bigelow CE, Lugade AA, Foster TH, Frelinger JG, Lord EM.

Preferential attachment of peritoneal tumor metastases to omental immune aggregates and possible role of a unique vascular microenvironment in metastatic survival and growth.

Am J Pathol. 2006;169:1739-52.

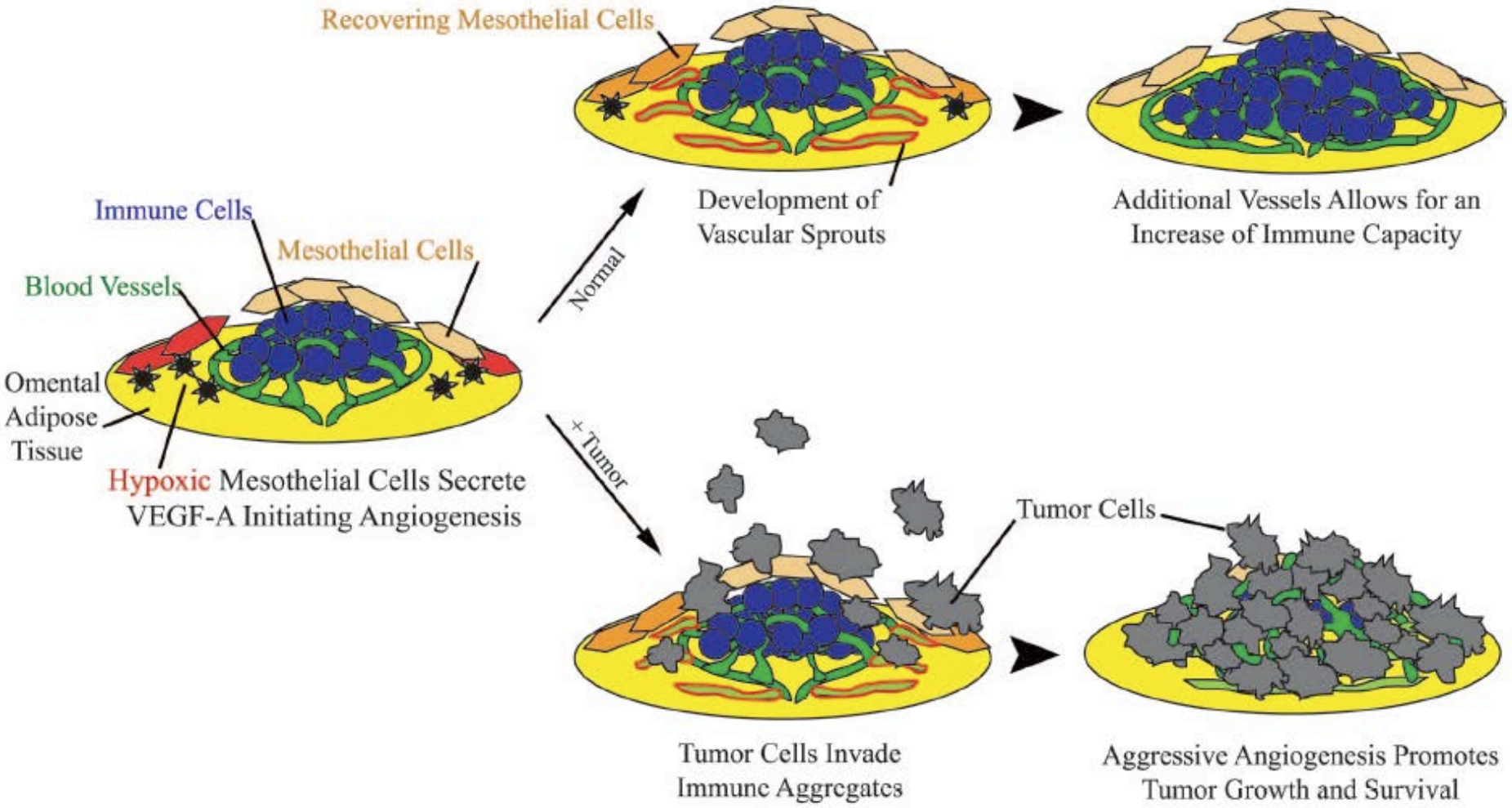
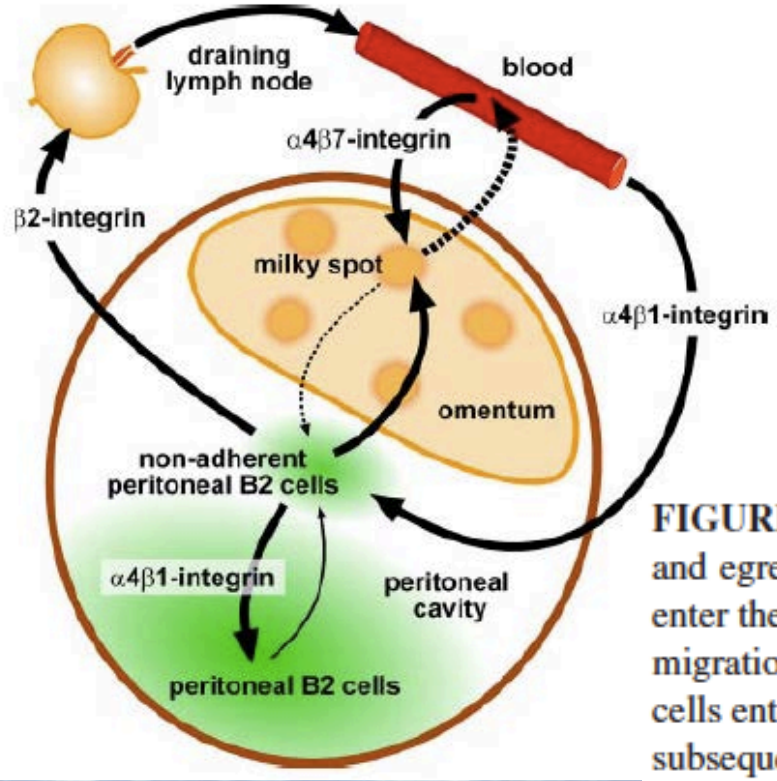


Figure 8. Proposed model. As described, omental immune aggregates contain mesothelial cells, some of which are hypoxic (red) and therefore secrete VEGF-A (**black asterisks**). In a normal physiological setting (top), VEGF-A production can stimulate blood vessels to produce vascular sprouts (green outlined in red), resulting in the induction of angiogenesis and recovery of once-hypoxic mesothelial cells. The increase of vessels delivers more immune cells, along with additional oxygen and nutrients necessary to support the influx of cells. In a metastasis model (bottom), tumor cells invade aggregates and co-opt the existing dense vasculature. Because angiogenesis is already induced, new blood vessel formation is rapid, resulting in aggressive tumor growth.

B CELL Migration in the PERITONEUM



Berberich et al J Immunol 2008

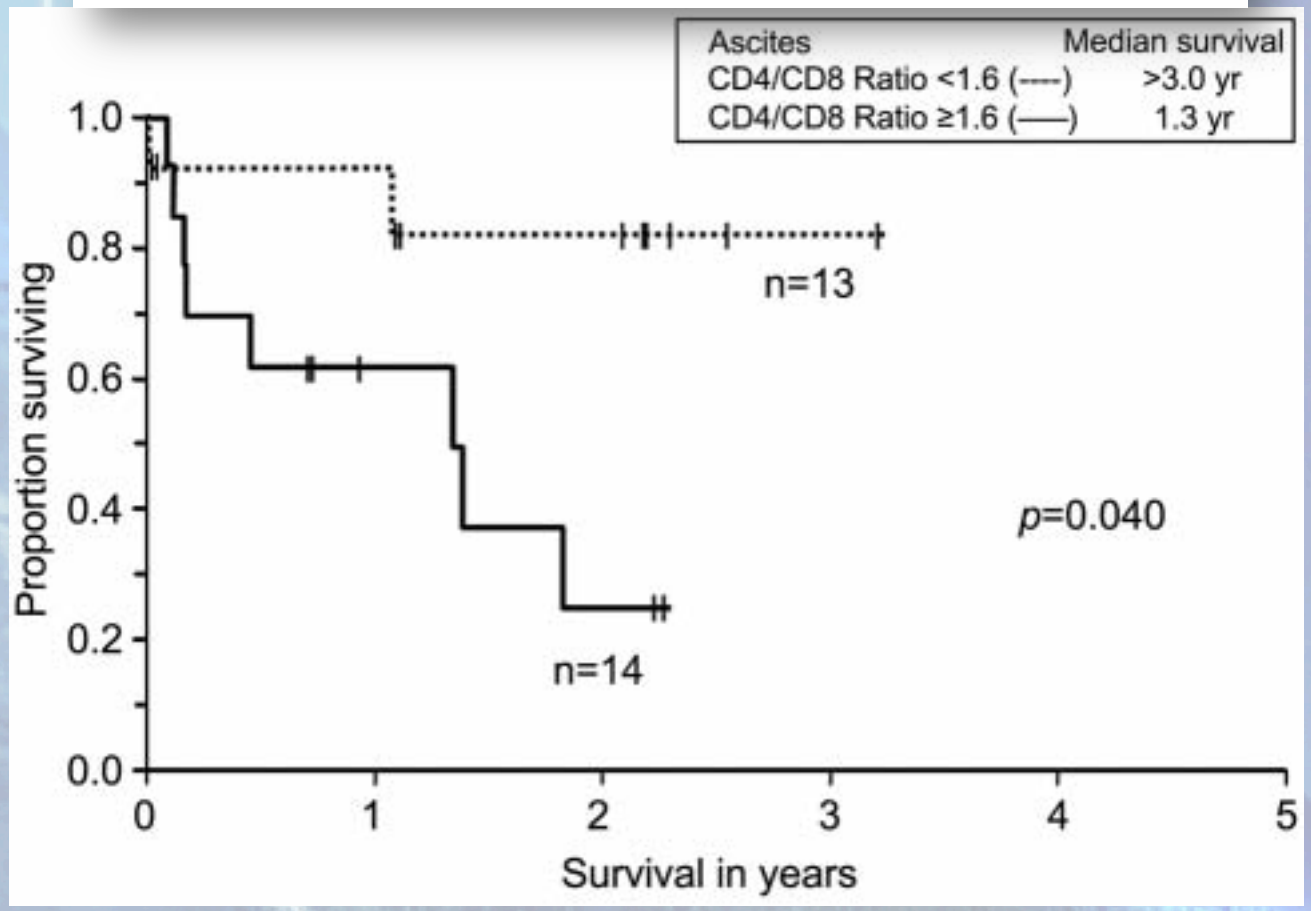
FIGURE 7. Schematic presentation of B2 cell migration into the PerC and egress from this compartment under homeostatic conditions. B2 cells enter the PerC via two independent routes: 1) $\alpha_4\beta_1$ integrin mediates direct migration of B2 from the circulation into the PerC and 2) blood-borne B2 cells enter omental milky spots by β_7 integrin-MAdCAM-1 interaction and subsequently might transit into the PerC. Inside the PerC, the majority of B2 cells are retained in the compartment by α_4 integrin-dependent adhesion to the local matrix. This interaction limits the pool of nonadherent peritoneal B2 cells that can exit this compartment in a β_2 integrin-mediated mechanism via the draining lymph nodes or alternatively enter omental milky spots from the peritoneal side. Dashed lines indicate putative migratory routes that have not yet been experimentally shown.

ANTICANCER RESEARCH 29: 2875-2884 (2009)

Ovarian Cancer-associated Ascites Demonstrates Altered Immune Environment: Implications for Antitumor Immunity

ROBERT L. GIUNTOLI, II[1], TONYA J. WEBB[2], ALESSIA ZOSO[2], OPHELIA ROGERS[2], TERESA P. DIAZ-MONTES[1], ROBERT E. BRISTOW[1] and MATHIAS OELKE[2]

37 patients with advanced ovarian cancer



- The peritoneum is a secondary lymphoid organ !!

In a rat model of subcutaneous tumor !

The peritoneum is an important lymphoid organ

- We demonstrate the migration of antigen presenting cells, macrophages, and dendritic cells from the subcutaneous site to the peritoneum after they have picked up the antigen.

- Our results suggest the peritoneum to function as an organ with lymphoid characteristics, which causes immune cell (APCs and T, B, and NK cells) migration and stimulation, leading to tumor regression.

» Mitra et al FASEB journal 2004

Immunity
Article

Omental Milky Spots Develop in the Absence of Lymphoid Tissue-Inducer Cells and Support B and T Cell Responses to Peritoneal Antigens

Javier Rangel-Moreno,[1,3] Juan E. Moyron-Quiroz,[2,3] Damian M. Carragher,[2] Kim Kusser,[1] Louise Hartson,[1] Amy Moquin,[2] and Troy D. Randall[1,*]
[1]Division of Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY 14642, USA
[2]Trudeau Institute, Saranac Lake, NY 12983, USA
[3]These authors contributed equally to this work
*Correspondence: troy_randall@urmc.rochester.edu
DOI 10.1016/j.immuni.2009.03.014

These results indicate that the milky spots of the omentum function as unique secondary lymphoid organs that promote immunity to peritoneal antigens.

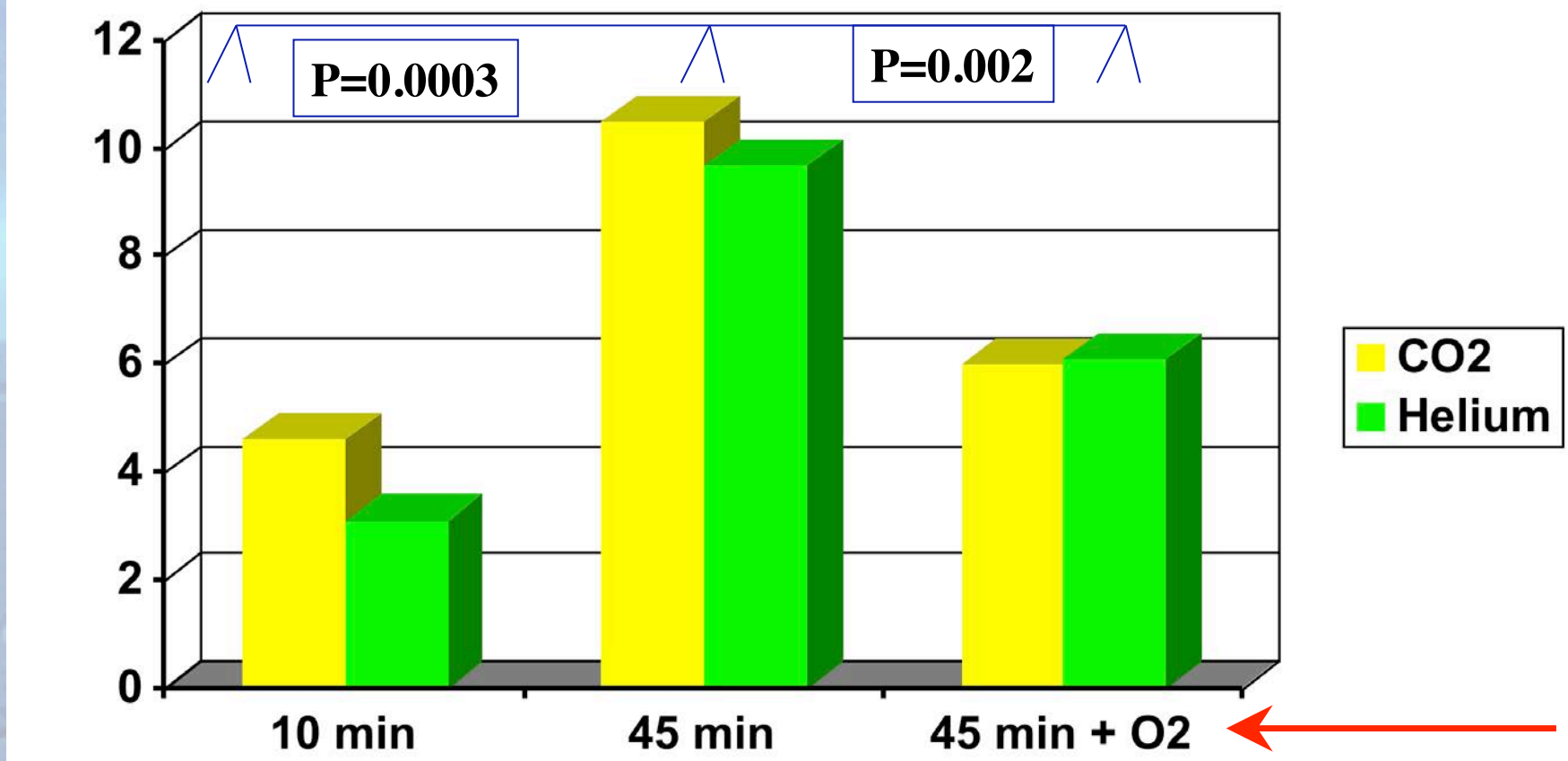
Hypoxia

- Tissue oxygenation is one of the most important determinants in wound healing, adhesion formation, tumor growth.

Adhesions ; Hypoxemia ; Duration

Rabbbit Model ; Standard laparoscopic Trauma

Molinas et al Hum reprod 2000



Peritoneal tissue oxygen tension

Peritoneal tissue oxygen tension (1)

- PitO2 measure
  - Peritoneal tissue oxygen tension was measured using a polarographic oxygen electrode placed in the retroperitoneal space using a 16 gauge intravenous catheter.
  - The PitO2 level were monitored continuously.
  - Following the trauma of implantation, the intraoperative values were averaged across the last 30 minutes of the procedure.

Peritoneal tissue oxygen tension (2)

- 40 mice randomized in eight groups
  - Anesthesia alone (4 groups)
    - Control
    - 2 mmHg CO2 pneumoperitoneum
    - 8 mmHg CO2 pneumoperitoneum
    - laparotomy
  - Anesthesia with controlled respiratory support (4 groups)
    - Control
    - 2 mmHg CO2 pneumoperitoneum
    - 8 mmHg CO2 pneumoperitoneum
    - laparotomy

Normal level of tissue oxygen tension is considered to be around 40 mmHg Gayton and Hall 2000

Peritoneal tissue oxygen tension (PitO2)
in mice with controlled respiratory support

	Control (anesthesia alone) (n=5)	C02 pneumoperitoneum 2mmHg (n=5)	C02 pneumoperitoneum 8 mmHg (n=5)	Laparotomy (n=5)
PaO2 (mmHg)	106.6 ± 4.2	106.0 ± 3.2	112.2 ± 3.6	105.4 ± 4.4
PitO2 (mmHg)	45.0 ± 3.5	104.2 ± 7.8 [a]	61.2 ± 9.6	49.8 ± 15.0

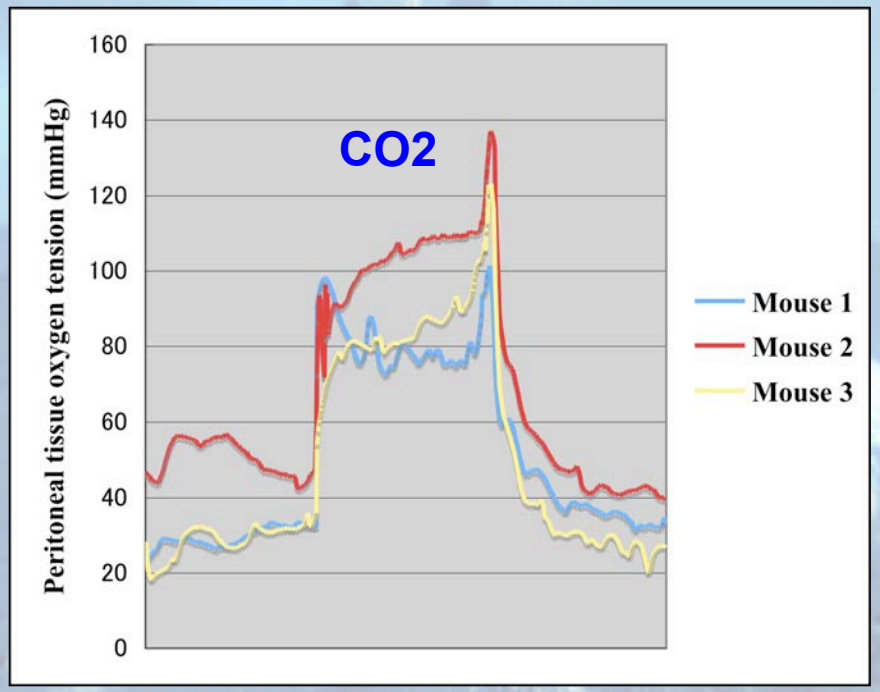
Data are mean ± SEM
a:p< 0.05 vs Control, CO2 pneumoperitoneum at high IPP, Laparotomy

Peritoneal tissue oxygen tension (3)

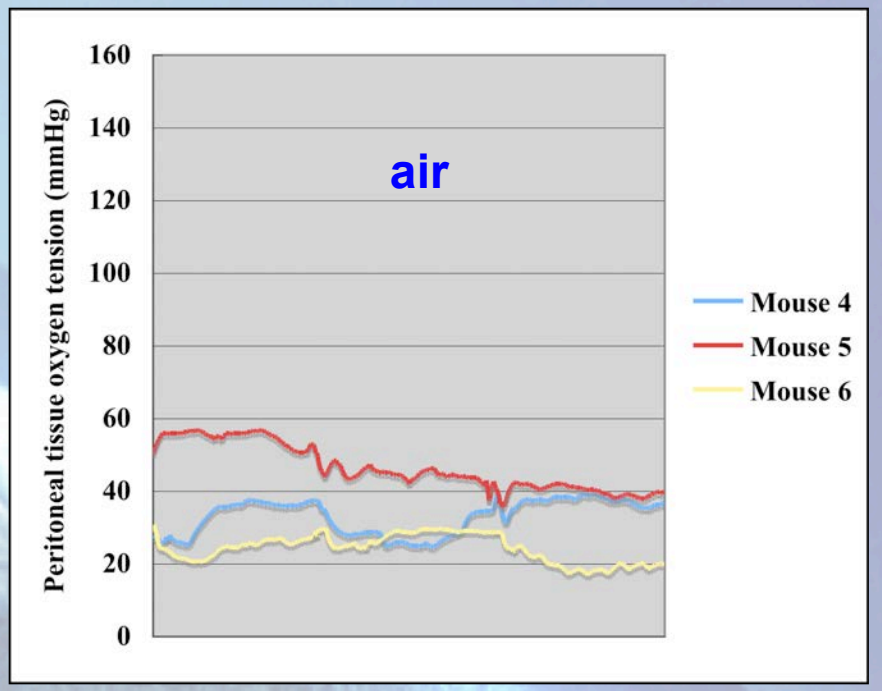
- To understand whether this result is related to pressure or to CO2
    - Two groups of 3 animal with controlled respiratory support
        - 3 with C02
        - 3 with air
        - Each animal had
            - » anesthesia for 1 hour,
            - » pneumoperitoneum for 1 hour
            - » and laparotomy for 1 hour

Peritoneal tissue oxygen tension during anesthesia alone, CO2 or Air pneumoperitoneum and laparotomy within same mice

Anesthesia alone 1 hour | **Laparoscopy CO2 1 hour** | **Laparotomy 1 hour**



Anesthesia alone 1 hour | **Laparoscopy Air 1 hour** | **Laparotomy 1 hour**



Comments

- Surprising result

- PitO2 depends on the following factors
  - Delivery of oxygen from the lung to the tissue
  - Transport of oxygen from blood to the tissue
  - Oxygen consumption in the tissue
- The peritoneum pH is very low even in animal with control respiratory system (Hanly et al 2005), so CO2 pneumoperitoneum could increase the transport of oxygen through the Bohr effect
- In ventiliated pigs, a CO2 pneumoperitoneum 5 - 12 mmHg increases peritoneal blood flow and this may increase the delivery of oxygen to the tissue

- This has to be confirmed at the cellular and the molecular level.

Effects of supplemental perioperative oxygen on post-operative abdominal wound adhesions in a mouse laparotomy model with controlled respiratory support*

Sachiko Matsuzaki[1,2,5], Michel Canis[1,2], Jean-Etienne Bazin[1,3], Claude Darcha[4], Jean-Luc Pouly[1,2] and Gérard Mage[1,2]

[1]Université d'Auvergne—Clermont I, Faculté de Médecine, Centre d'Endoscopie et des Nouvelles Techniques Interventionnelles (CENTI), Clermont-Ferrand, France; [2]CHU Clermont-Ferrand, Polyclinique-Hôtel-Dieu, Gynécologie Obstétrique et Médecine de la Reproduction, Boulevard Léon Malfreyt, 63058 Clermont-Ferrand Cédex, France; [3]CHU Clermont-Ferrand, Hôtel Dieu, Service d'Anesthésie Réanimation, Clermont-Ferrand, France; and [4]CHU Clermont-Ferrand, Hôtel-Dieu, Service d'Anatomie et cytologie pathologiques, Clermont-Ferrand, France

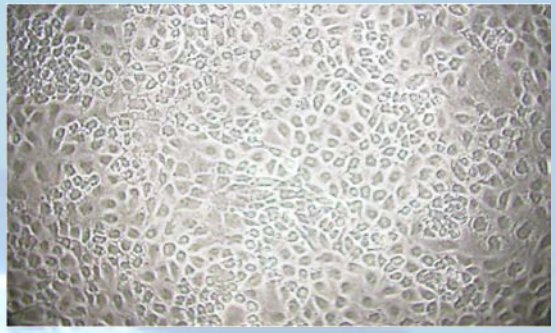
[5]Correspondence address: Tel: +33-4-73-75-01-38; Fax: +33-4-73-93-17-06. E-mail: sachikoma@aol.com

BACKGROUND: Post-operative adhesion formation is a major clinical problem. Tissue oxygenation is one of the most important determinants in adhesion formation. The objective of this study was to investigate whether supplemental perioperative oxygen could reduce post-operative adhesion formation through increasing the peritoneal tissue oxygen tension ($PitO_2$) in a mouse model. METHODS: Adult C57BJ6 mice were randomly assigned to two groups: Group 1 ($n = 20$), Fraction of Inspired Oxygen (FiO_2): 0.21; Group 2 ($n = 20$), FiO_2: 0.80. On day 0, over the course of the 90 min procedure including the 60 min of laparotomy, $PitO_2$ was continuously monitored. On day 7, a second laparotomy was performed to assess abdominal wound adhesions. Real-time RT–PCR was performed to measure expression levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) mRNA in peritoneal tissues. RESULTS: The $PitO_2$ levels in Group 2 were significantly higher compared to Group 1 ($P < 0.001$) and controls ($P < 0.003$). There was no significant difference in the incidence of abdominal wound adhesions; however, the severity of adhesions was significantly reduced in Group 2 compared to Group 1 ($P < 0.03$). A significantly higher tPA/PAI-1 mRNA ratio was detected in Group 2 and the controls compared to Group 1 ($P < 0.02$ and $P < 0.002$, respectively). CONCLUSIONS: Supplemental perioperative oxygen may help to reduce post-operative adhesion formation.

Model of ovarian rupture

ID 8, Mouse epithelial ovarian cancer cell line

Dr. K. Roby, University of Kansas Medical Center (Carcinogenesis 2000)



1 x10^6 cells

intraperitonéal

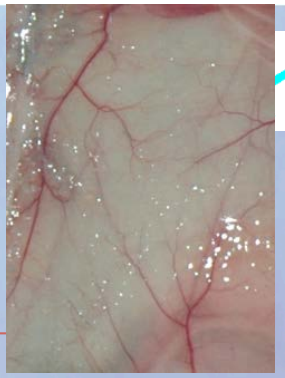
Immunocompetents C57BL/J6 8 weeks, mice,

Cyst rupture model

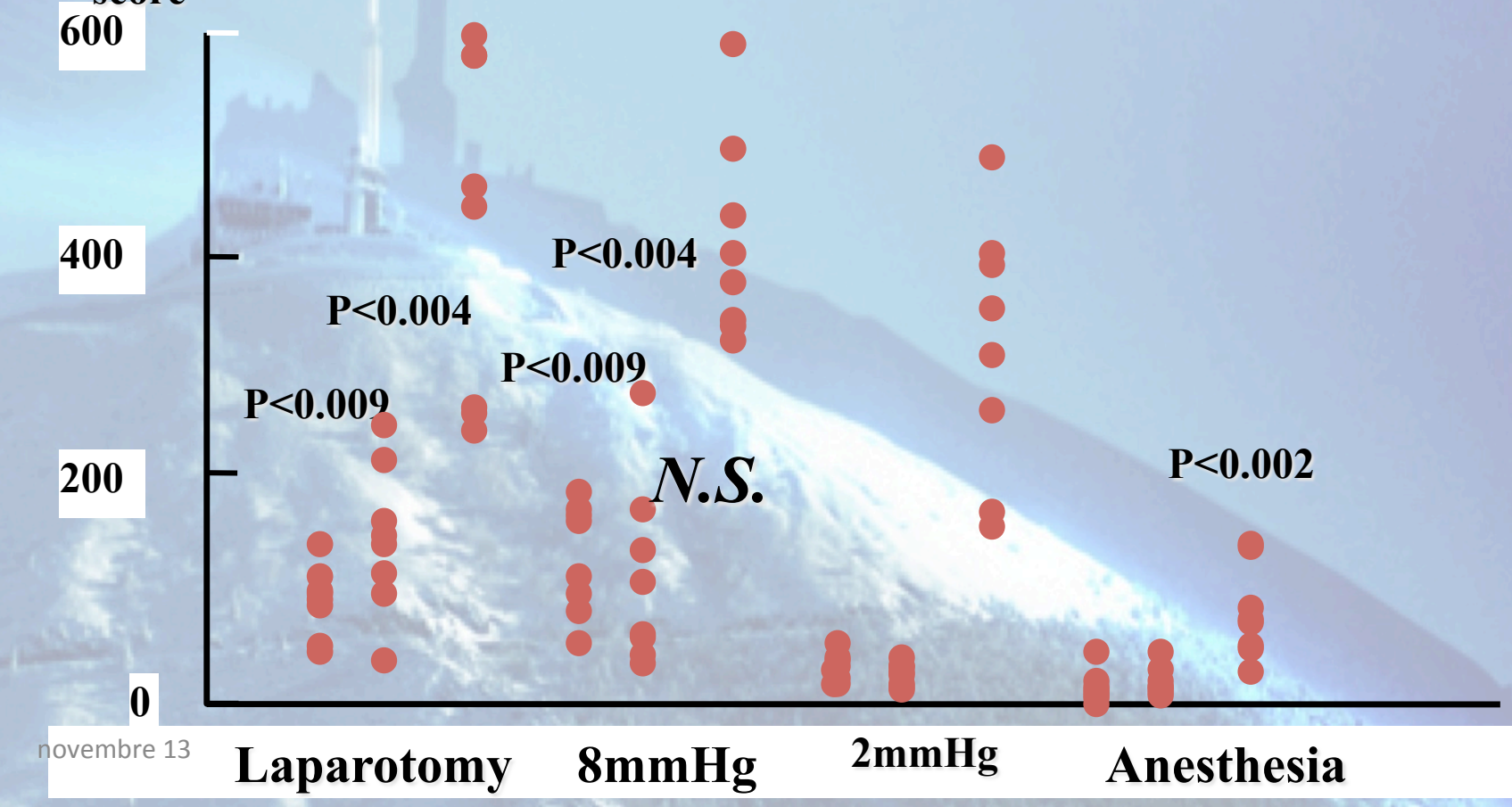
Molecular mechanisms underlying postoperative peritoneal tumor dissemination may differ between a laparotomy and carbon dioxide pneumoperitoneum: a syngeneic mouse model with controlled respiratory support

Sachiko Matsuzaki · Nicolas Bourdel · Claude Darcha · Pierre J. Déchelotte · Jean-Etienne Bazin · Jean-Luc Pouly · Gérard Mage · Michel Canis

Results: Peritoneum Dissemination score



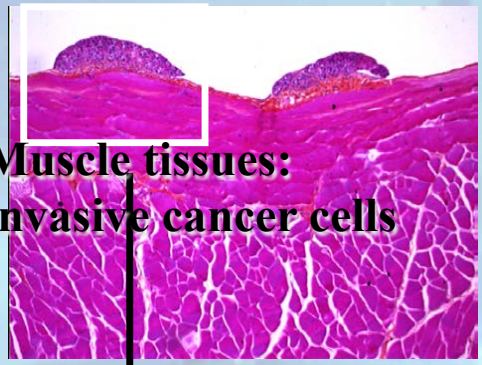
POD14



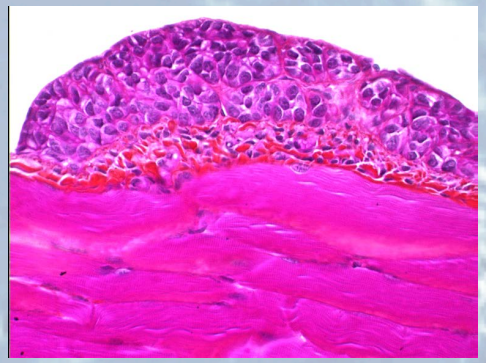
The role of pressure was confirmed using pathology

Invasion: negative

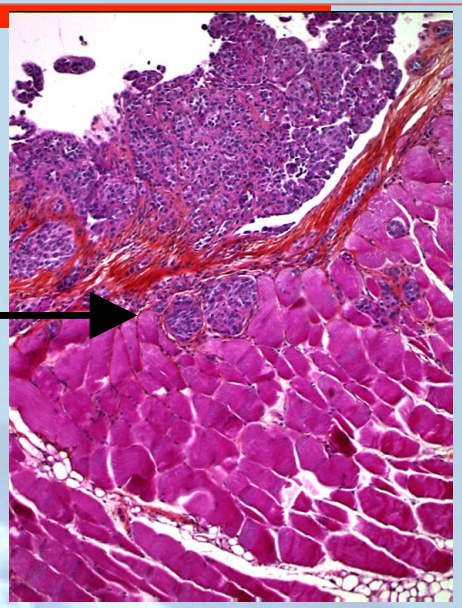
Invasion: positive

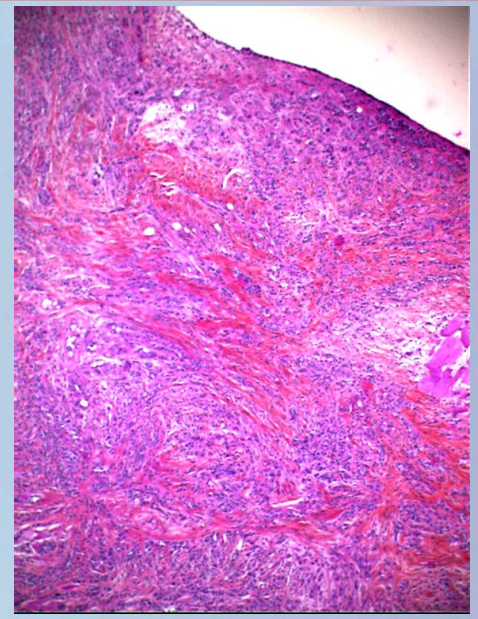


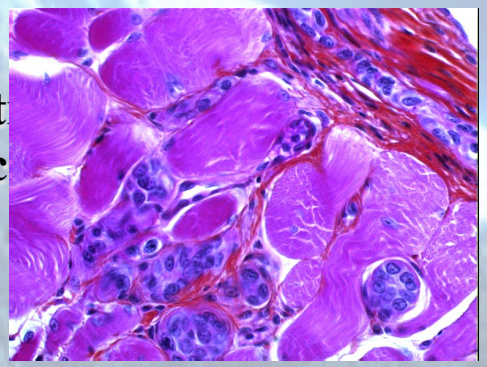
Muscle tissues:
invasive cancer cells

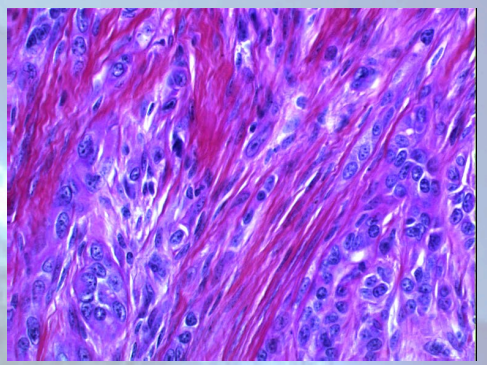


Muscle t
free of c



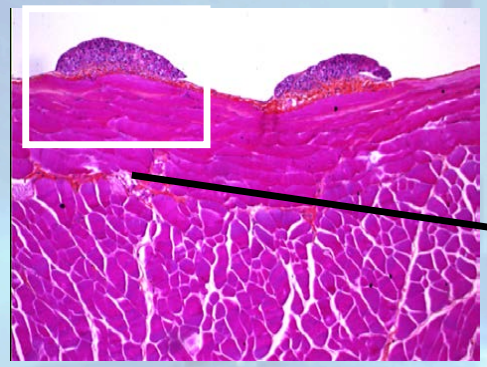


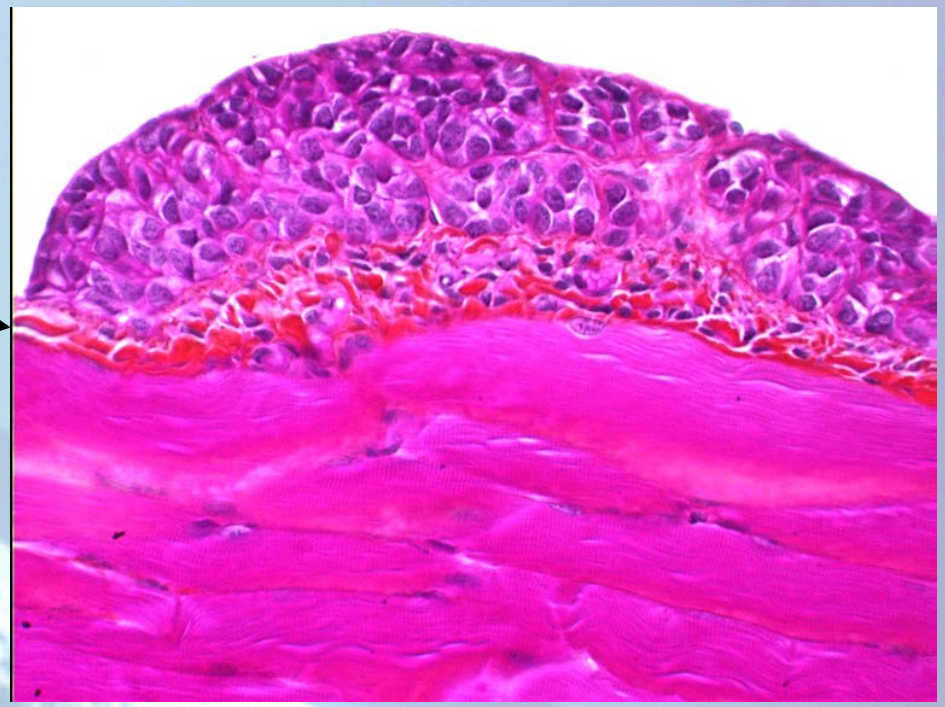




The role of pressure was confirmed using pathologic examination of the implants

Invasion: negative

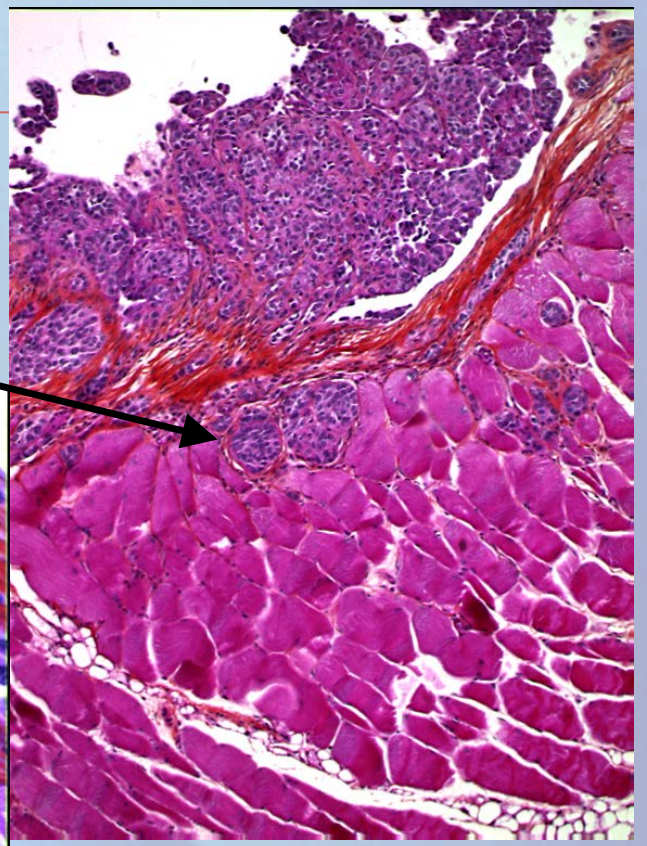


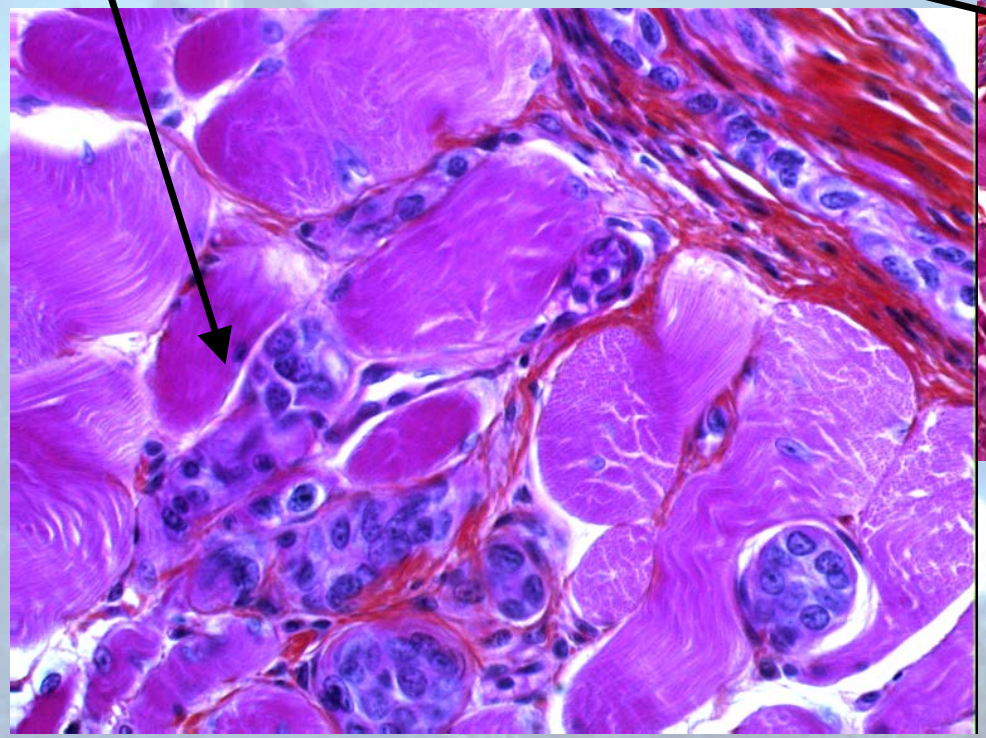


Muscle tissues:
free of cancer cells

Invasion: Positive Minimal

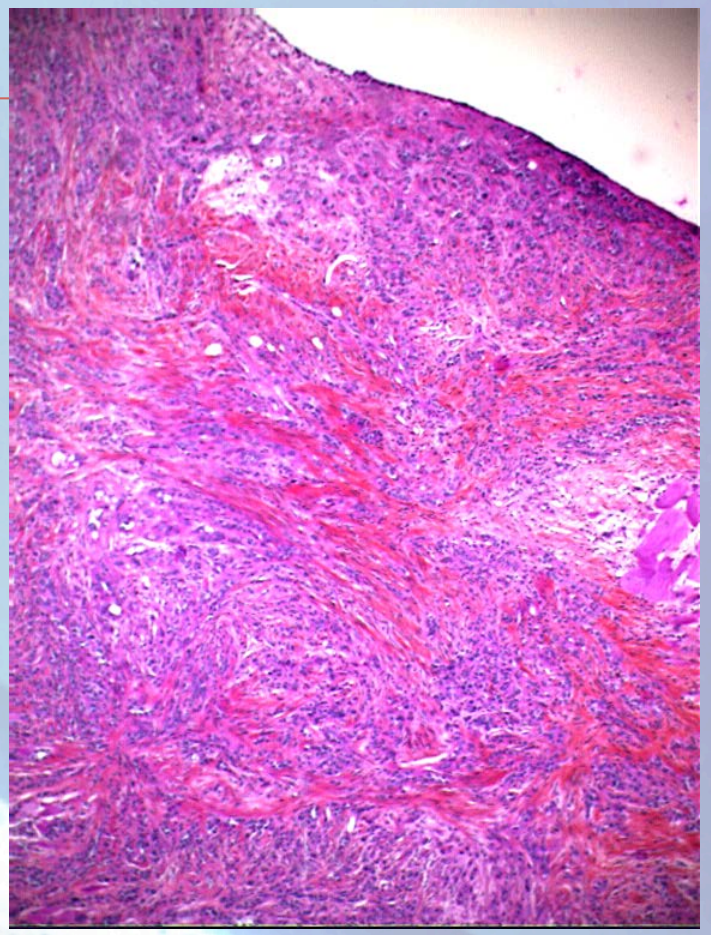
Muscle tissues:
invasive cancer cells

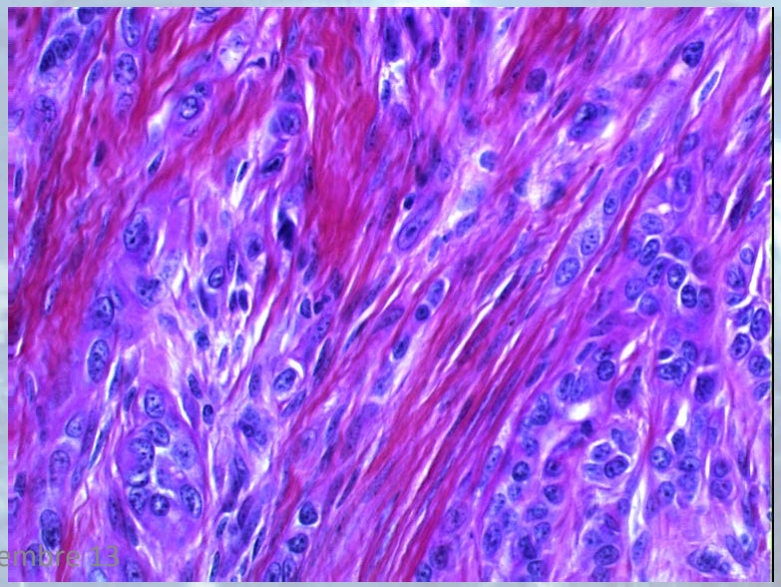




Invasive: Positive Massive

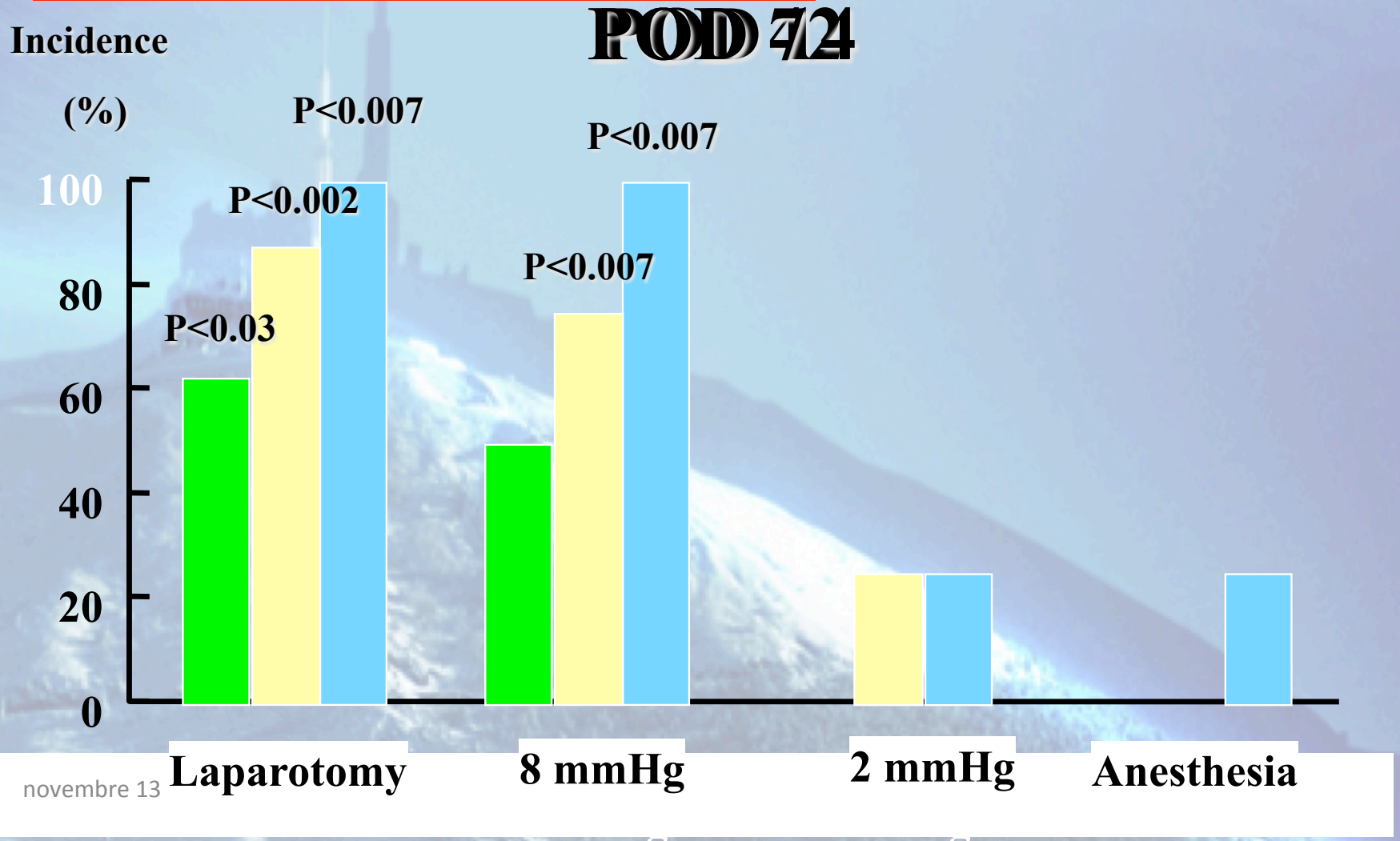
The structure of the muscle is destroyed





Results: Peritoneum

Invasion of cells into muscle tissues



Surg Endosc (2009) 23:705–714
DOI 10.1007/s00464-008-0041-7

Molecular mechanisms underlying postoperative peritoneal tumor dissemination may differ between a laparotomy and carbon dioxide pneumoperitoneum: a syngeneic mouse model with controlled respiratory support

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Dissemination to the Diaphragm

Table 5 Results of dissemination score on the diaphragm[a]

	Laparotomy ($n = 8$)	High IPP ($n = 8$)	Low IPP ($n = 8$)	Control ($n = 8$)
POD 7	1.0 ± 0.08	0.38 ± 0.26	0 ± 0	1.38 ± 0.38[b]
POD 14	0.5 ± 0.33	0.63 ± 0.20	0 ± 0	2.13 ± 0.55[b]
POD 42	5.38 ± 1.01	0.5 ± 0.38[c]	1.75 ± 0.56[d]	4.75 ± 0.77

IPP, intraperitoneal pressure; POD, postoperative day

[a] All data are expressed as mean ± standard error of the mean

[b] $p < 0.01$ vs laparotomy; $p < 0.001$ vs high IPP, low IPP

[c] $p < 0.0001$ vs Lapartomy, control

[d] $p < 0.0001$ vs laparotomy; $p < 0.01$ vs control

Dissemination to the Bowel

Table 6 Dissemination to the bowels

	Laparotomy ($n = 8$)	High IPP ($n = 8$)	Low IPP ($n = 8$)	Control ($n = 8$)
Incidence (%)	100[a]	87.5	62.5	37.5
Dissemination score[b]	5.0 ± 0.0[c]	1.62 ± 0.32	1.38 ± 0.42	0.88 ± 0.44

IPP, intraperitoneal pressure

[a] $p < 0.01$ vs controls

[b] Data are mean ± standard error of the mean

[c] $p < 0.0001$ vs high IPP, low IPP, and control

Dissemination to the liver

Table 7 Dissemination to the liver

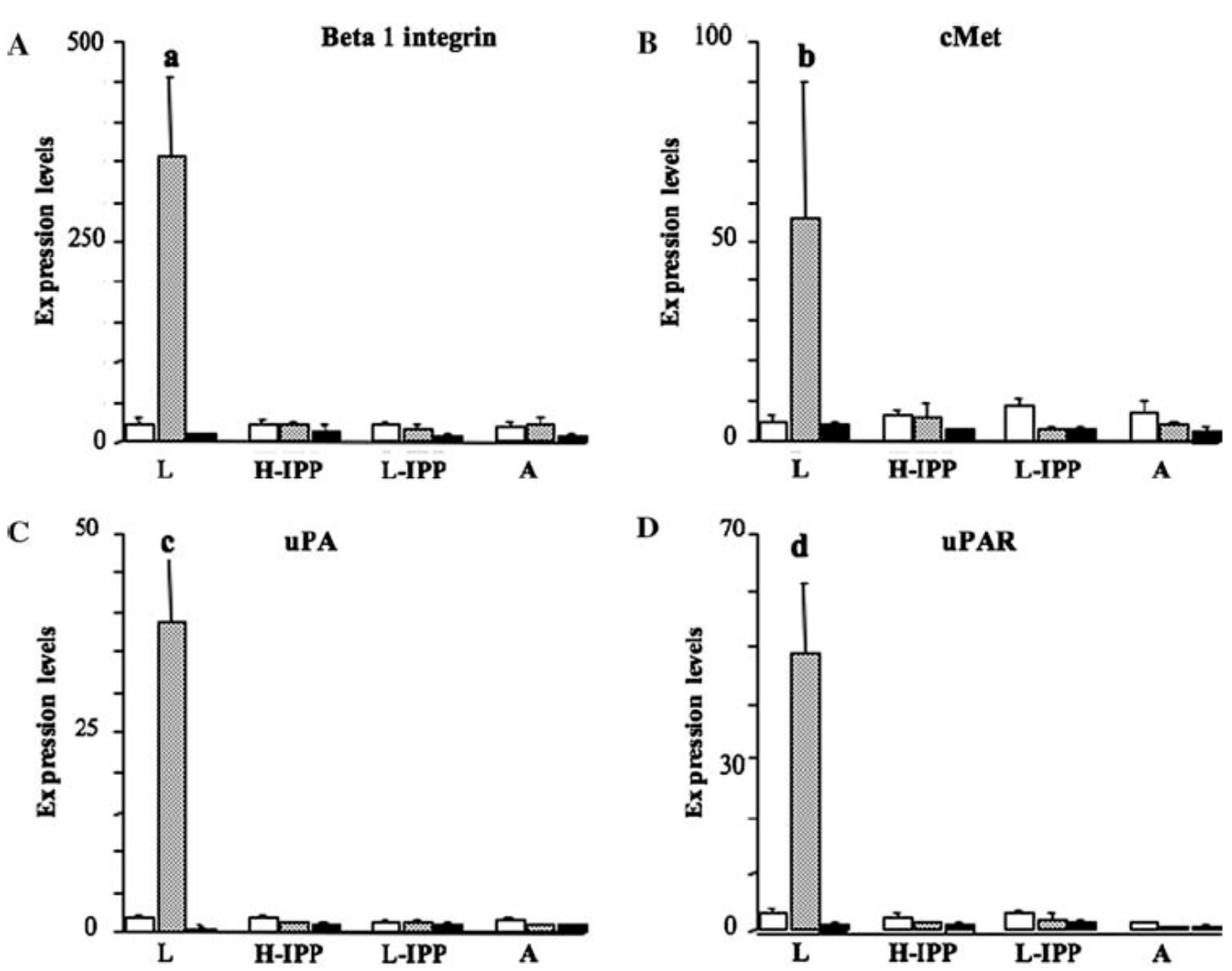
	Laparotomy ($n = 8$)	High IPP ($n = 8$)	Low IPP ($n = 8$)	Control ($n = 8$)
Incidence (%)	100[a]	12.5	37.5	12.5
Dissemination score[b]	3.5 ± 0.59[c]	0.13 ± 0.13	0.74 ± 0.49	0.13 ± 0.13

[a] $p < 0.01$ vs high IPP; $p < 0.03$ vs low IPP, control

[b] Data are mean ± standard error of the mean

[c] $p < 0.0001$ vs high IPP, low IPP, and control

Molecular analysis



Peritoneal

Carcinomatosis Model

Objectives

1./ To **modelize** : surgery performed on a preexisting ovarian cancer model

2./ To **study** : the influence of surgical environment, represented by surgical option and insufflation pressure, on peritoneal dissemination and tumor growth

3./To **analyze** : this impact in early post-operative period

Materials and Methods

	Preimplanted tumor cells
Intraperitoneal Injection *	7 days before randomization
Surgery	Randomisation : Laparotomy, Low Pressure Pneumoperitoneum (LPP), High PP (HPP), Anesthesia
Evaluation	POD 1-2-7-14

Post operative

Dissemination scores

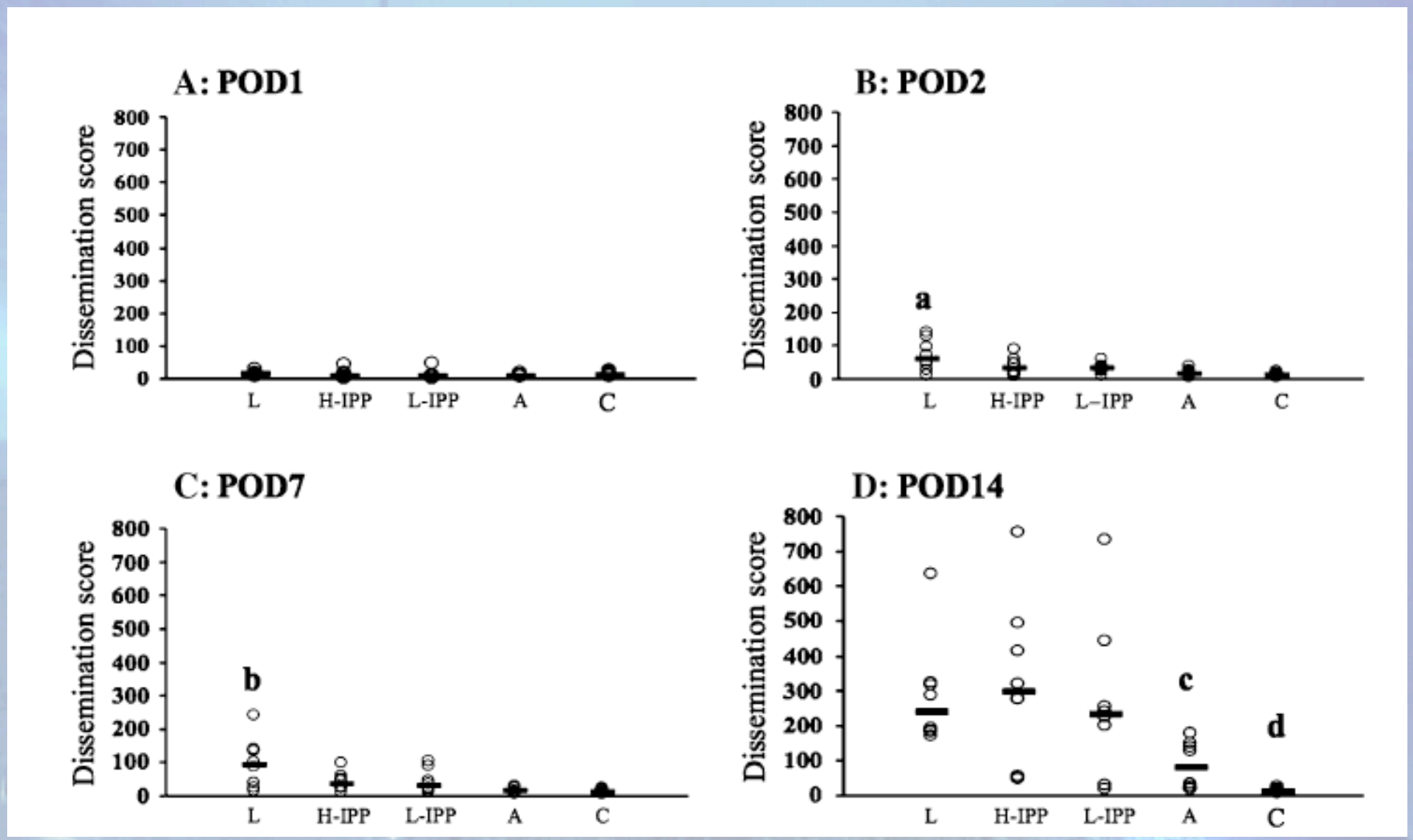

A: POD1
B: POD2
C: POD7
D: POD14
Dissemination score
800
700
600
500
400
300
200
100
0
L
H-IPP
L-IPP
A
C
a
b
c
d

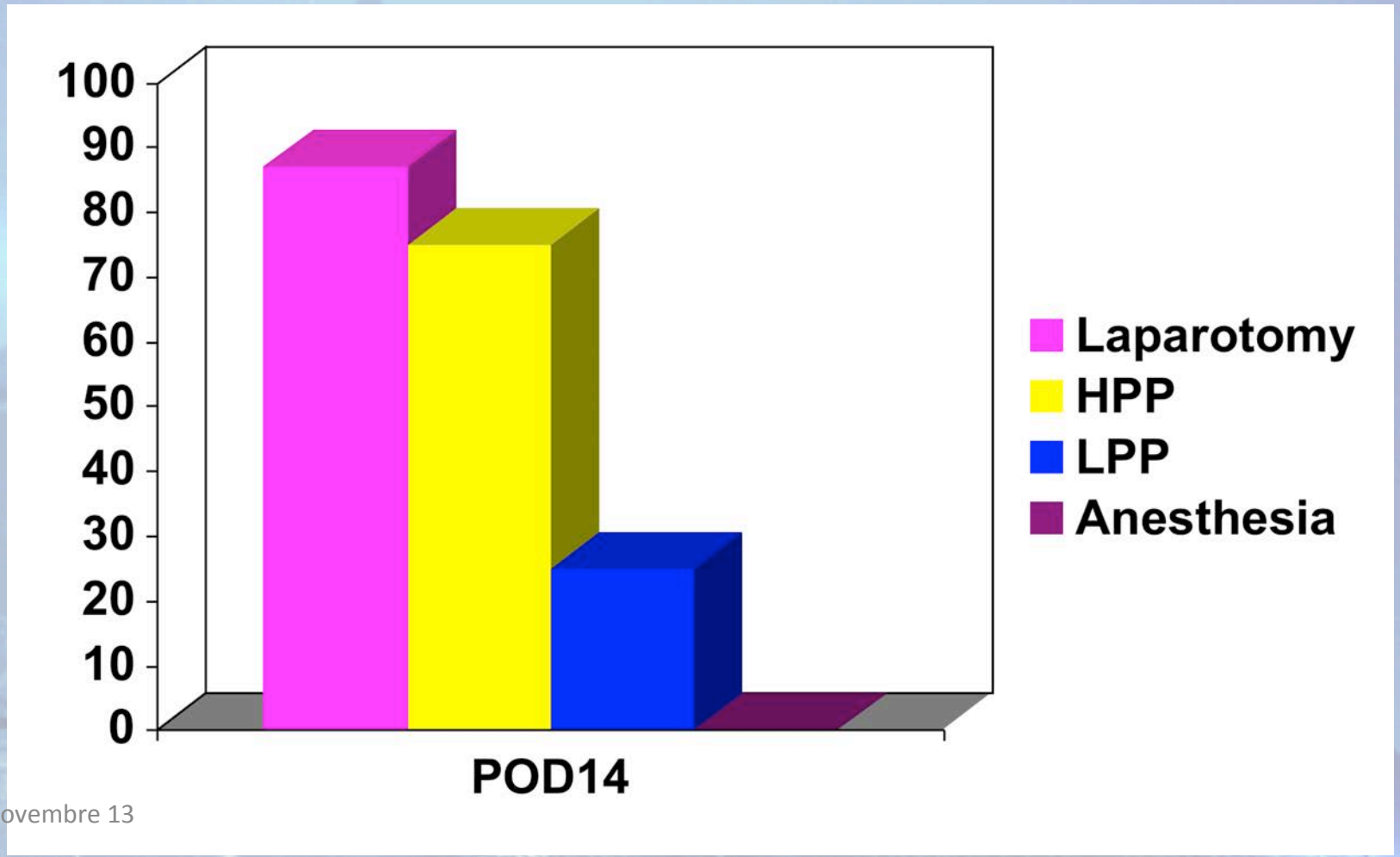
Table 4 Results of dissemination score on the diaphragm

	Laparotomy ($n = 8$)	H-IPP ($n = 8$)	L-IPP ($n = 8$)	Anesthesia ($n = 8$)	Control ($n = 8$)
POD 0	N.A.	N.A.	N.A.	N.A.	1.00 ± 0.26
POD 1	0.75 ± 0.16	1.00 ± 0.32	1.13 ± 0.35	1.00 ± 0.32	N.A.
POD 2	2.25 ± 0.92	1.38 ± 0.53	1.13 ± 0.48	2.38 ± 0.98	N.A
POD 7	1.88 ± 0.55	2.25 ± 0.64	1.75 ± 0.92	1.00 ± 0.33	N.A.
POD 14	4.00 ± 1.04[a]	4.38 ± 1.27[b]	4.25 ± 1.08[c]	3.63 ± 1.05	N.A.

All data are expressed as mean ± standard error of the mean (SEM). H-IPP, CO_2 pneumoperitoneum at high IPP; L-IPP, CO_2 pneumoperitoneum at low IPP; N.A., not available

Intramuscular invasion

Intramuscular Invasion



Conclusion

- **Surgical environment** has a **huge influence** on **peritoneal dissemination**
- On a preimplanted ovarian cancer model, **laparoscopy performed under low pressures**, could create an **optimal environment** to minimize peritoneal dissemination
- On a preimplanted tumor model, surgical environment has no influence, either on tumor growth or on trocar site metastases incidence

Impact of the Surgical Peritoneal Environment on Pre-implanted Tumors on a Molecular Level: A Syngeneic Mouse Model

Sachiko Matsuzaki, M.D.,*,†,[1] Anne-Sophie Azuar, M.D.,*,† Gérard Mage, M.D.,*,† and Michel Canis, M. D.*,†

*Université d'Auvergne-Clermont I, Centre dÉndoscopie et des Nouvelles Techniques Interventionnelles (CENTI), Clermont-Ferrand, France; and †CHU Clermont-Ferrand, Polyclinique-Hôtel-Dieu, Gynécologie Obstétrique et Médecine de la Reproduction, Clermont-Ferrand, France

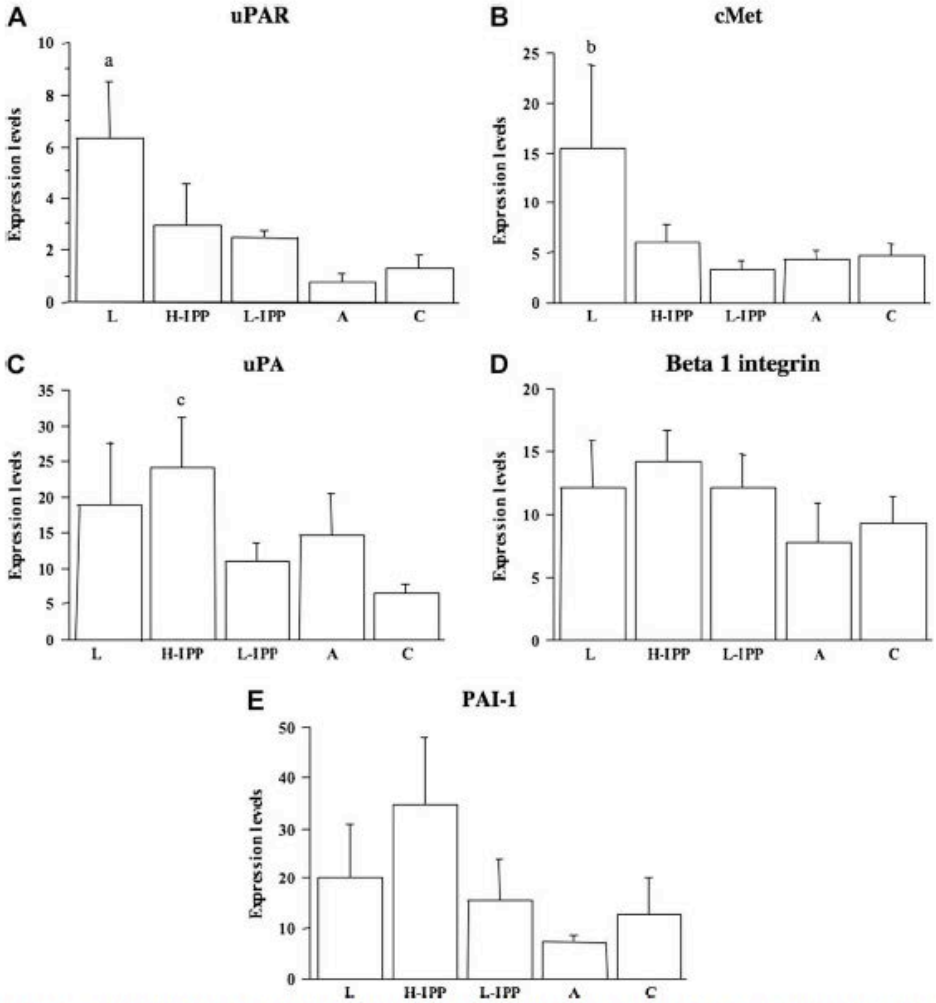


FIG. 2. Results of real-time RT-PCR of pre-implanted nodules from the laparotomy, CO_2 pneumoperitoneum at high and low IPP, anesthesia alone groups on POD 2, and those of the control group. Expression levels of uPAR (A), cMet (B), uPA (C), β-1 integrin (D), or PAI-1 (E) mRNA are given relative to the expression levels of the reference gene, GAPDH. Results are presented as the mean ± SD. Bars indicate the SD. L: Laparotomy: ($n = 8$); H-IPP: CO_2 pneumoperitoneum at high IPP ($n = 8$); L-IPP: CO_2 pneumoperitoneum at low IPP ($n = 8$); A: Anesthesia alone ($n = 8$); C: Control (POD 0: $n = 7$); a: $P < 0.04$ *versus* CO_2 pneumoperitoneum at low IPP, $P < 0.05$ *versus* anesthesia alone, $P < 0.05$ *versus* control; b: $P < 0.04$ *versus* CO_2 pneumoperitoneum at low IPP, $P < 0.04$ *versus* anesthesia alone; $P < 0.04$ *versus* control; c: $P < 0.04$ *versus* control.

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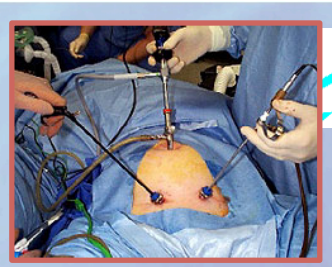
Results. **Expression levels of uPA, uPAR, and cMet mRNA were significantly higher in the laparotomy group than in the control group on POD 1. We detected significantly higher expression levels of uPAR and cMet in the laparotomy group than in the control group on PODs 2 and 7. There were no significant differences in the expression levels of any genes examined among the low IPP, anesthesia alone, and control groups on POD 1, 2, 7, or 14.**

Conclusion. **The impact of a CO_2 pneumoperitoneum at a low IPP on gene expression levels of preimplanted tumors might be minimal until POD 14 in the present mouse model.**

Conclusion

- **<u>Early post-operative windows</u>** has been underlined,
- Peri-operative treatments could be an interesting strategy in oncologic surgery and need to be assessed

Study design



Patients

Laparoscopic hysterectomy
with/without promontofixation

CO2 pneumoperitoneum
8 mmHg

CO2 pneumoperitoneum
12 mmHg

Gene expression profile
by PCR based Microarray

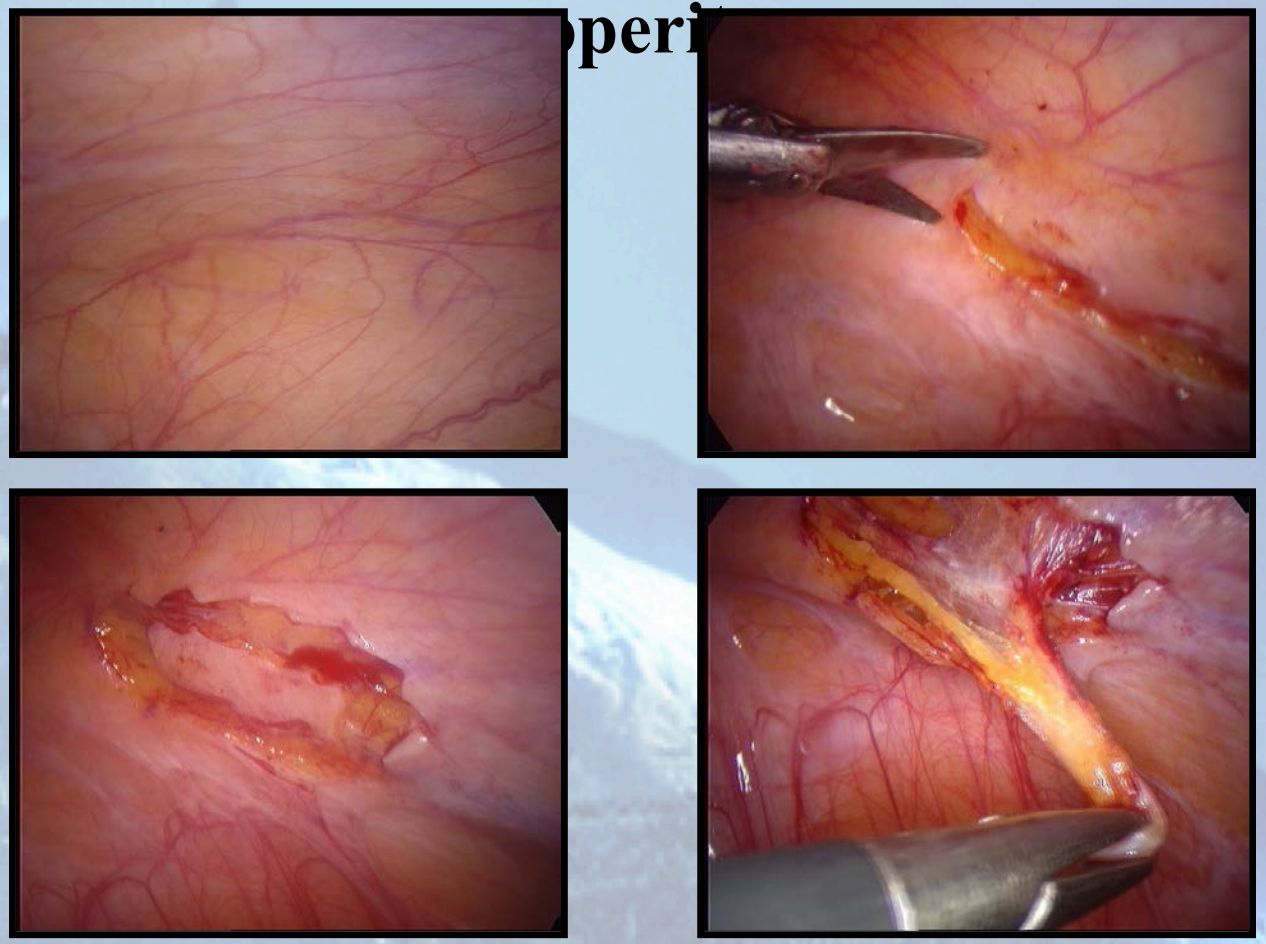
60 min

Peritoneal tissue collection

60 min

Peritoneal tissue collection

Molecular modifications of the peritoneum during a CO2



Peritoneal biopsy

Human Reproduction, Vol.26, No.5 pp. 1073–1081, 2011
Advanced Access publication on March 9, 2011 doi:10.1093/humrep/der055

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Impact of intraperitoneal pressure and duration of surgery on levels of tissue plasminogen activator and plasminogen activator inhibitor-1 mRNA in peritoneal tissues during laparoscopic surgery†

Sachiko Matsuzaki [1,2,*], Revaz Botchorishvili [1], Kris Jardon [1], Elodie Maleysson [1], Michel Canis [1,2], and Gérard Mage [1,2]

[1]Chirurgie Gynécologique, CHU Clermont-Ferrand, CHU Estaing, 1, Place Lucie Aubrac, 63003, Clermont-Ferrand, France [2]CENTI, University of Auvergne Clermont I, 2ETG, Bâtiment 3C, 28, Place Henri Dunan, 63000, Clermont-Ferrand, France

Human Reproduction, Vol.27, No.6 pp. 1613–1623, 2012
Advanced Access publication on March 27, 2012 doi:10.1093/humrep/des081

human reproduction

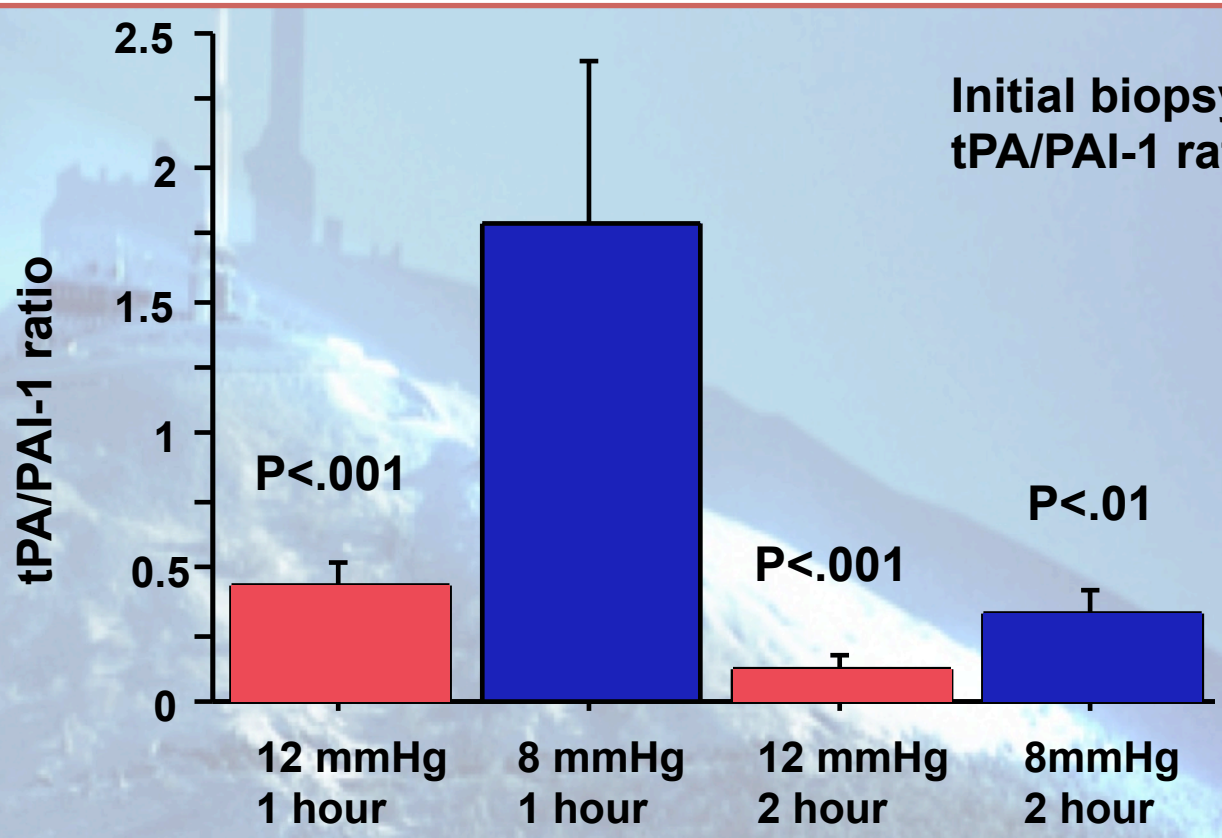
ORIGINAL ARTICLE *Gynaecology*

Table I Clinical characteristics of patients.

Group	12 mmHg	8 mmHg
No. of cases	36	32
Age[a]	48.5 (42–69)	48.0 (42–63)
Parity[a]	3 (0–6)	3 (0–5)
Menstrual cycle, *n* (%)		
Proliferative	0 (0)	0 (0)
Secretory	0 (0)	0 (0)
Anovulation		
With GnRH agonist	8 (22.2)	6 (18.8)
With oral progestogens	5 (13.9)	4 (12.5)
Post-menopausal	23 (63.9)	22 (68.8)
Indication, *n* (%)		
Uterine fibroma	12 (33.3)	10 (31.3)
Uterin fibroma + abnormal bleeding	8 (22.2)	7 (21.9)
Genital prolapse	16 (44.4)	15 (46.9)

[a]Median (range).

tPA/PAI-1 ratio during a CO_2 pneumoperitoneum



tPA: tissue plasminogen activator, PAI-1: plasminogen activator inhibitor-1

Conclusion

- The increase in tPA/PAI 1 ratio is explained by an increase in PAI 1 and results in a decreased fibrinolytic activity and increased post operative adhesion formation

- In conclusion, the results of the present study suggest that a low IPP (8 mmHg) may be better than the standard IPP (12 mmHg) to minimize the impact on the peritoneal fibrinolytic system during a CO2 pneumoperitoneum.

- In addition, the results of the present mouse study suggest that the critical time for the prevention of post-operative adhesion formation by increasing peritoneal fibrinolytic activity might be during surgery and up to 4 h after surgery.

Human Reproduction, Vol.27, No.6 pp. 1613–1623, 2012
Advanced Access publication on March 27, 2012 doi:10.1093/humrep/des081

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Impact of intraperitoneal pressure of a CO_2 pneumoperitoneum on the surgical peritoneal environment†

Sachiko Matsuzaki[1,2,3,*], Kris Jardon[1], Elodie Maleysson[1], Francis D'Arpiany[4], Michel Canis[1,2,3], and Revaz Botchorishvili[1,2,3]

[1]CHU Clermont-Ferrand, CHU Estaing, Chirurgie Gynécologique, 1, Place Lucie Aubrac, 63003 Clermont-Ferrand, France [2]Clermont Université, Université d'Auvergne, ISIT UMR6284, Bâtiment 3C, 28, Place Henri Dunant, BP10448, F-63000 Clermont-Ferrand, France [3]CNRS, ISIT UMR6284, Bâtiment 3C, 28, Place Henri Dunant, BP10448, F-63000 Clermont-Ferrand, France [4]Centre International de la Chirurgie Endoscopique (CICE), Clermont-Ferrand, France

Pathophysiology of the Peritoneal Membrane during Peritoneal Dialysis: The Role of Hyaluronan

Hyaluronan as an Immune Regulator in Human Diseases

DIANHUA JIANG, JIURONG LIANG, AND PAUL W. NOBLE

Department of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Duke University School of Medicine, Durham, North Carolina

Contributes to the protective role of the glycocalyx, acts as a lubricant	Induces chemokine and cytokine secretion by infiltrating, mesothelial, renal tubular epithelial and endothelial cells
Transportation and distribution of plasma proteins	Induces phosphorylation of signaling pathways, for example, MAPK
Contributes to water balance and regulation of tissue hydration	Induces cell migration, for example, tumor cells
Contributes to tissue integrity and maintenance of epithelial cell phenotype	Induces cell proliferation in chondrocytes, endothelial cells, and fibroblasts
Protects against tissue damage by scavenging free radicals	Activates NFκB
Protects against apoptosis	Induces nitric oxide synthase
Antiangiogenic	Promotes angiogenesis
Inhibits phagocytosis by monocytes and macrophages	Increases matrix protein synthesis, for example, collagen type I
Anti-inflammatory, can inhibit activation of inflammatory cells	Increases transcription of matrix metalloproteinases
Promotes cell quiescence	Suppresses cell death and apoptosis in cell culture
Immunosuppressive (prevents ligand binding to surface receptors)	Induces heat-shock protein expression

LMW hyaluronan: ranges from 4 to 40 saccharide units.

Conclusions 12 mmHg group

- In vivo
  - HAS 1 and 3 decreased
  - Hyal 1 and 2 Increased
- In vitro
  - HAS 123 decreased
  - Hyal 2 Increased
  - HA synthesis decreased

Hyaluronan synthesis is increased at 8 mmHg suggesting a better regeneration of the peritoneum

Conclusion 12 mmHg increased Fibrosis ?

- Increased MMP9
- Increased CTGF
-

Increased Fibrosis and adhesions

MM
fib
group

TGFß is activated by TSP-1 and this is inhibited by TSP-2 which was decreased

Increased PAI 1, decreased tPA/PAI 1

Intraperitoneal pressure

From 12mmHg to 8mmHg

- No additional cost
- No additional instrument
- No additional time
- However, skilled hands
  - Dr. Revaz Botchorhisvili , personal communication

Progression of solid tumors

Epithelial-to-mesenchymal transition

(EMT)

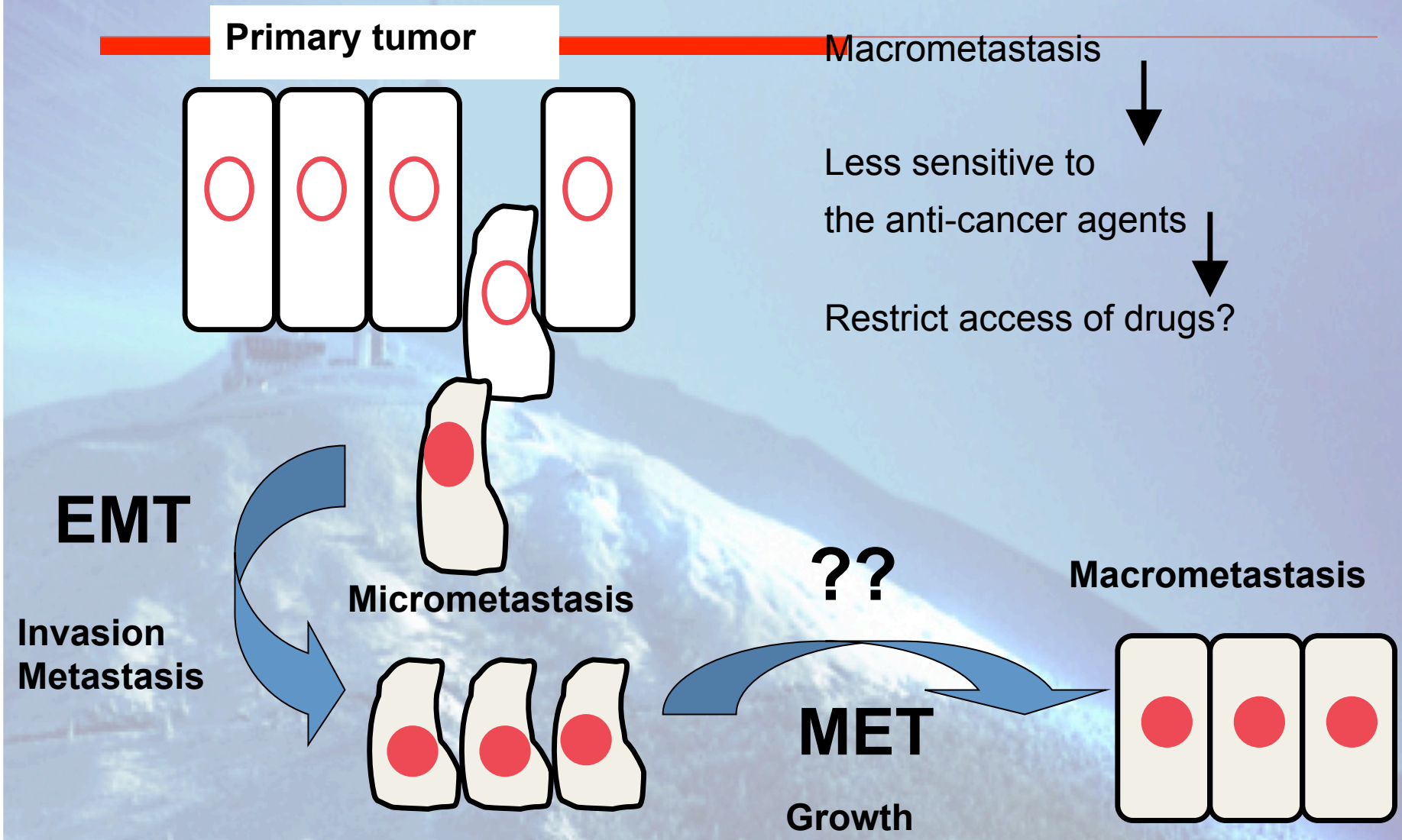
&

Mesenchymal-to-epithelial transition

(MET)

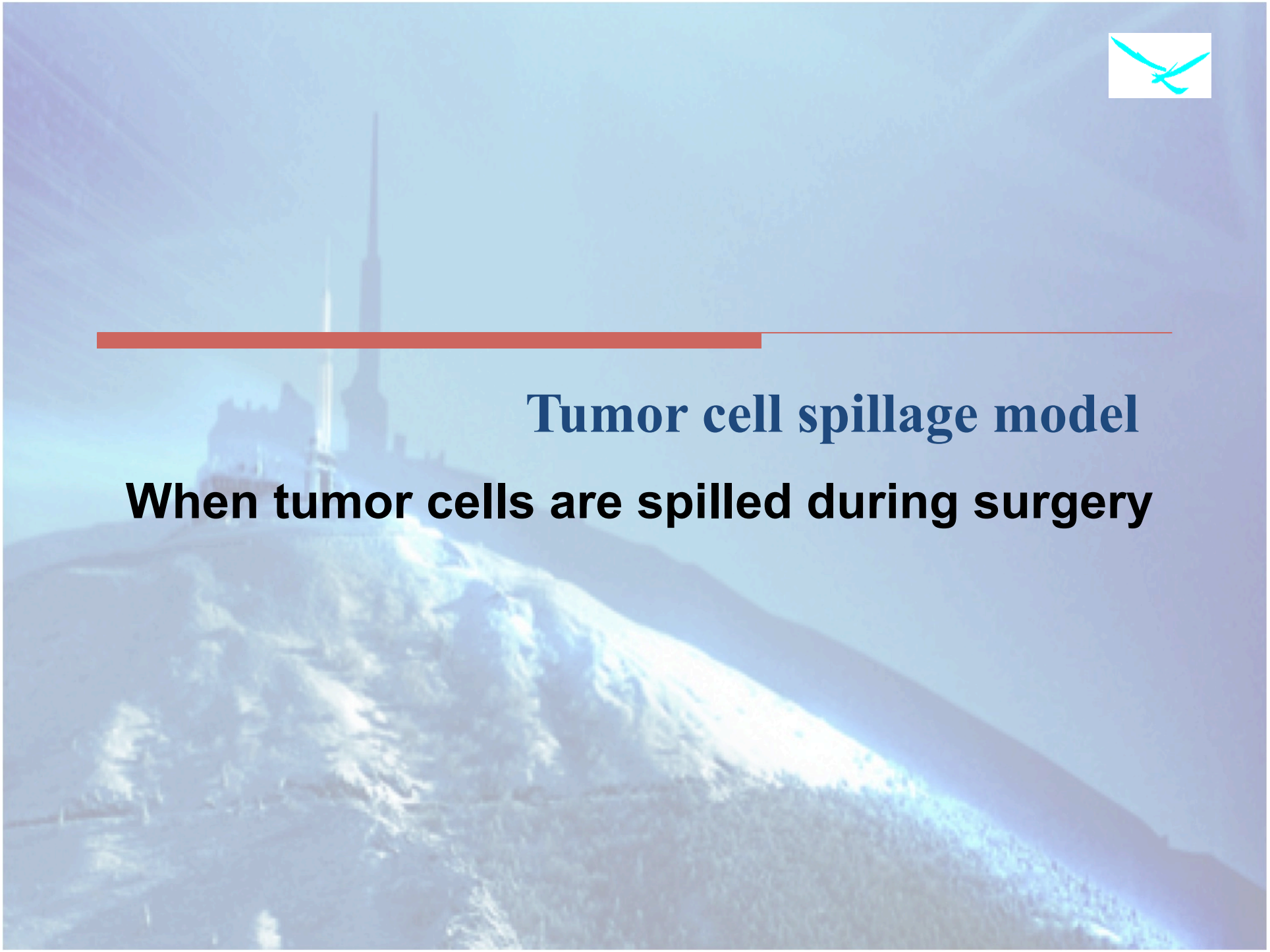
However, still controversial

EMT & MET in progression of solid tumors



Does surgical peritoneal environment affect Epithelial-to-mesenchymal transition in disseminated nodules?

Cadherin-11 (mesenchymal marker)
E-cadherin (epithelial marker)
in disseminated nodules



Tumor cell spillage model

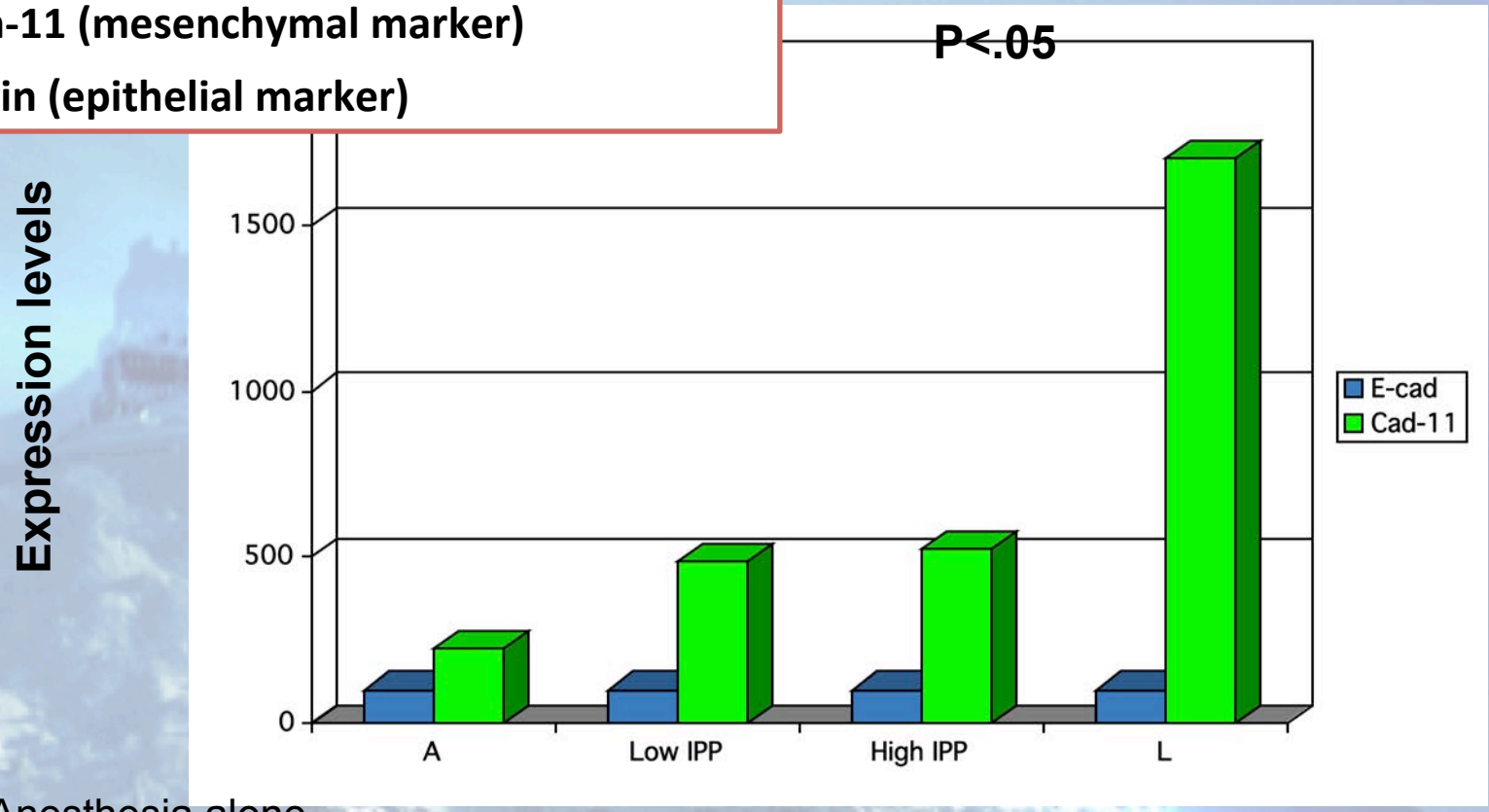
When tumor cells are spilled during surgery

Cadherin-11/E-cadherin mRNA expression

POD14

Cadherin-11 (mesenchymal marker)

E-cadherin (epithelial marker)



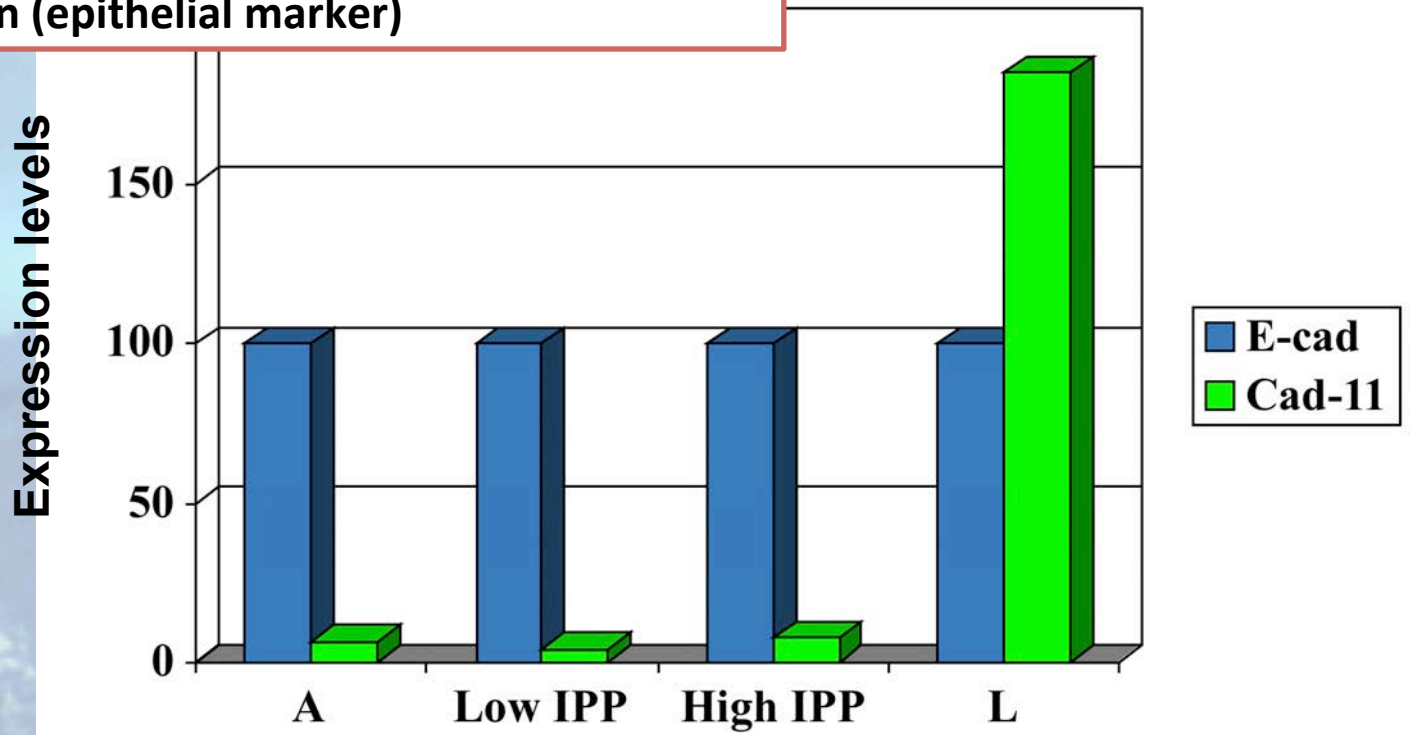
A: Anesthesia alone
Low IPP: CO2 pneuoperitoneum at a low intraperitoneal pressure
High IPP: CO2 pneuoperitoneum at a high intraperitoneal pressure
L: Laparotomy

Cadherin-11/E-cadherin mRNA expression POD42

Cadherin-11 (mesenchymal marker)

E-cadherin (epithelial marker)

P<.05



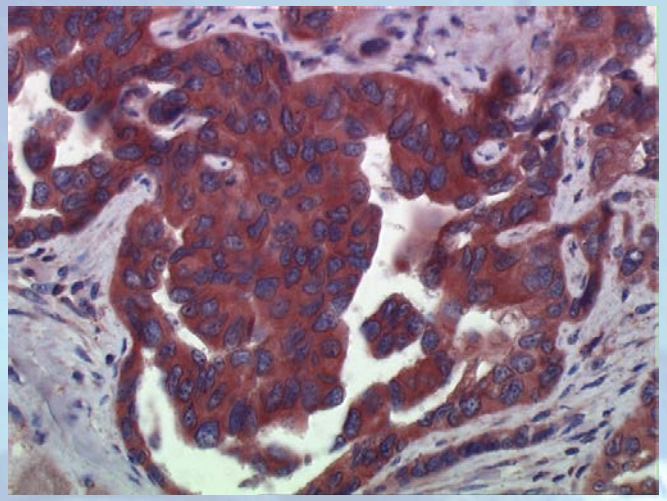
A: Anesthesia alone
Low IPP: CO2 pneuoperitoneum at a low intraperitoneal pressure
High IPP: CO2 pneuoperitoneum at a high intraperitoneal pressure
L: Laparotomy

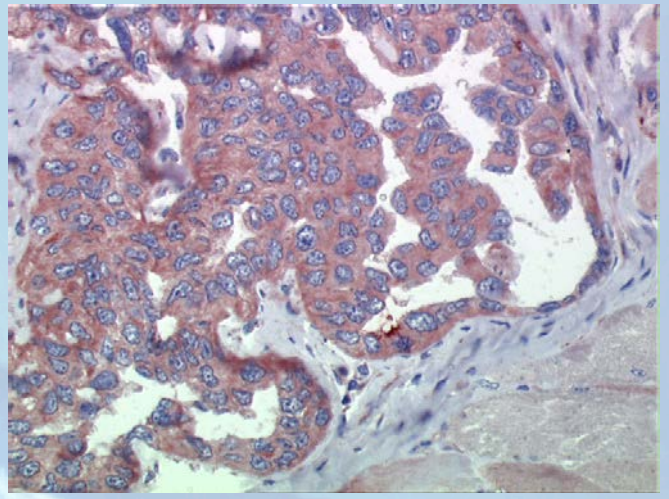
POD 42

Cadherin-11 (mesenchymal marker)

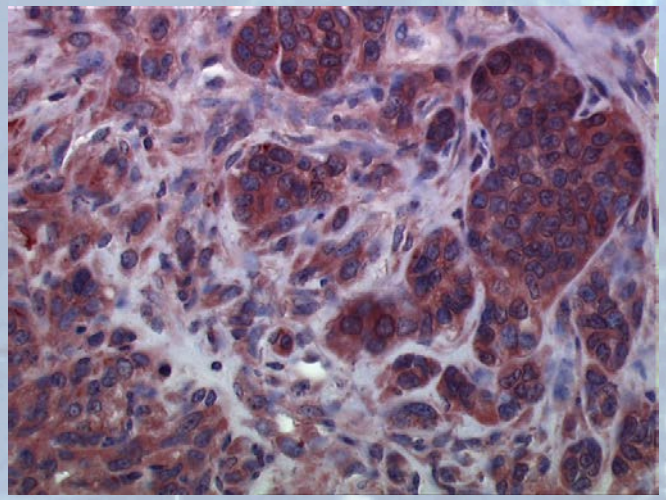
E-cadherin (epithelial marker)

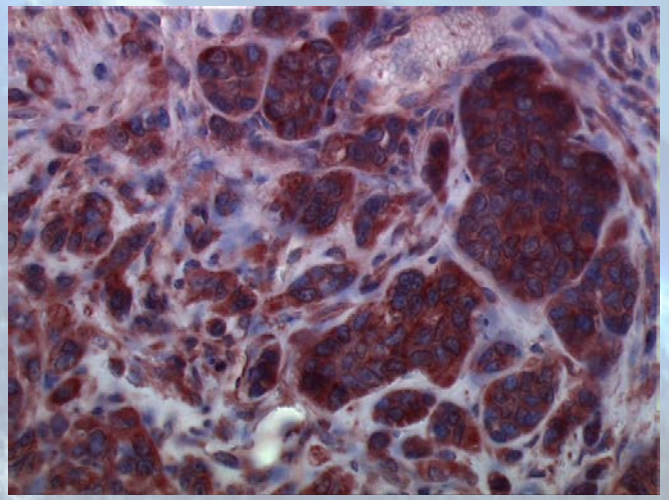
E-cadherin **Cadherin-11**





Laparoscopy
High Pessure





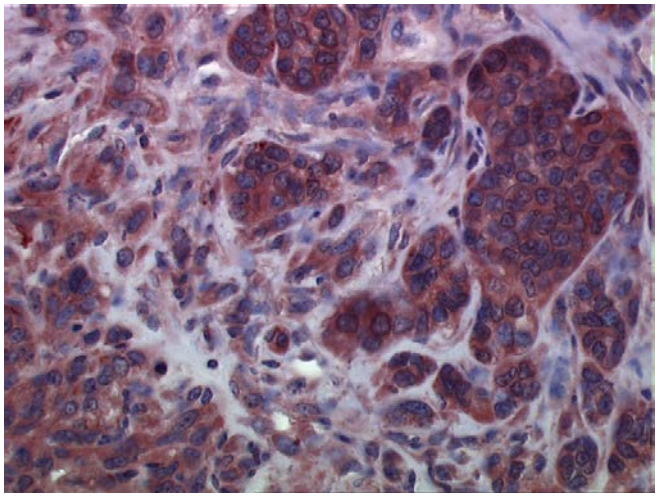
Laparotomy

More mesenchymal phenotype

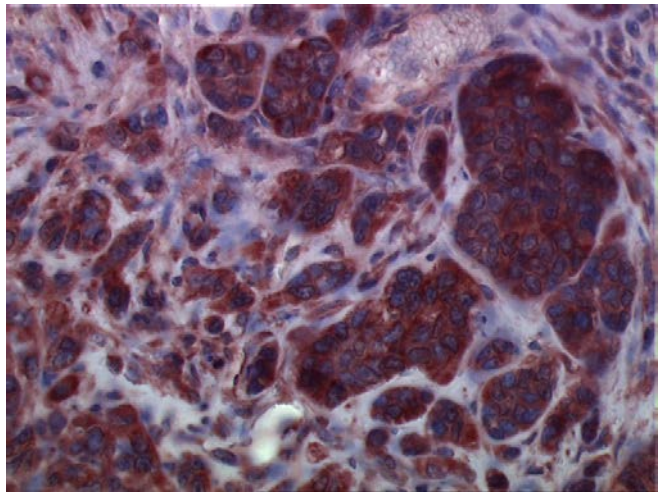
When tumor cells were spilled during surgery

- Less differentiated and more aggressive disseminated tumors after **laparotomy**
  - More drug resistant?

E-cadherin



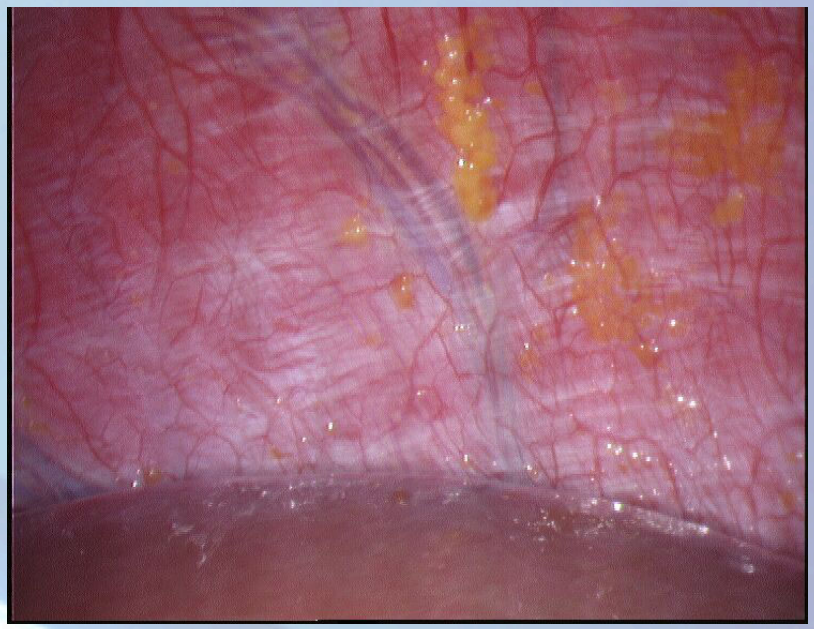
Cadherin-11



Laparotomy

More mesenchymal phenotype

Révolution ?



Open

Closed

Tomorrow ….

- Lparoscopic picture will improve, access to the peritoneum will change …
- Peritoneal atmosphere will become a surgical tool
- Those who are working in open incision with their eyes will have to change their practice closing their spaces and using video camera ……..
- But to use this new surgical tool we have to improve our knowledge of peritoneal and retroperitoneal perioperative pathophysiology.

THE REVOLUTION IS STILL AHEAD !!