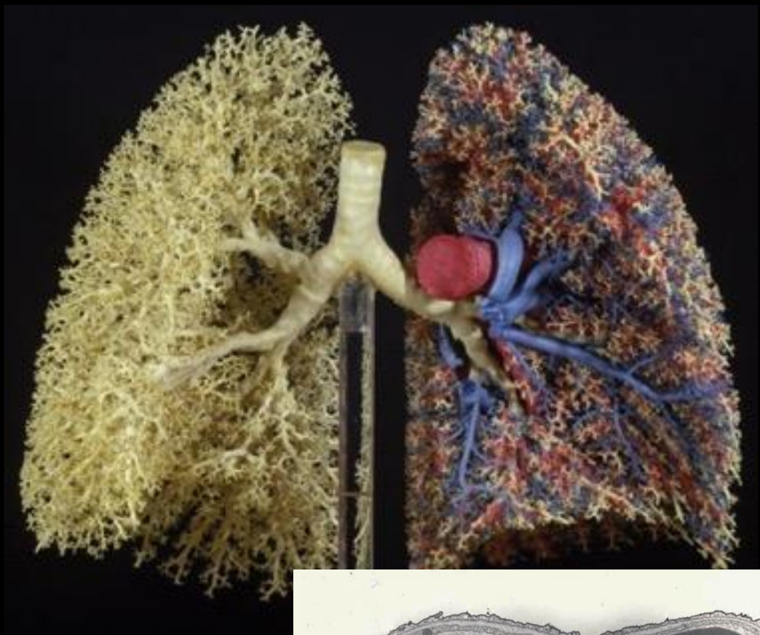
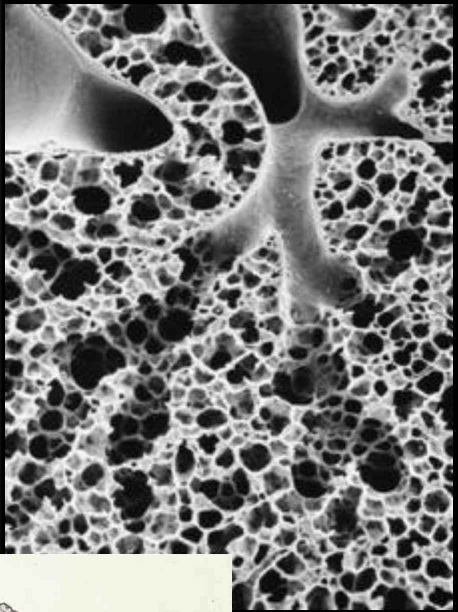
Grüess Ech!

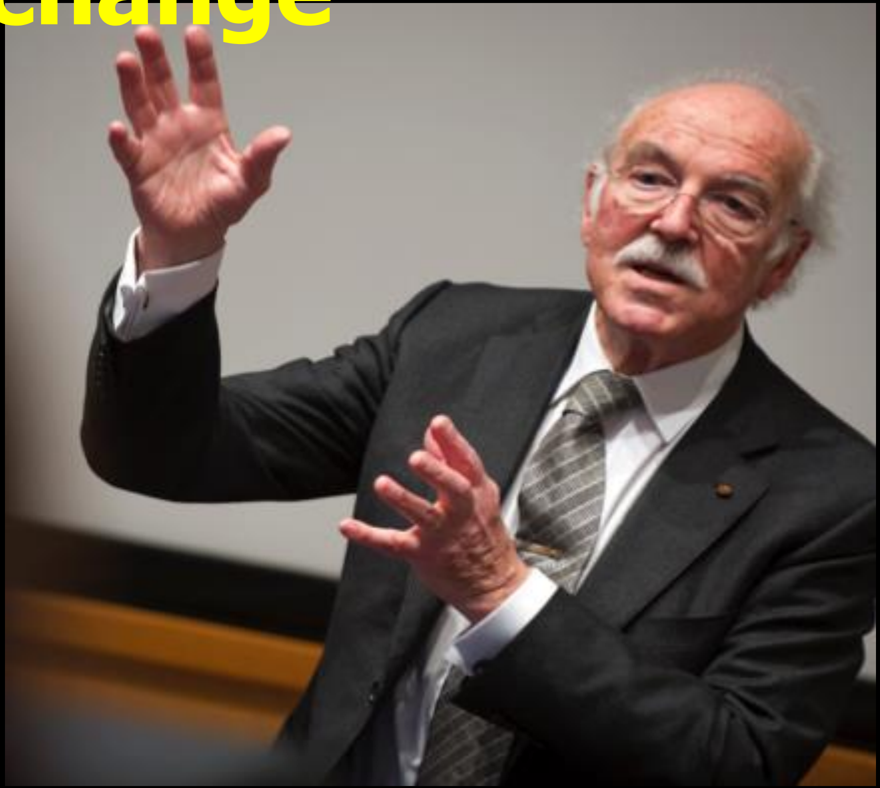
Greetings from Ewald Weibel
in Herrenschwanden

What Makes a Good Lung?

Structural Challenges for Efficient Gas Exchange



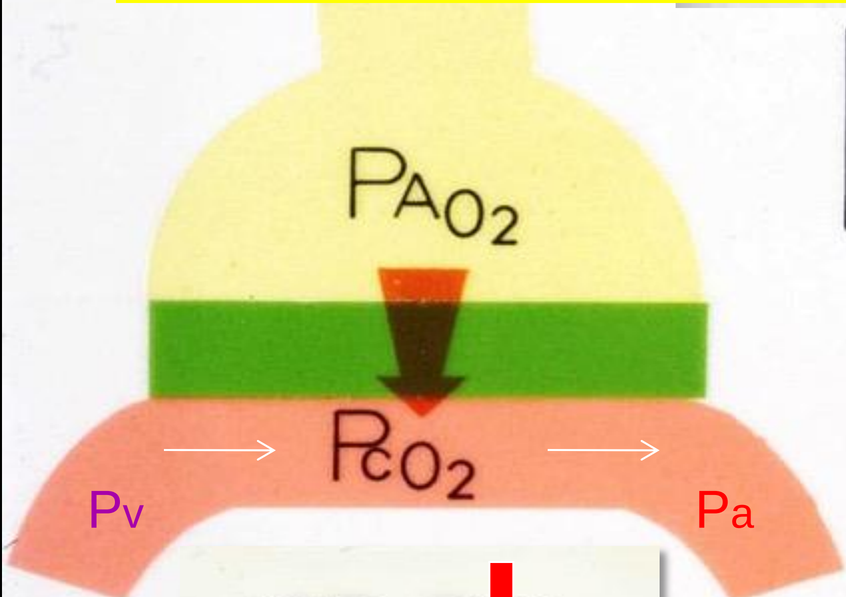


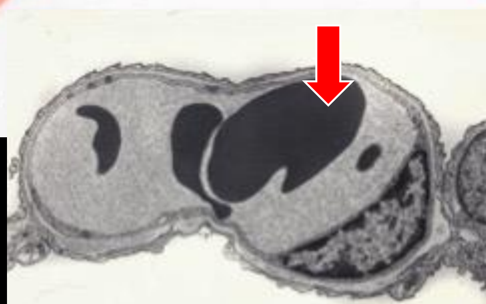


Ewald R. Weibel
University of Bern

Physiology of gas exchanger

1909 *Chr. Bohr* ***1910*** *Marie & August Krogh*





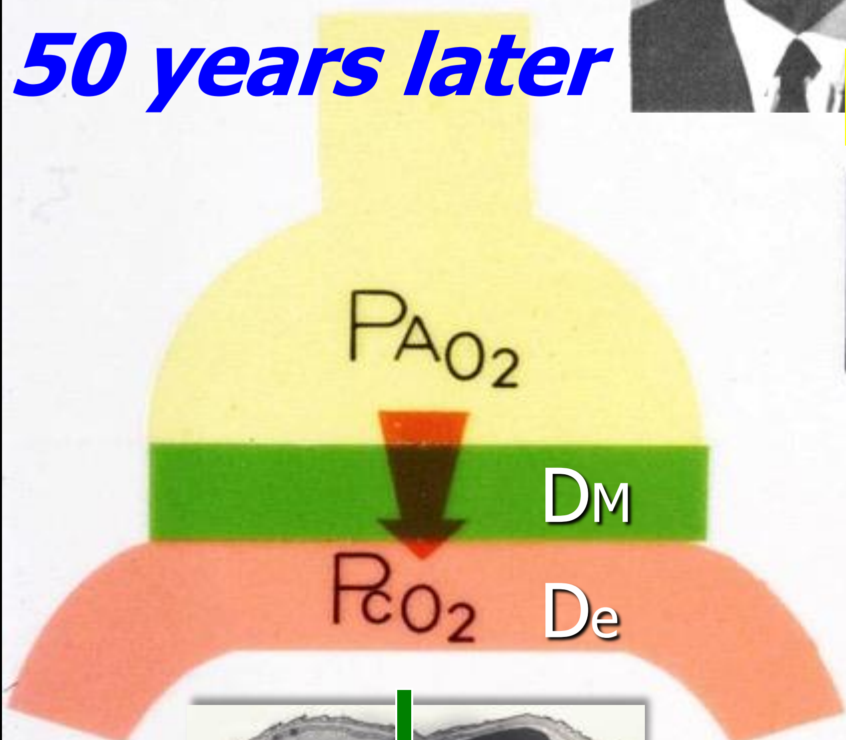
$$\dot{V}_{O_2} = (P_{A_{O_2}} - \bar{P}_{c_{O_2}}) \cdot D_{L_{O_2}}$$

O_2 is transported from air to blood ***by diffusion***

Pulmonary diffusing capacity DL_{O2}

Function & structure of gas exchanger

50 years later



***1957** Roughton & Forster*

$$\dot{V}_{O_2} = (P_{A_{O_2}} - \bar{P}_{c_{O_2}}) \cdot D_{L_{O_2}}$$

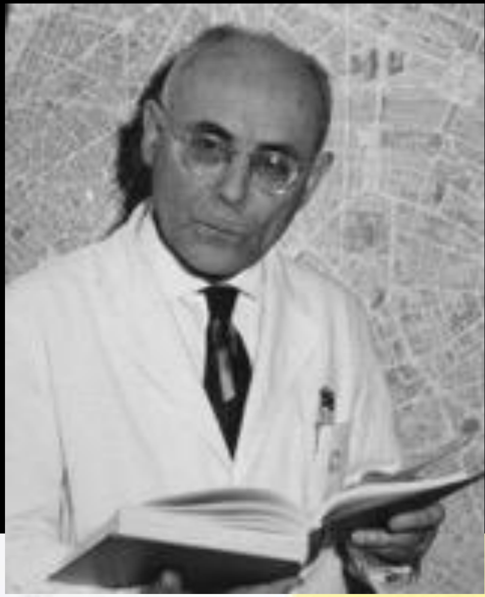
Pulmonary diffusing capacity $\mathbf{D_{L_{O_2}}}$ has 2 components:

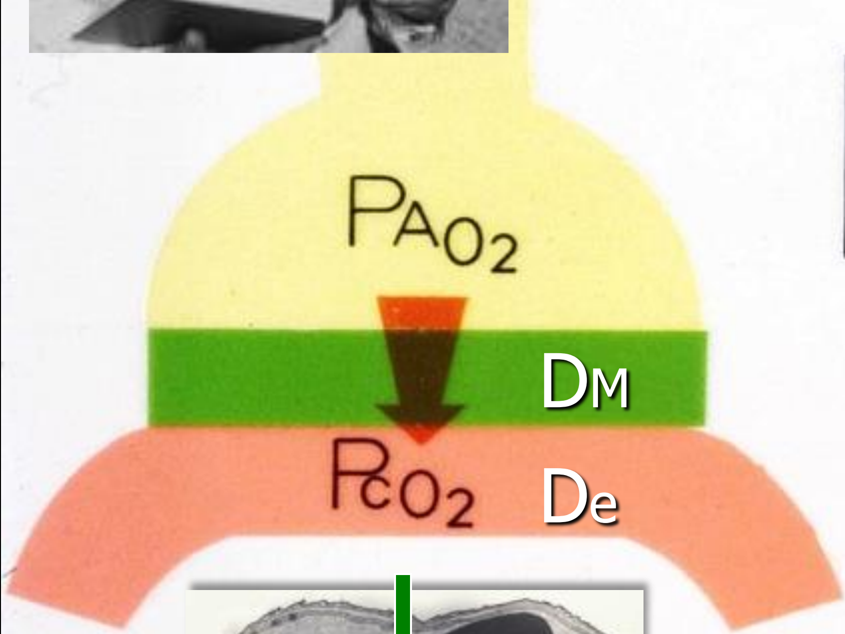
- Membrane $\mathbf{D_{M_{O_2}}}$
- Blood $\mathbf{De_{O_2}}$

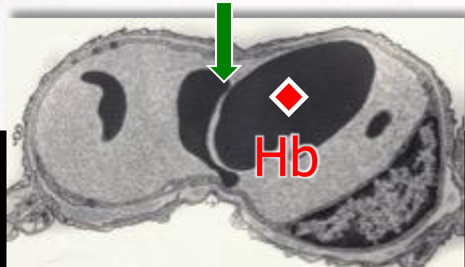
$$1/D_L = 1/D_M + 1/(\theta \cdot V_c)$$

1959: André F. Cournand:

"Do anything on the structure of the lung that is of interest to physiology"







$$\dot{V}_{O_2} = (P_{A_{O_2}} - \bar{P}_{c_{O_2}}) \cdot D_{L_{O_2}}$$

Pulmonary diffusing capacity $\mathbf{D_{L_{O2}}}$ has 2 components:

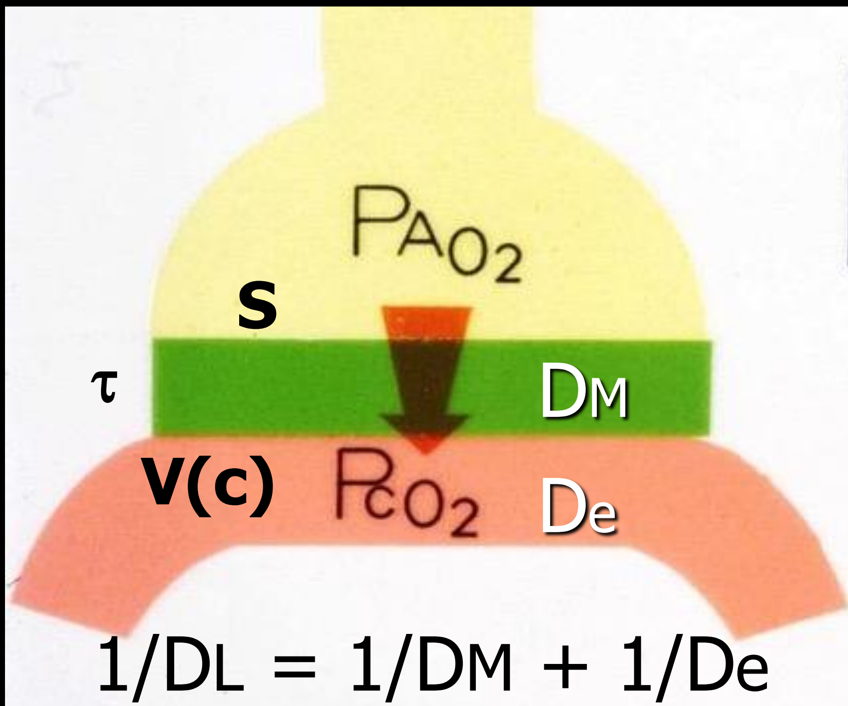
Membrane	$\mathbf{D_{M_{O2}}}$
Blood	$\mathbf{D_{e_{O2}}}$

$$1/D_L = 1/D_M + 1/(\theta \cdot V_c)$$

Vision of Domingo Gomez (1959):

Predict Lung Function from first principles

Physics and Morphometry determine gas exchange capacity

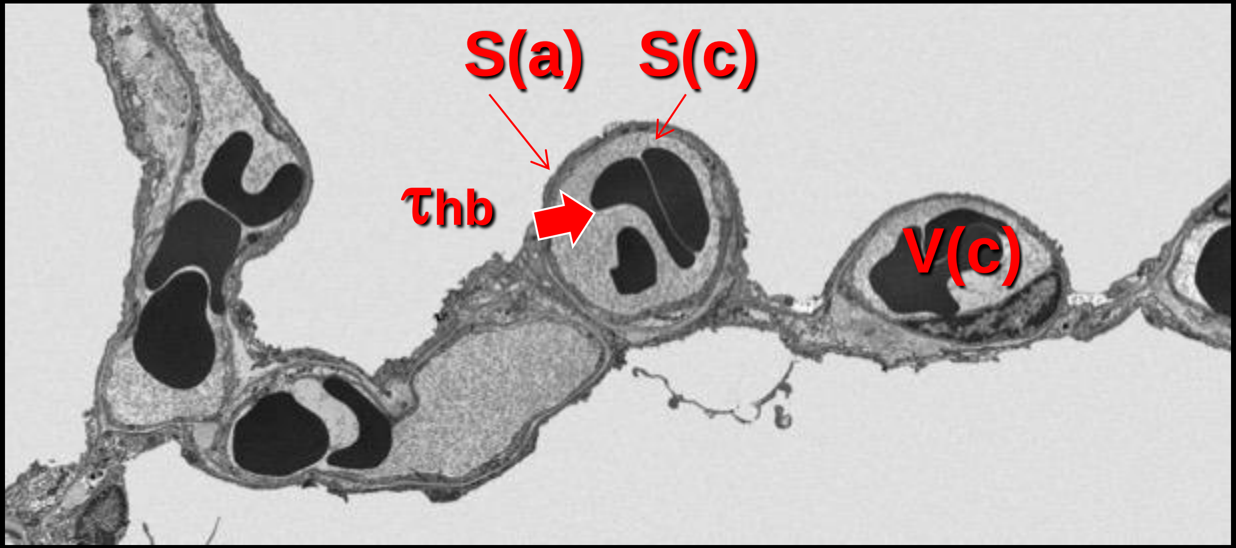


$$\dot{V}_{O_2} = (P_{A_{O_2}} - \bar{P}_{c_{O_2}}) \cdot D_{L_{O_2}}$$

Pulmonary diffusing capacity $\mathbf{D_{L_{O2}}}$ has 2 components:

Membrane	$\mathbf{D_{M_{O2}} \sim S/\tau}$
Blood	$\mathbf{D_{e_{O2}} \sim V(c)}$

Morphometric Model for predicting DL_{O2}



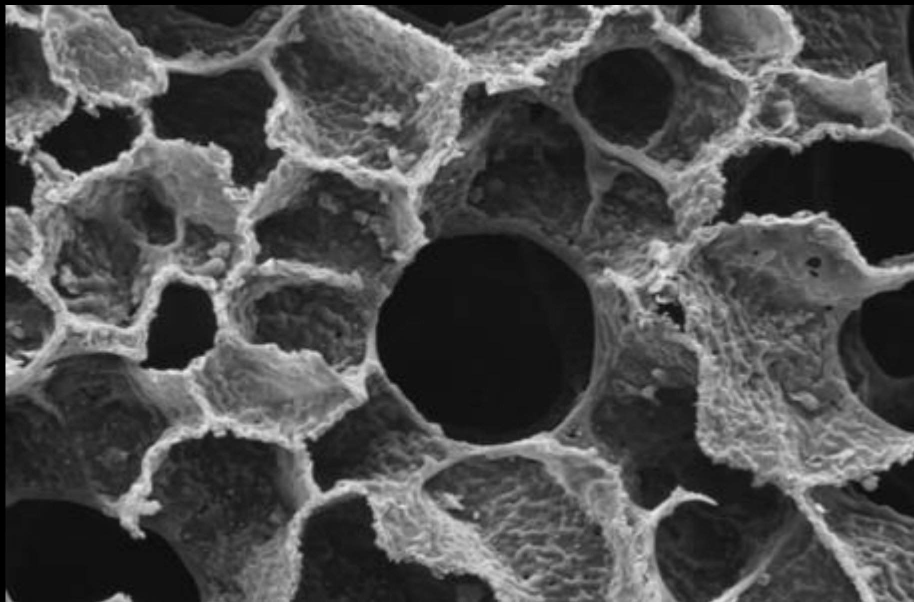
$$1/DL_{O2} = 1/DM_{O2} + 1/De_{O2}$$

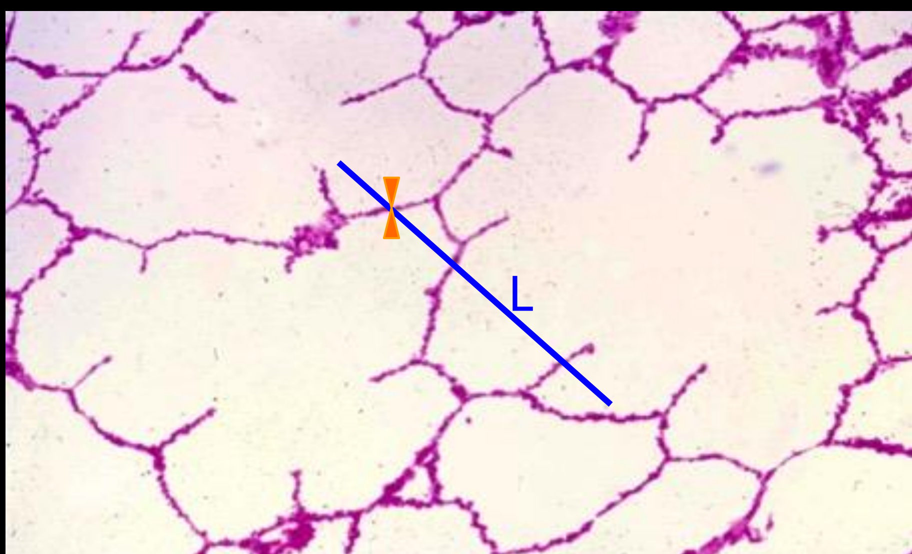
$$DM_{O2} = K_{O2} \cdot (S(a) + S(c))/2 \cdot \tau hb$$

$$De_{O2} = \theta_{O2} \cdot V(c)$$

D.M. Gomez, B.W. Knight, E.R. Weibel (1962-64) based on Roughton & Forster (1957)

Methods for morphometry of human lung





$S(a)$ $S(c)$ $V(c)$ τ_{hb}

Elektron Microscopy &
Stereology

Morphometry of Human Lung & DL_{O2}

- **Body mass** **74 ± 4 kg**
- **Alveolar surface** **130 ± 12 m^2**

Gehr, Bachofen, Weibel 1978/93

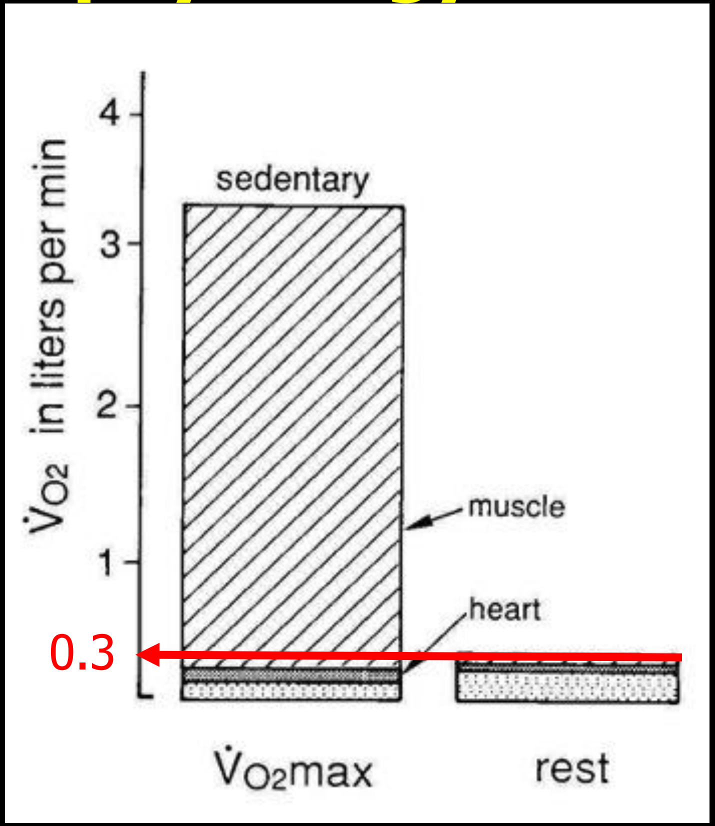
Morphometry of Human Lung & DL_{O_2}

• **Body mass**	**74**	**±**	**4**	**kg**
• **Alveolar surface**	**130**	**±**	**12**	**m^2**
• **Capillary surface**	**115**	**±**	**12**	**m^2**
• **Capillary volume**	**194**	**±**	**30**	**ml**
• **Tissue barrier thickness**	**0.62**	**±**	**0.04**	**µm**
• **Total barrier thickness**	**1.15**	**±**	**0.01**	**µm**

Diffusing capacity DL_{O_2} 158 $mlO_2 . min^{-1} . mmHg^{-1}$

Gehr, Bachofen, Weibel 1978/93

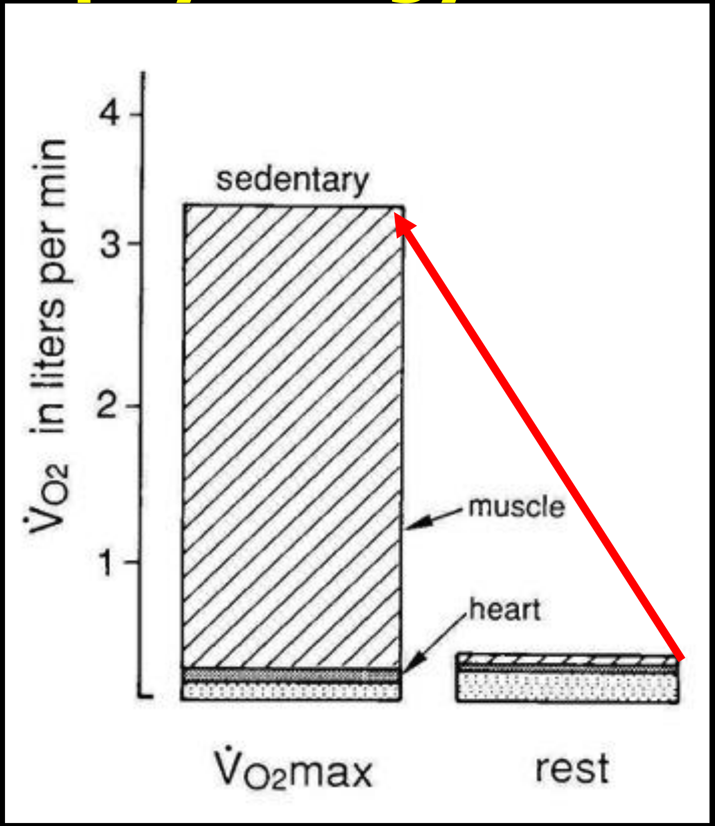
Morphometry and physiology



Morphometric DL_{O2} 158 $mlO_2.min^{-1}·mmHg^{-1}$

Physiological DL_{O2} rest 30 $mlO_2.min^{-1}·mmHg^{-1}$

Morphometry and physiology



Morphometric DL_{O2}	**158**	$mlO_2.min^{-1} \cdot mmHg^{-1}$
Physiological DL_{O2} rest	30	$mlO_2.min^{-1} \cdot mmHg^{-1}$
exercise	**100**	$mlO_2.min^{-1} \cdot mmHg^{-1}$

Morphometry and physiology

Does the normal human lung have excess DL_{O2} ?

Morphometric DL_{O2}	**158**	$mlO_2.min^{-1}\cdot mmHg^{-1}$
Physiological DL_{O2} rest	30	$mlO_2.min^{-1}\cdot mmHg^{-1}$
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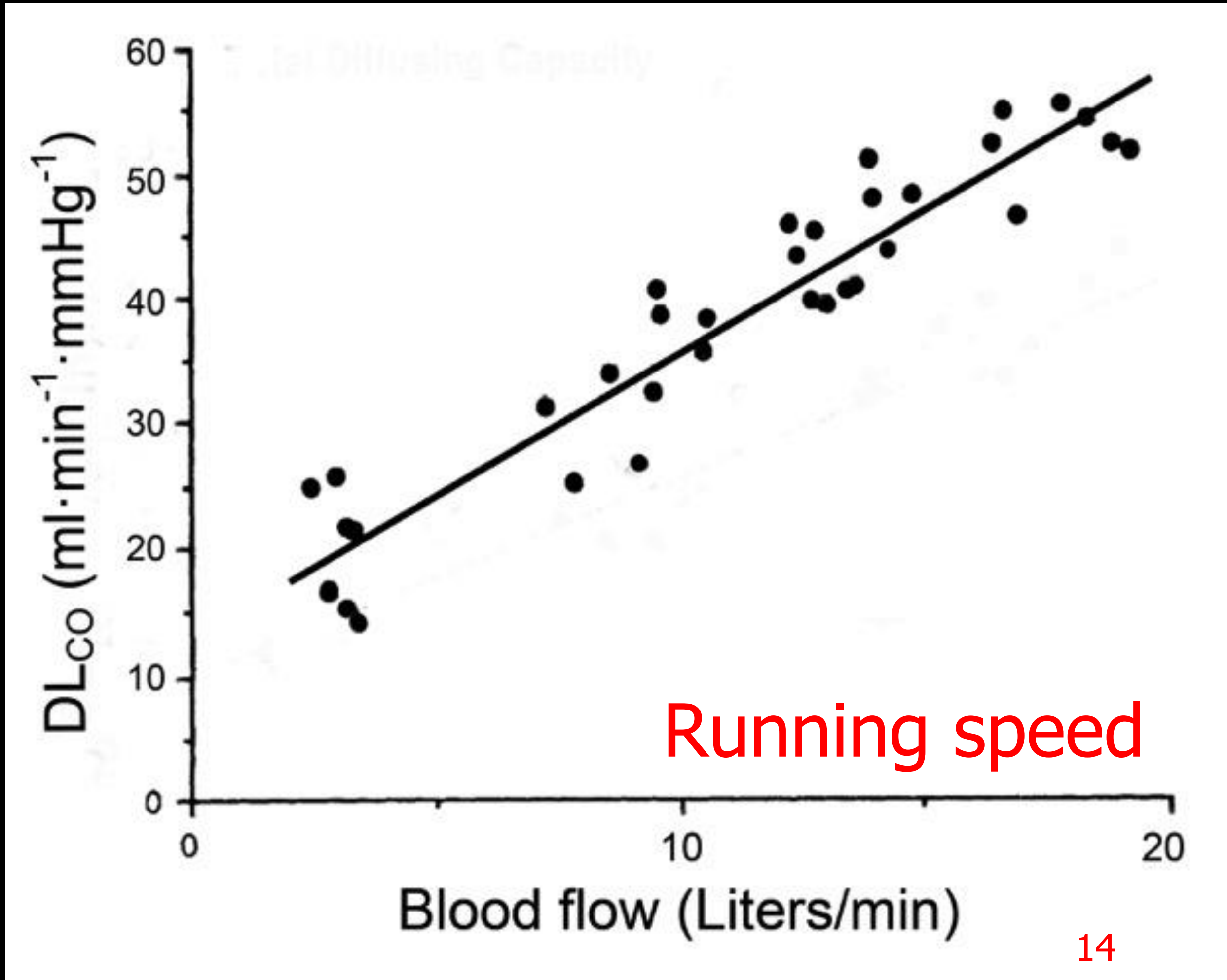
How good is morphometric diffusing capacity?

Test by DL_{CO} in running dogs (1992)

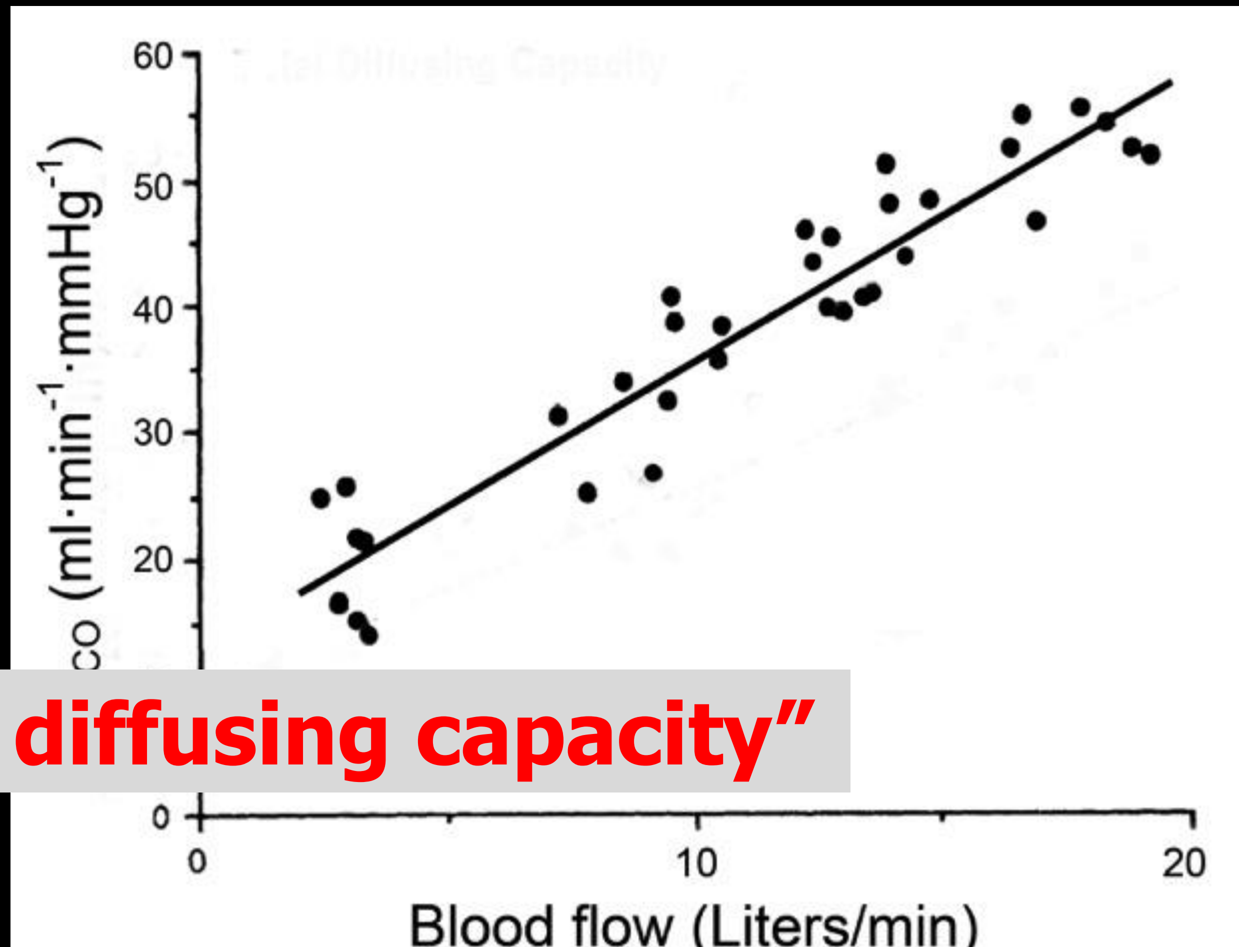
Connie Hsia, Dallas



Do we have excess diffusing capacity?

Test by DL_{CO} in running dogs

Connie Hsia, Dallas

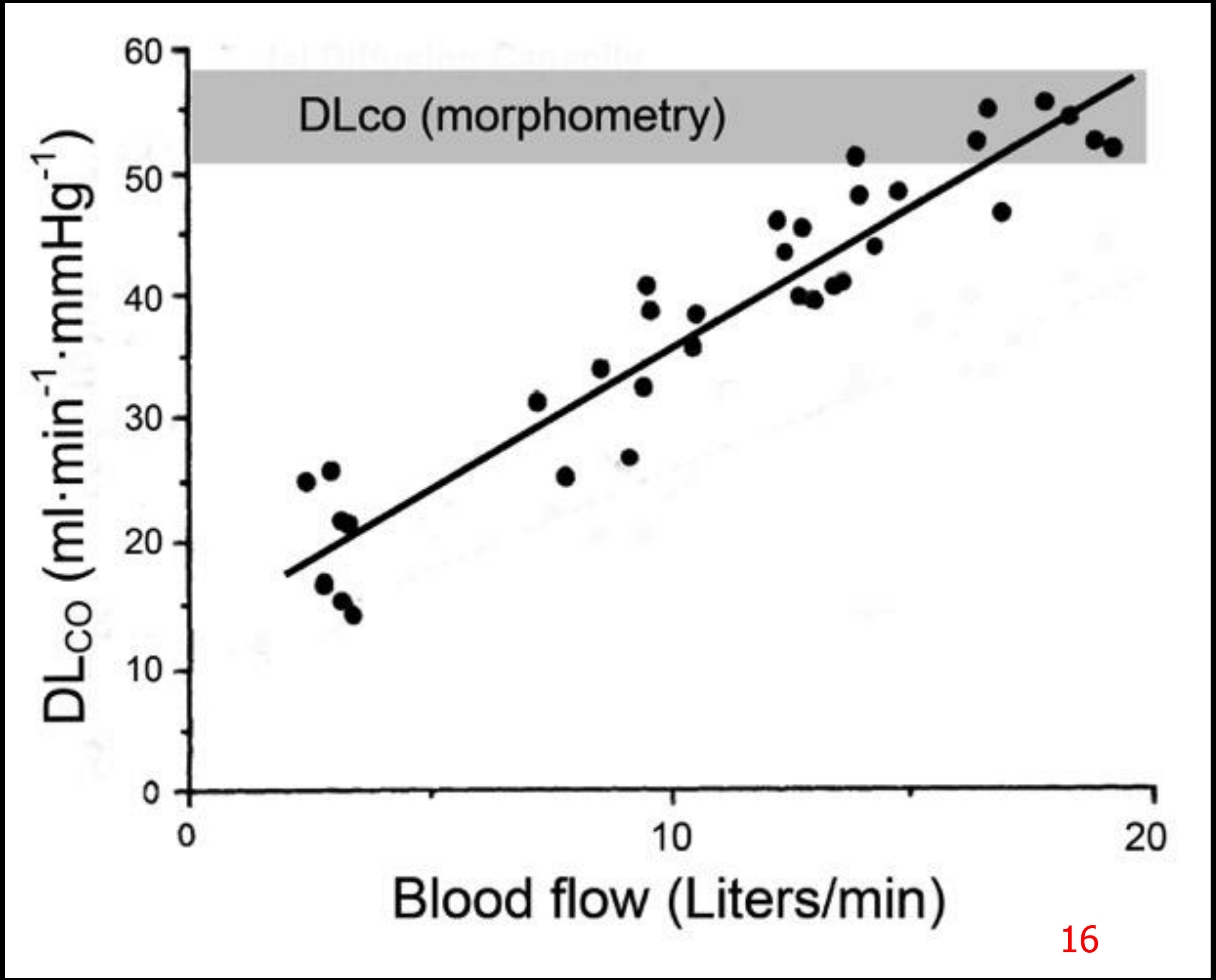


"Recruitment of diffusing capacity"

Do we have excess diffusing capacity?

Test by DL_{CO} in running dogs

Connie Hsia, Dallas



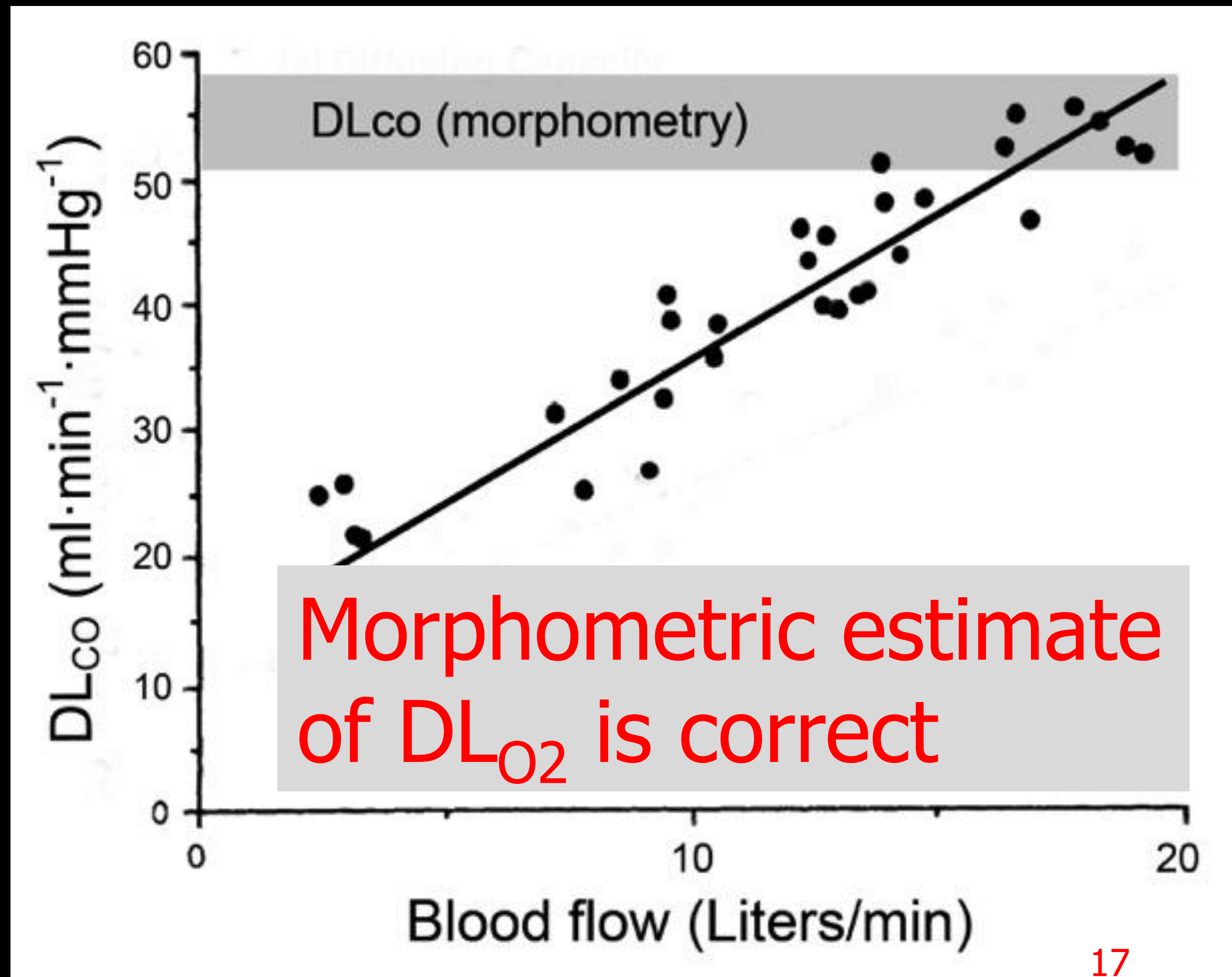
DL_{CO} by morphometry

Do we have excess diffusing capacity?

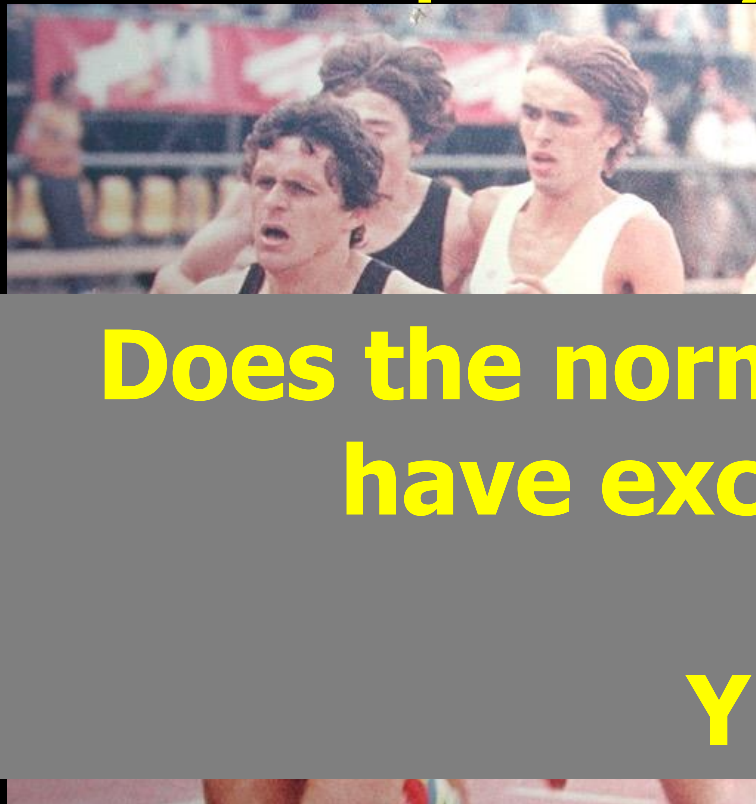
Test by DL_{CO} in running dogs

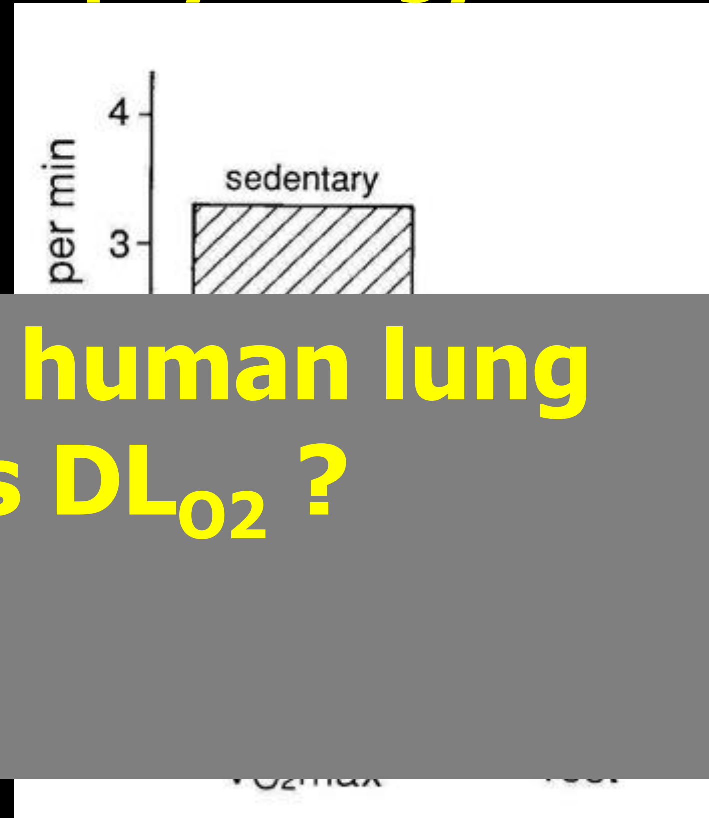
Connie Hsia, Dallas

DL_{CO} in running dogs
& by morphometry



Morphometry and physiology



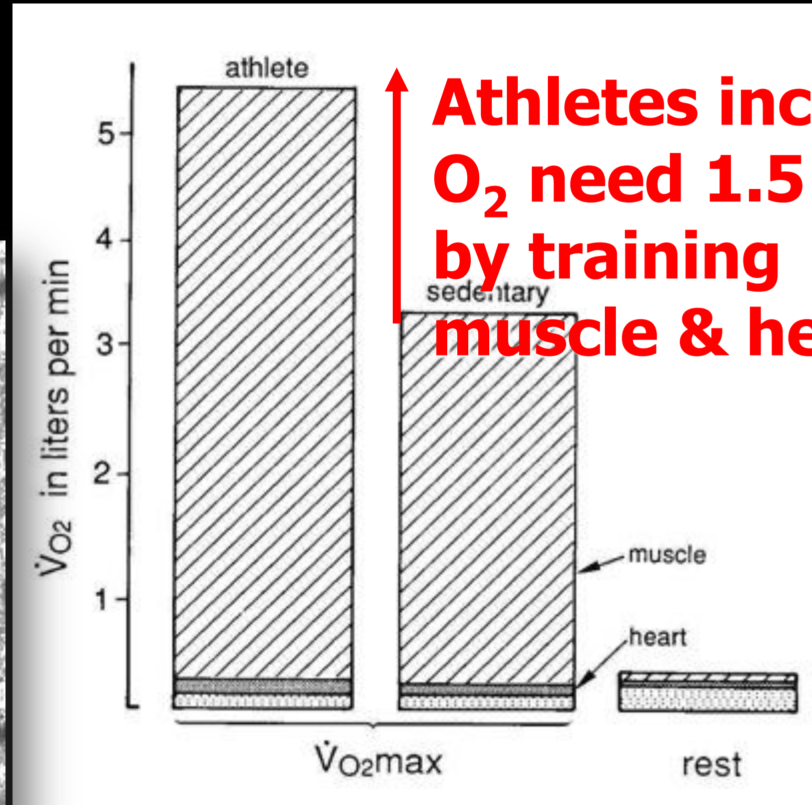


Does the normal human lung have excess DL_{O2} ?

YES!

Morphometric DL_{O2}	**158**	$mlO_2.min^{-1} \cdot mmHg^{-1}$
Physiological DL_{O2} rest	30	$mlO_2.min^{-1} \cdot mmHg^{-1}$
exercise	**100**	$mlO_2.min^{-1} \cdot mmHg^{-1}$

Is 1.5x excess capacity useful ?



Athletes increase O_2 need 1.5 fold by training muscle & heart

Adult lung cannot grow:

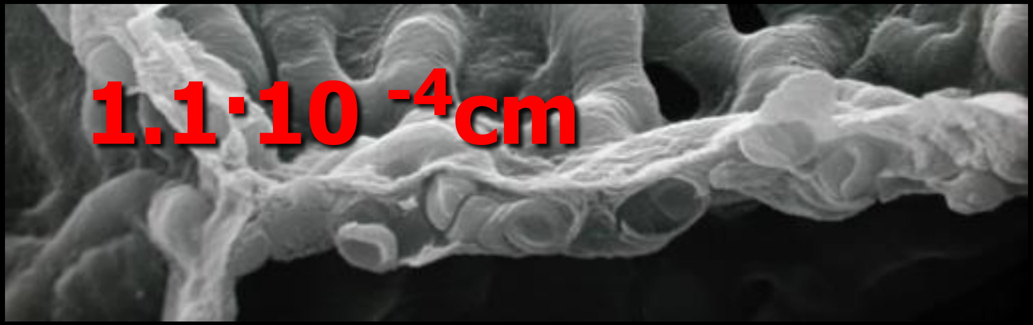
Athletes can train for higher $\dot{V}_{O_2}$max (more mito)

"up to their DL_{O_2}"

acquired during growth

What is a Good Lung ?

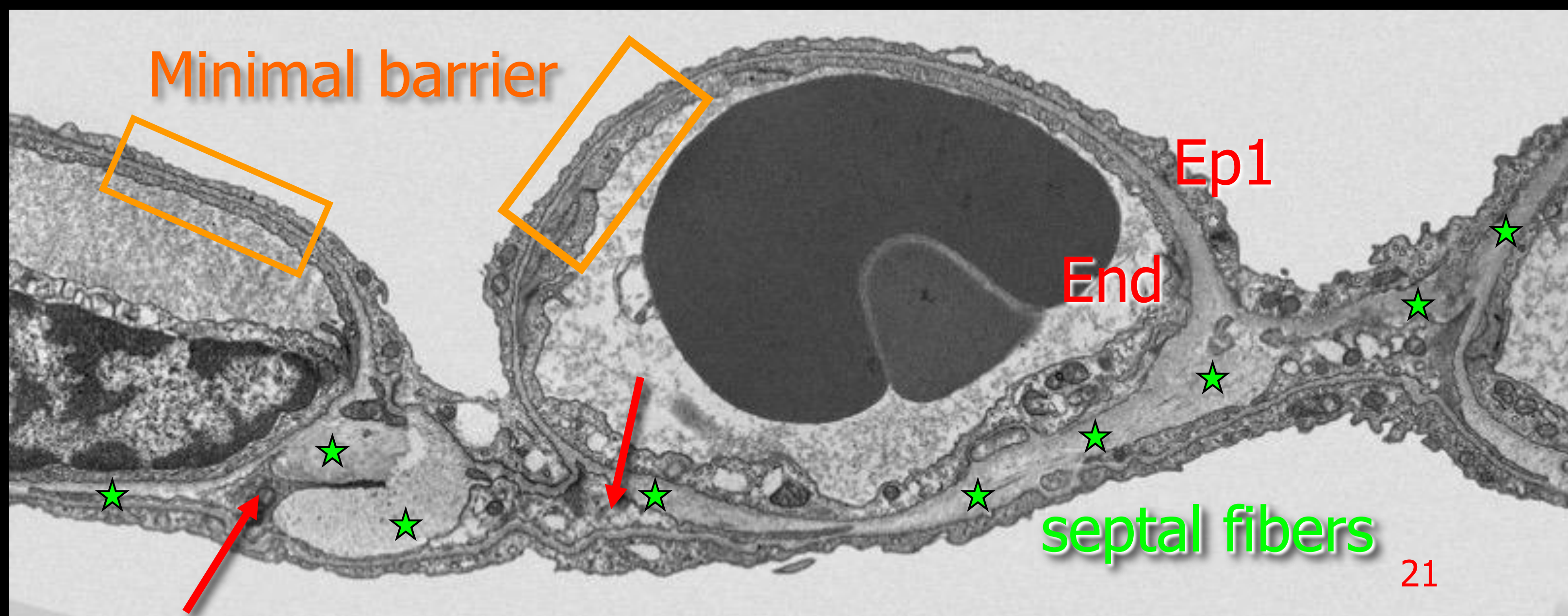
Large Surface — Thin Barrier



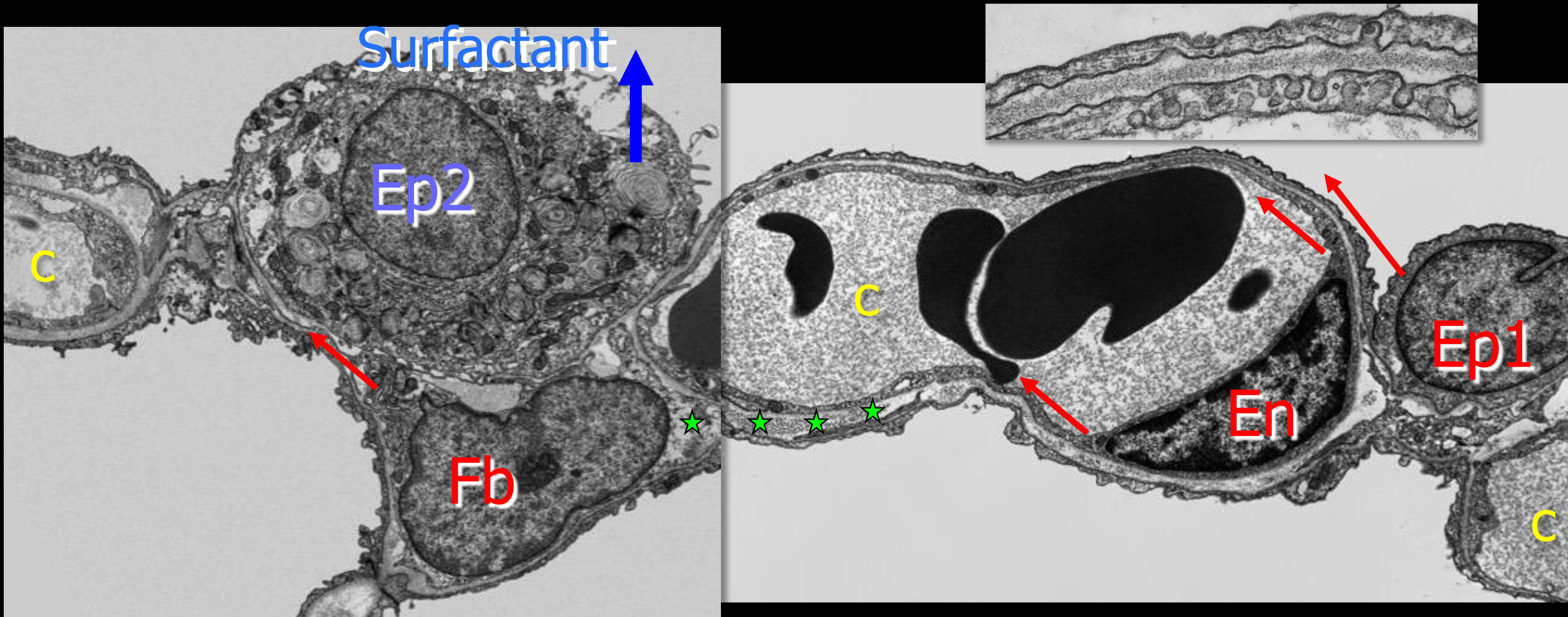
- Merits: High Conductance for O_2
  Recruit Diffusing Capacity up to V_{O2}max
- Problems:
  - build, ventilate & perfuse large surface
  - maintain surface large
  - **keep barrier thin & vital**

Building a thin extensive barrier

Capillaries interwoven with Septal fibers



Cell population making air-blood barrier

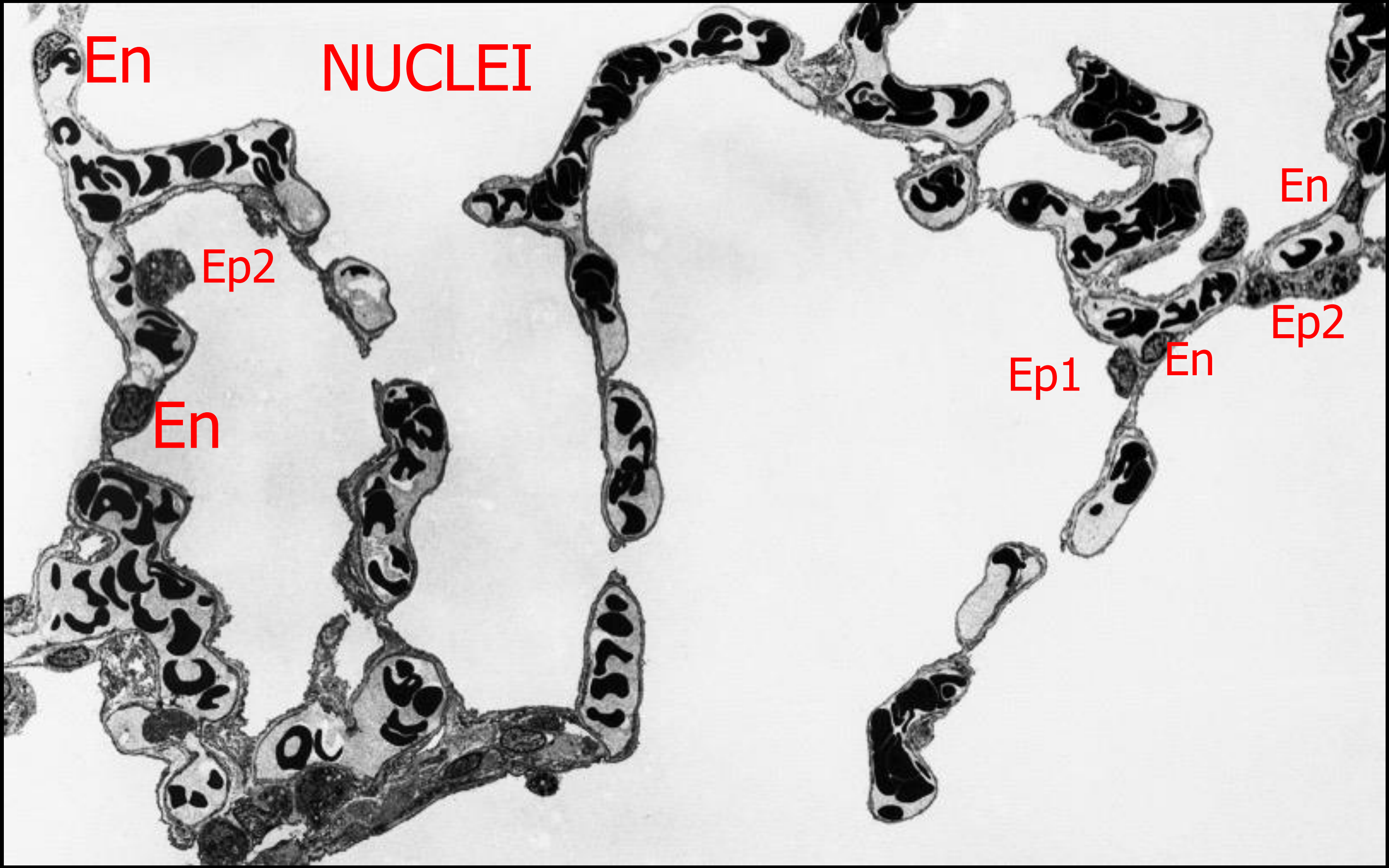


Alveolar Epithelium: Type 1 cell — Type 2 cell

Interstitium: Fibroblast

Capillary: Endothelial cell

The problem:
there are very few cells to coat large surface



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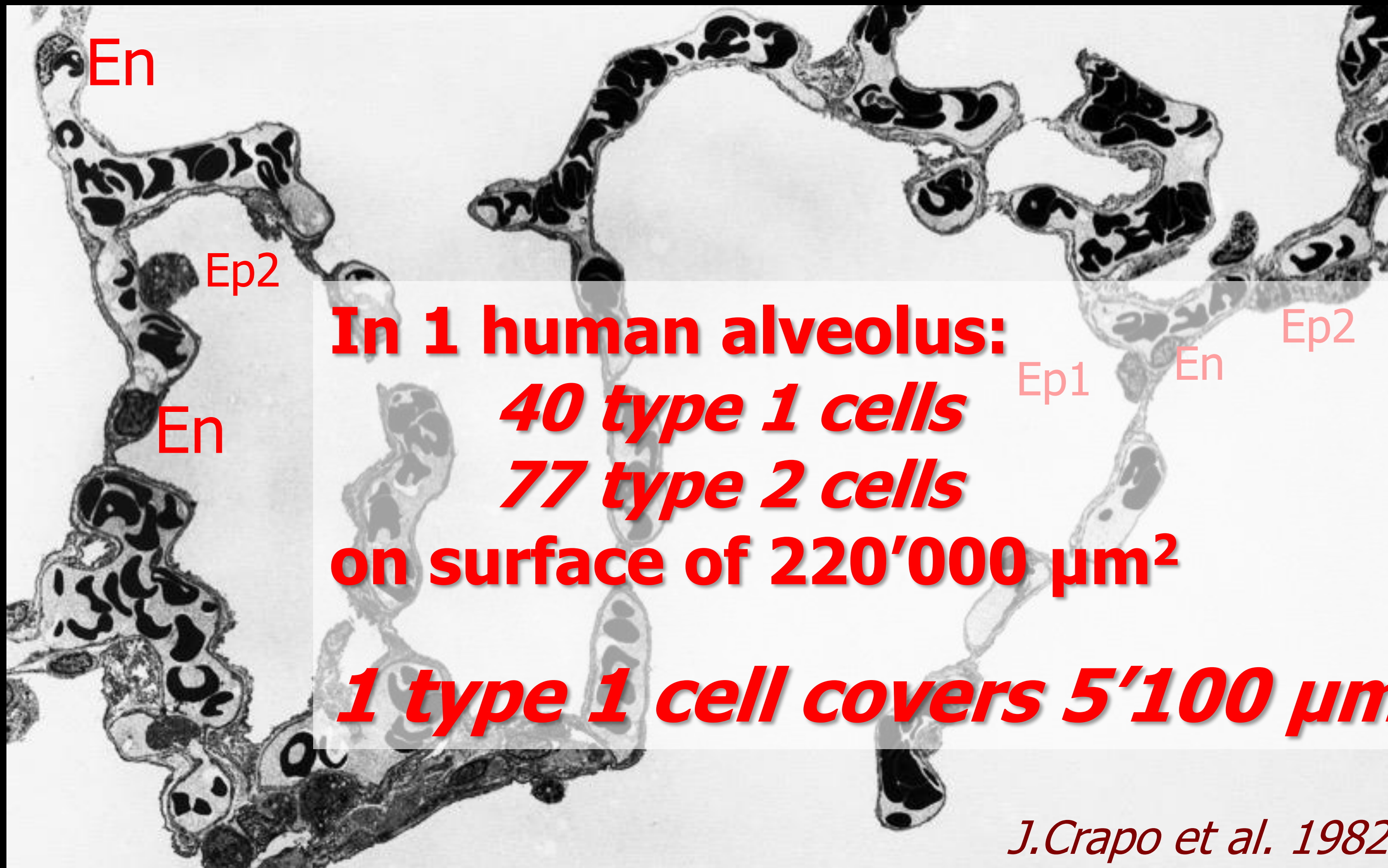


In 1 human alveolus:

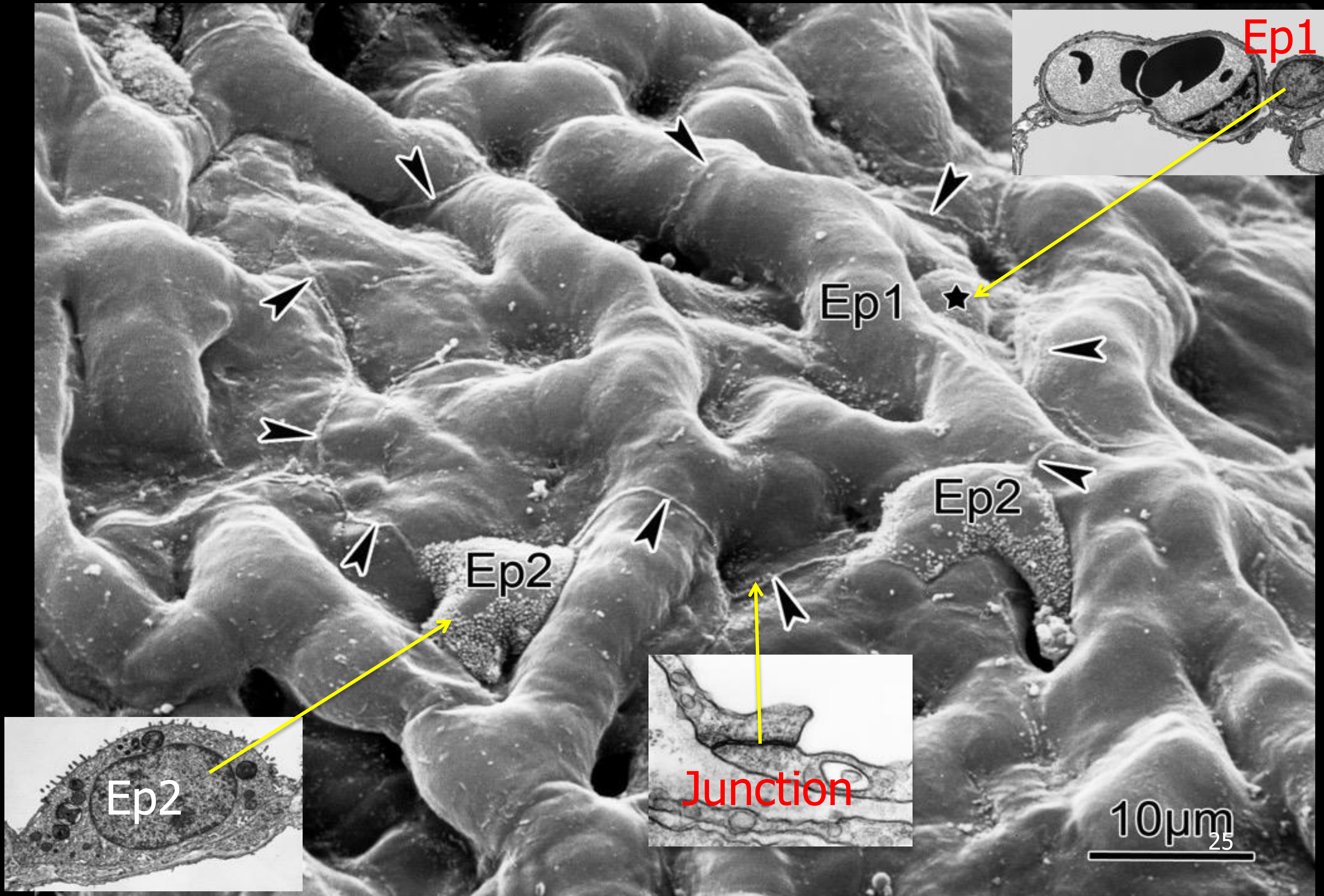
40 type 1 cells

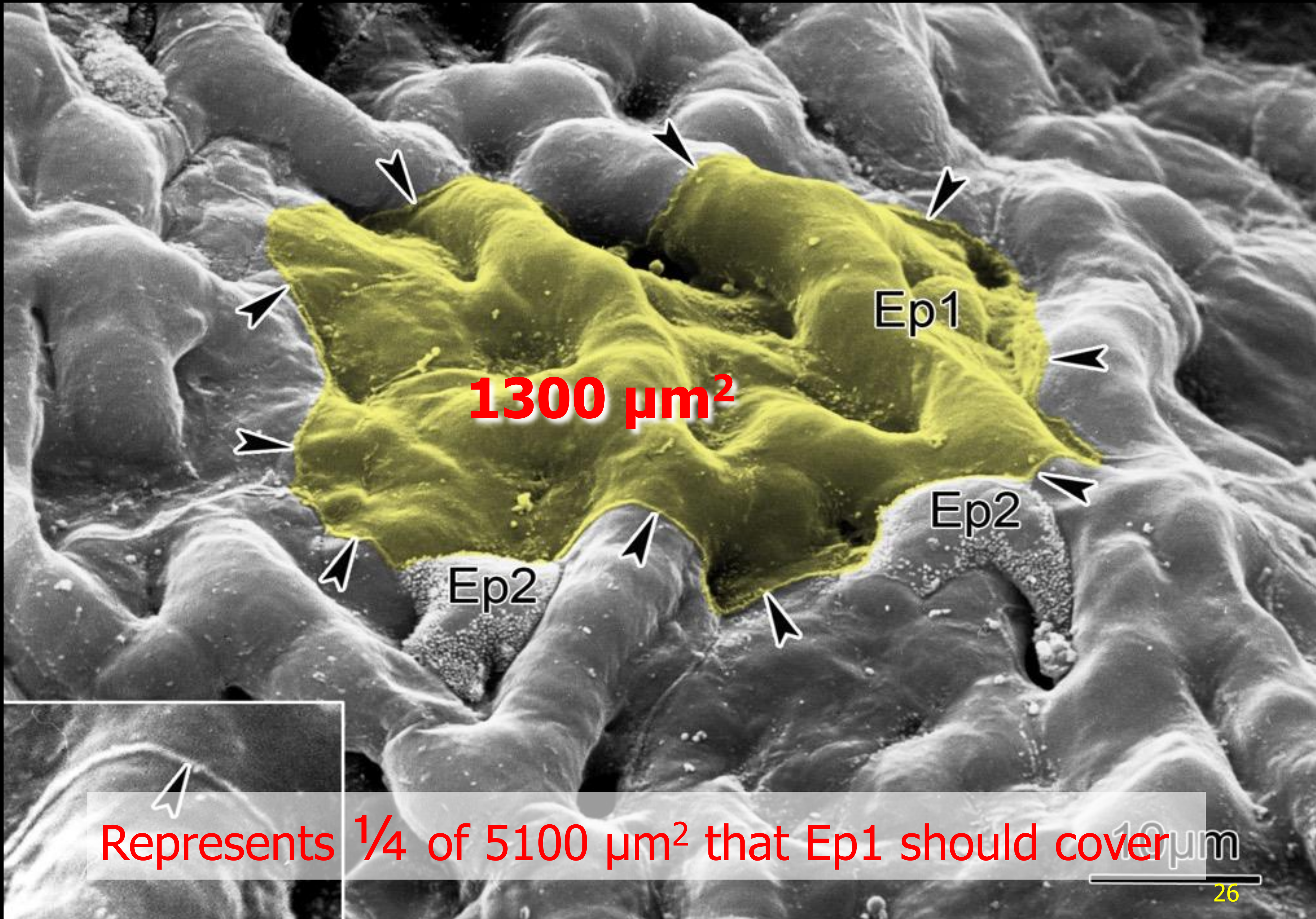
77 type 2 cells

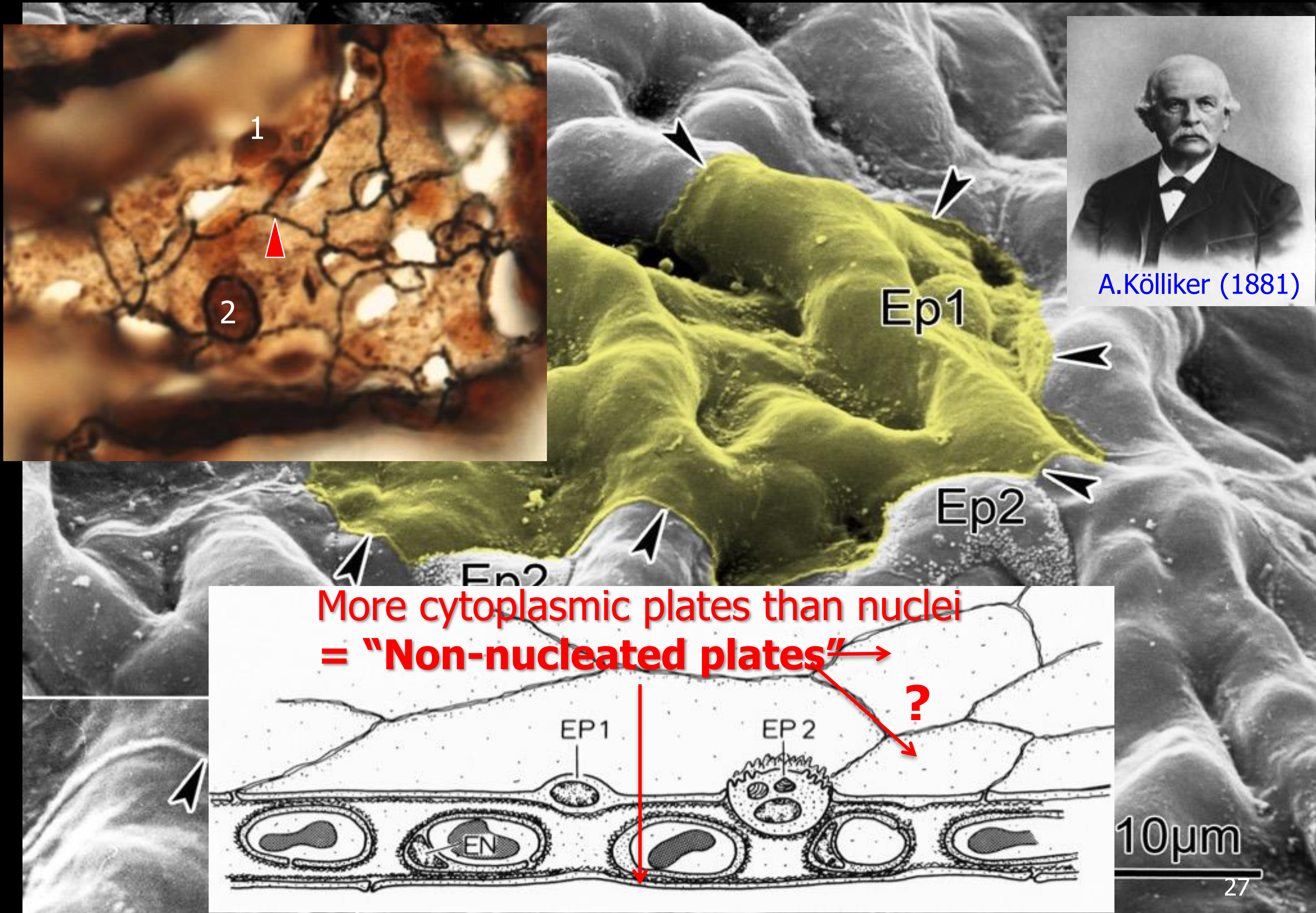
on surface of 220’000 μm²

1 type 1 cell covers 5’100 μm²

Type 1 cells line 95% of alveolar surface


Ep1
Ep1
Ep2
Ep2
Ep2
Junction
10μm


Ep1
$1300\ \mu m^2$
Ep2
Ep2
Represents ¼ of 5100 μm^2 that Ep1 should cover



More cytoplasmic plates than nuclei

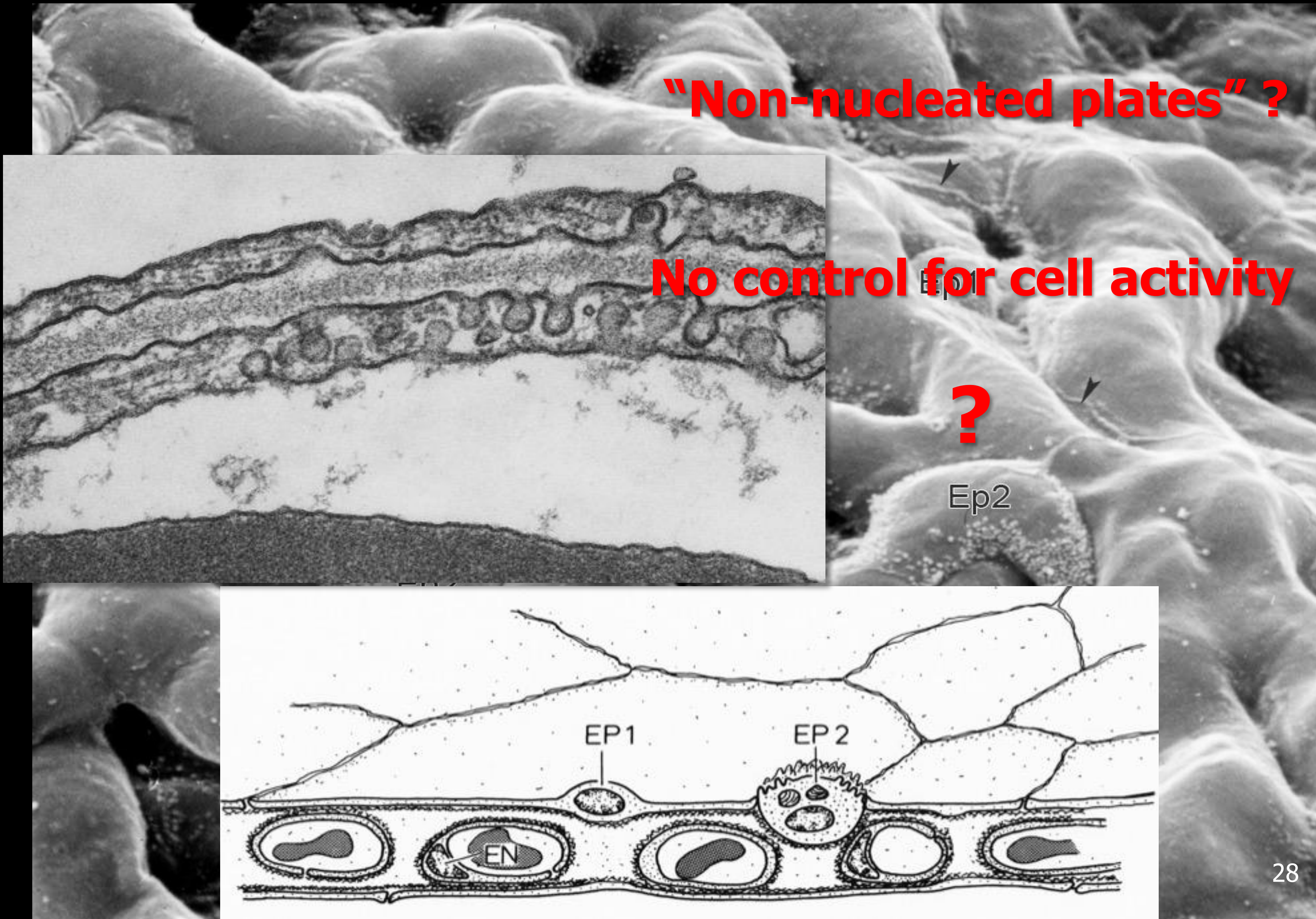
= "Non-nucleated plates"

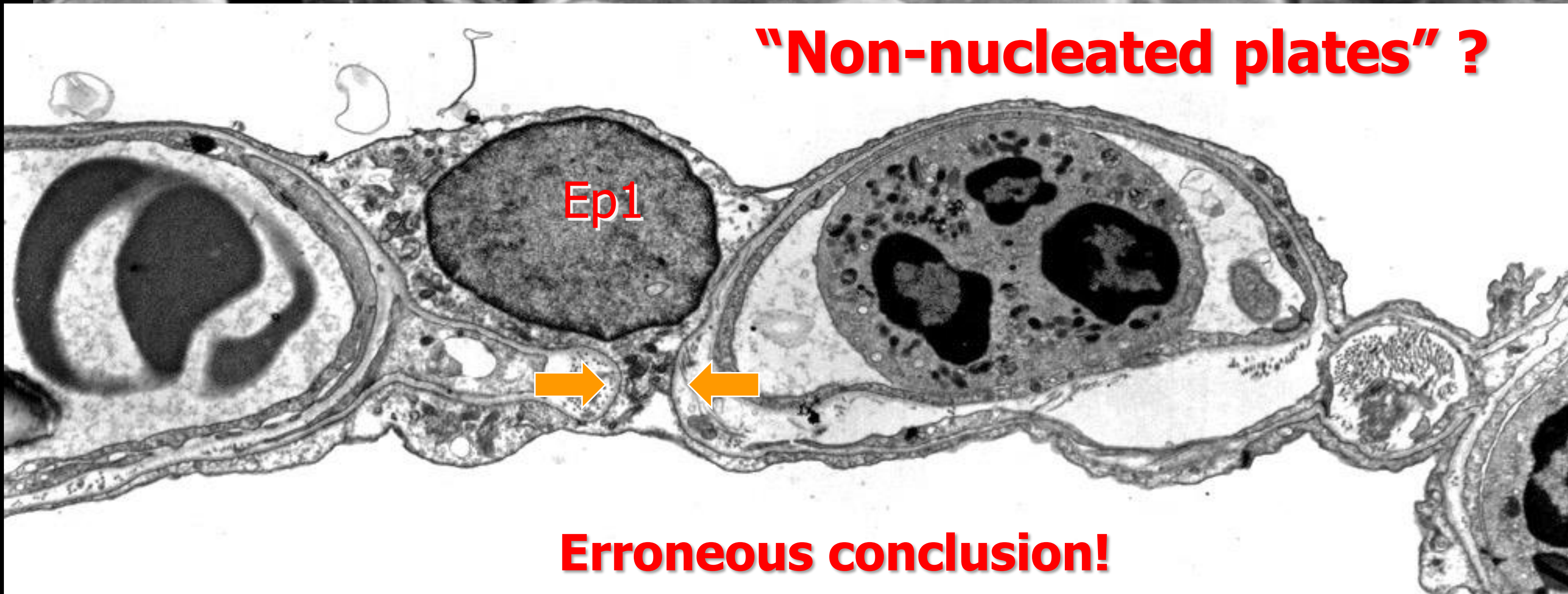
?

"Non-nucleated plates" ?

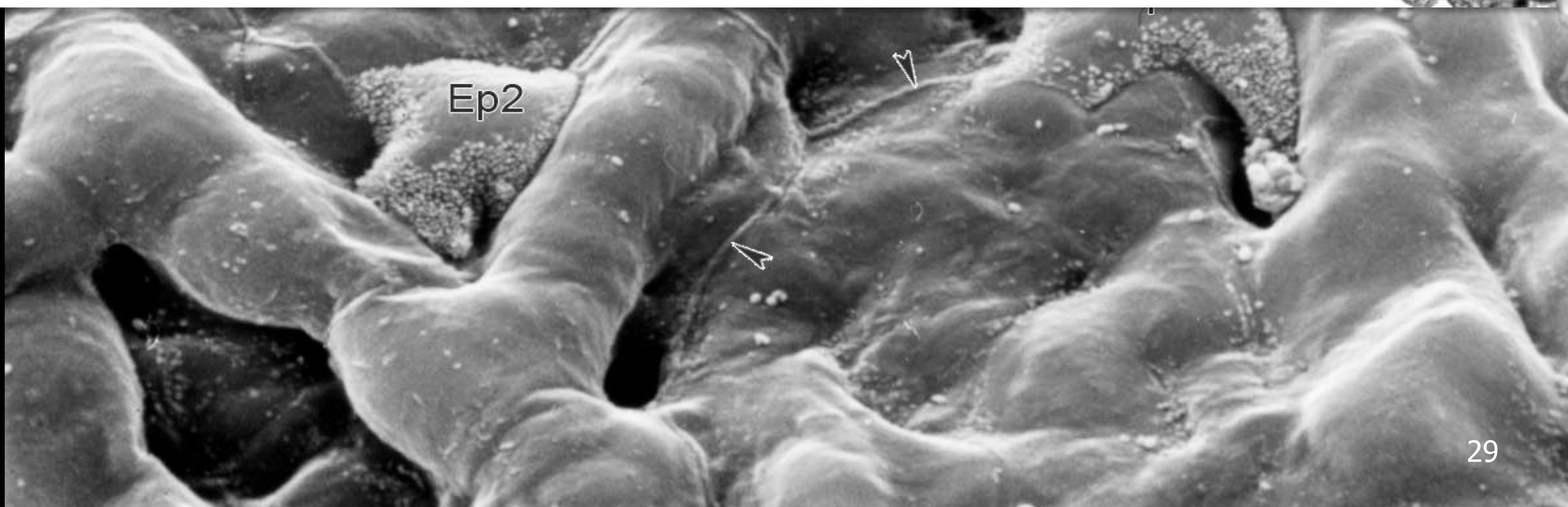
No control for cell activity

?

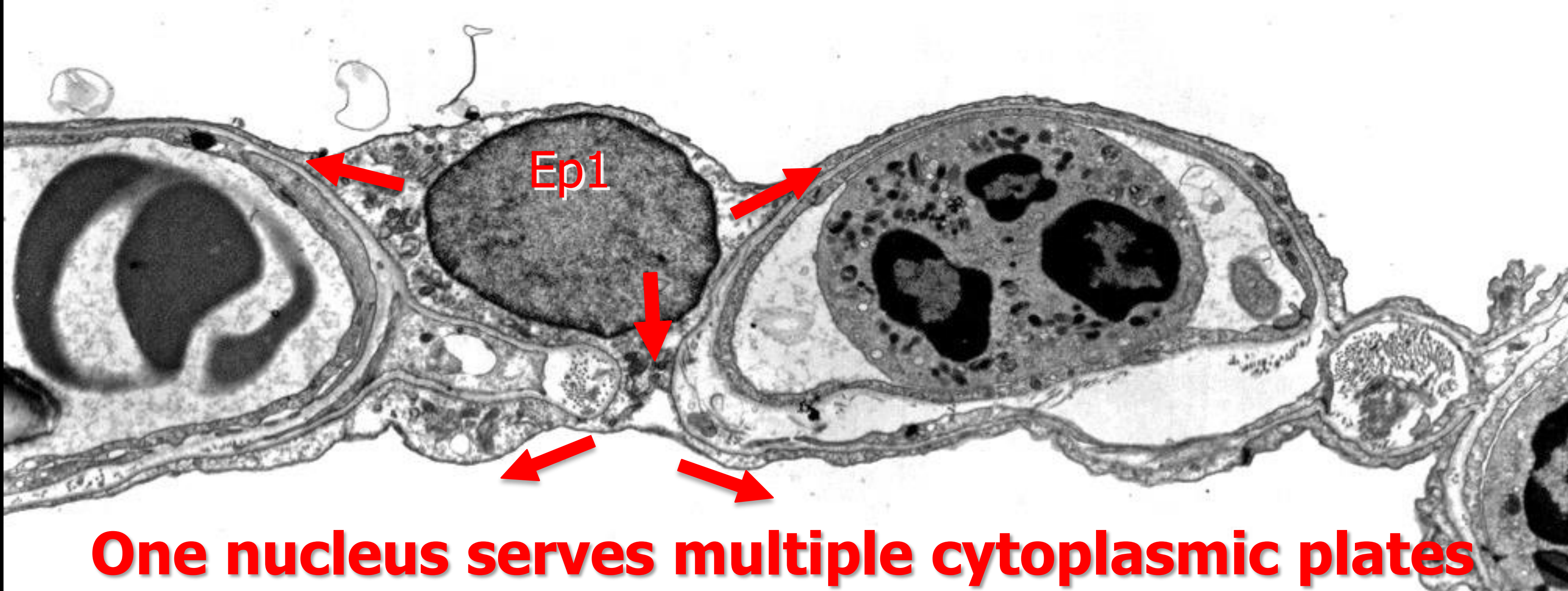


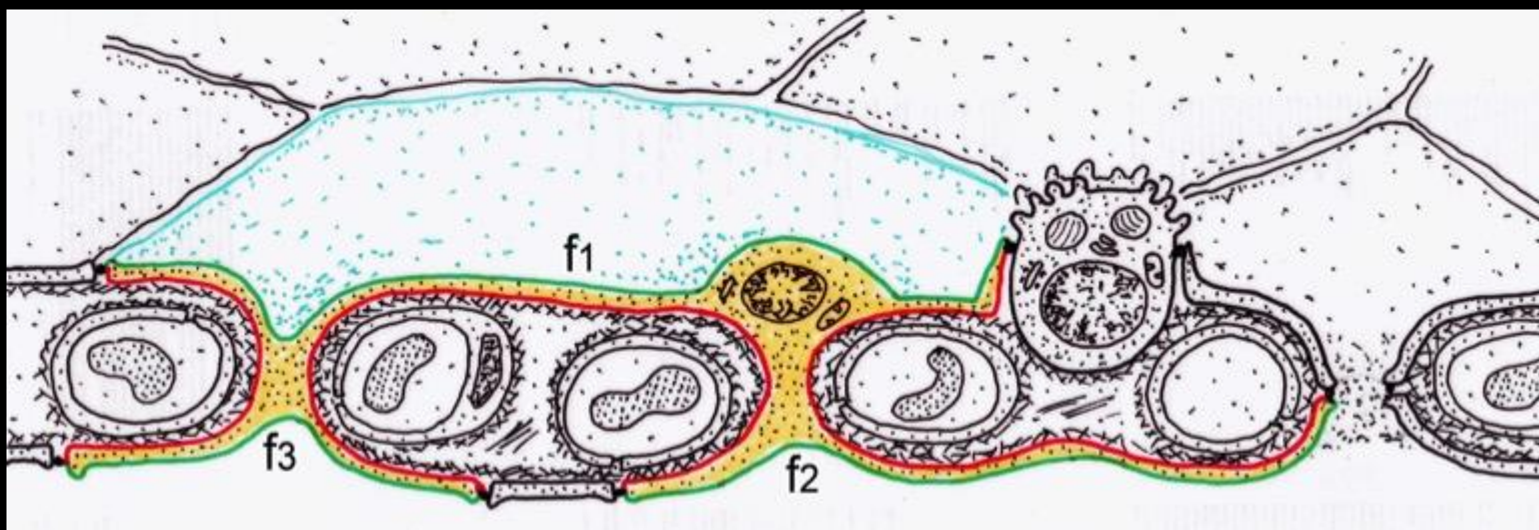


“Non-nucleated plates” ?
Ep1
Erroneous conclusion!

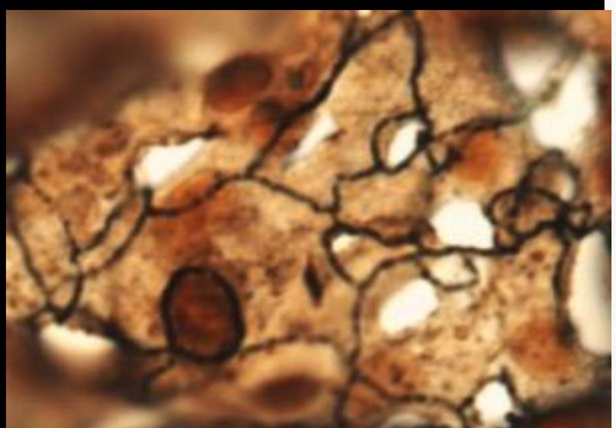


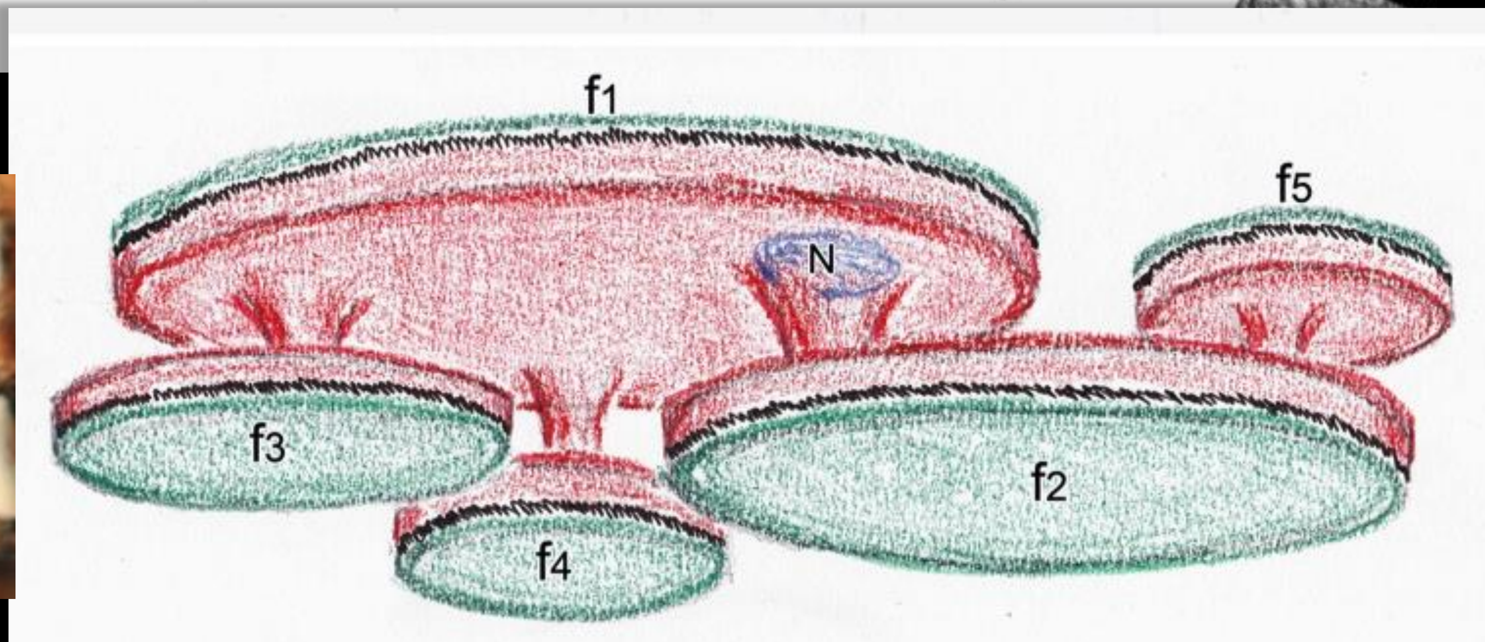
Ep2


Ep1
One nucleus serves multiple cytoplasmic plates

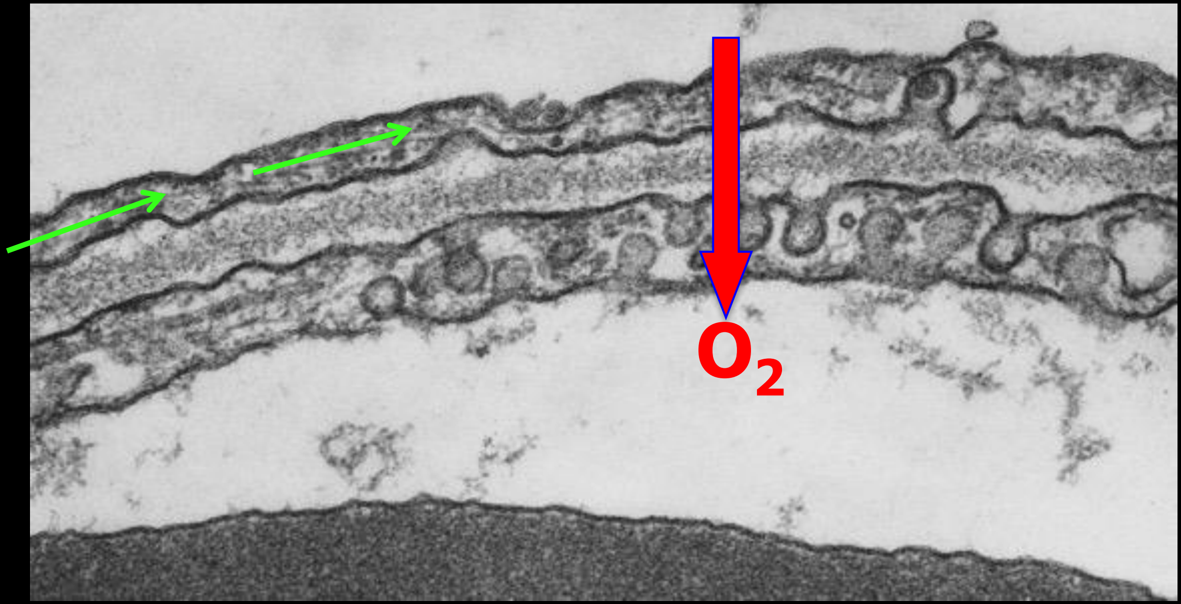

f1
f3
f2

Complex topology of Type1 cells





Why complex branching of type 1 cells?



Solve conflicting physiological problems:

(1) Minimize barrier thickness for gas exchange:
spread cytoplasmic leaflet to 5000 μm^2

(2) Ensure metabolic control & maintenance to periphery:
messengers, ATP, proteins etc.

Reduce distance to periphery from ~ 40 µm to ~ 20 µm

Surface coverage of one Ep1 species-independent:

Human	(74kg)	5’098 µm^2
Baboon	(29kg)	4’004 µm^2
Rat	(0.36kg)	5’320 µm^2

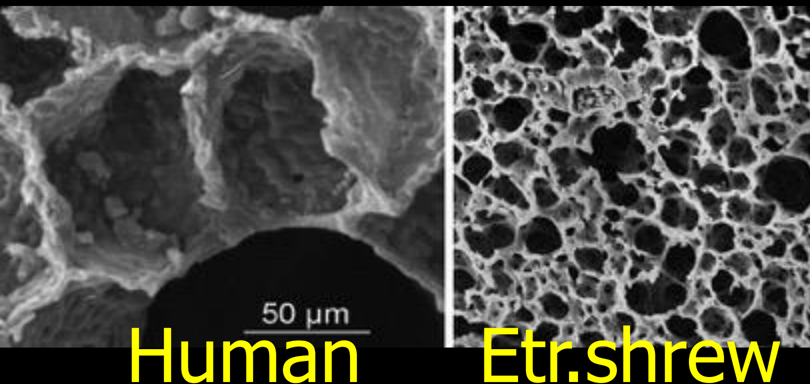
J.Crapo et al. 1980, 1982

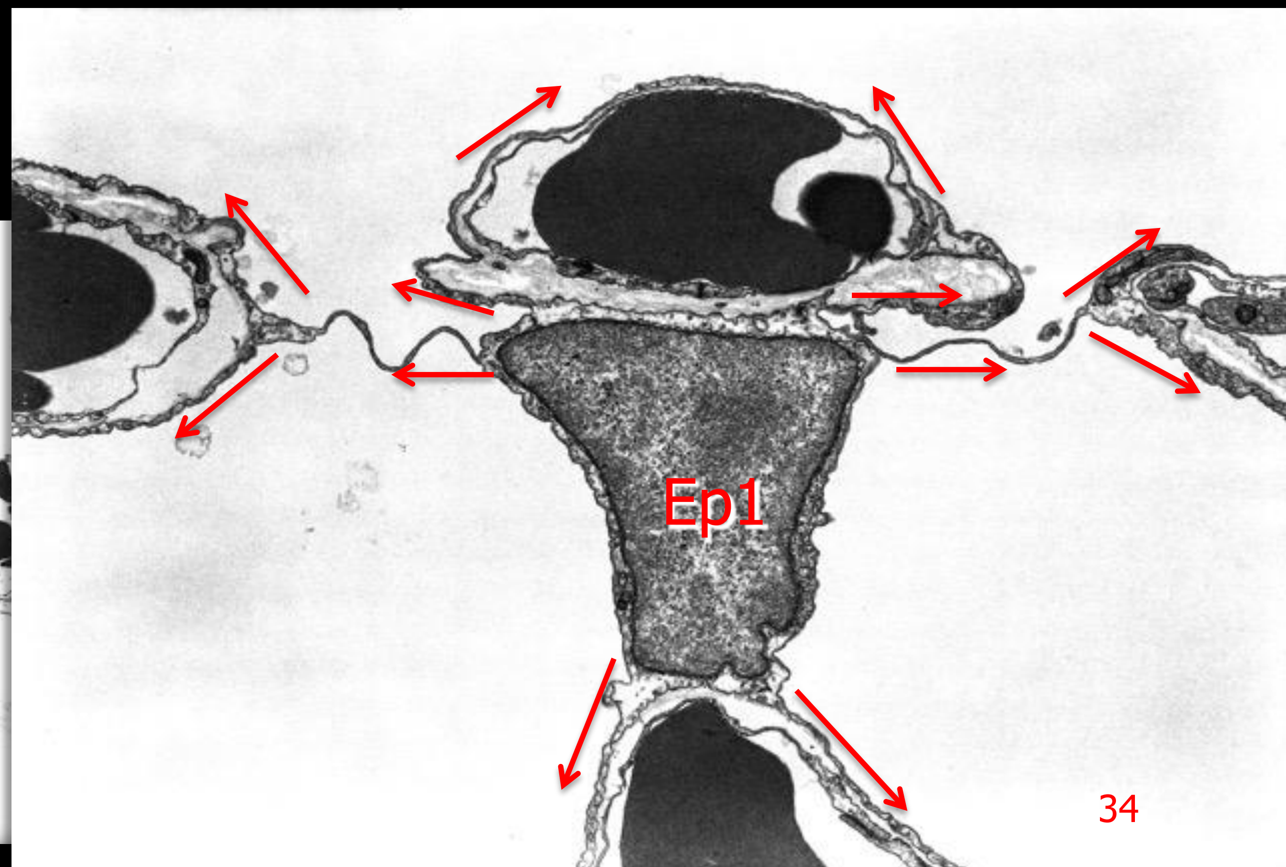
Ep1 architecture is interspecific phenotype

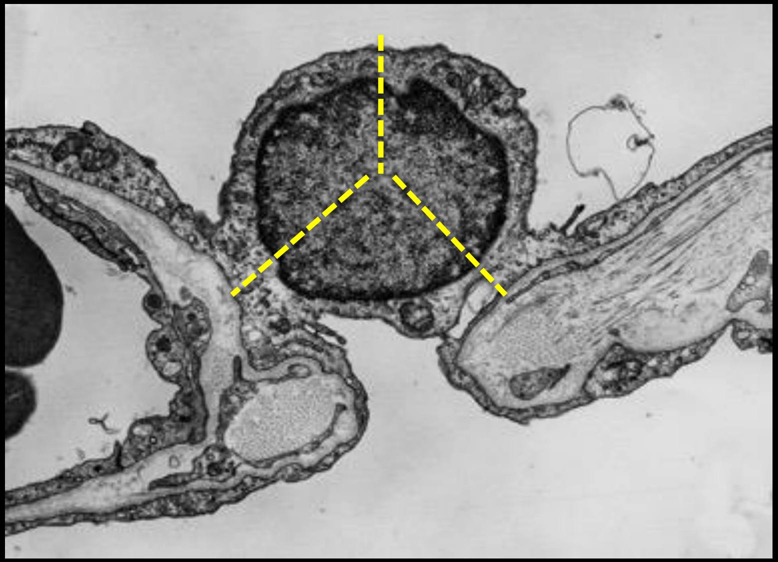
Functional importance of Ep1 architecture:

Etruscan Shrew 2g:

highest O_2 needs and DL_{O2}
thinnest barrier
greatest complexity of Ep1



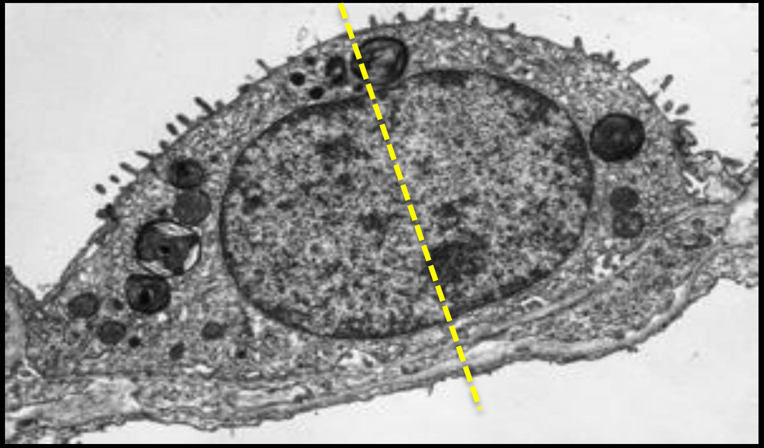




There is a price to everything

Branched Ep1 lost apical-basal polarity

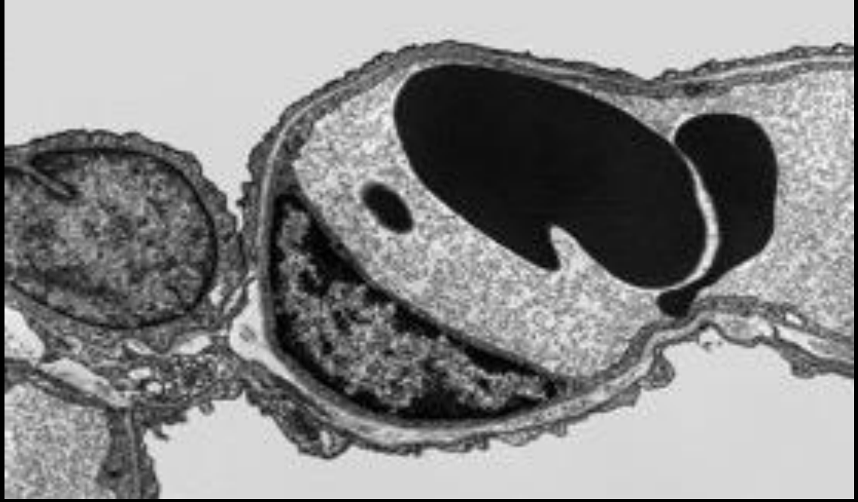
—> unable to divide by mitosis



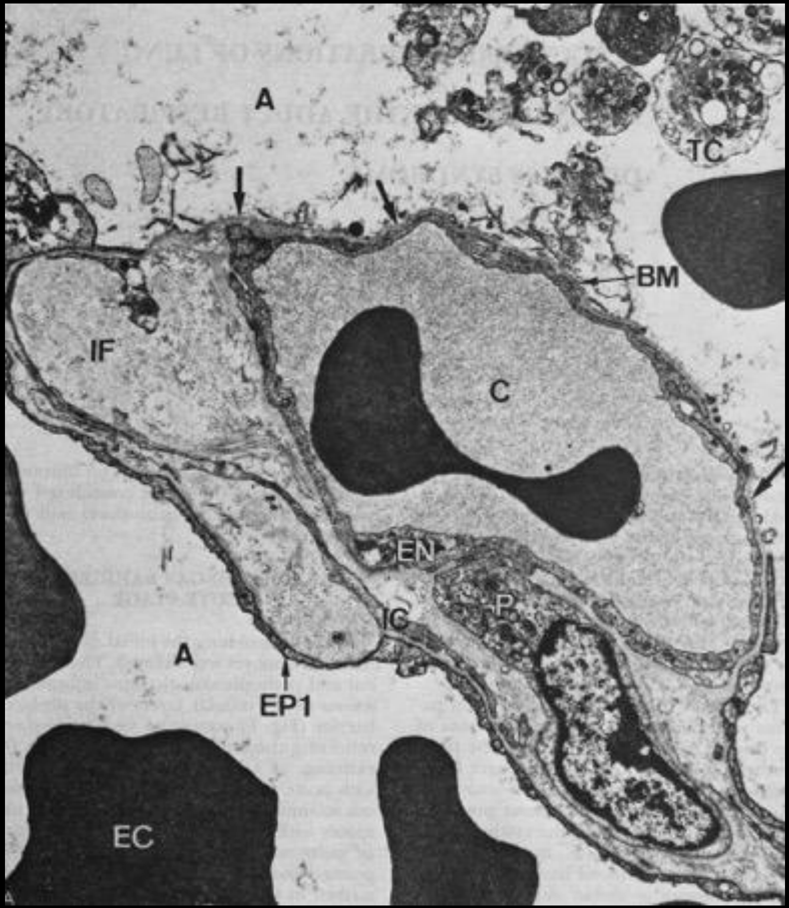
Ep1 *in situ* cannot proliferate:

in case of damage

replenished from stem cells = Ep2

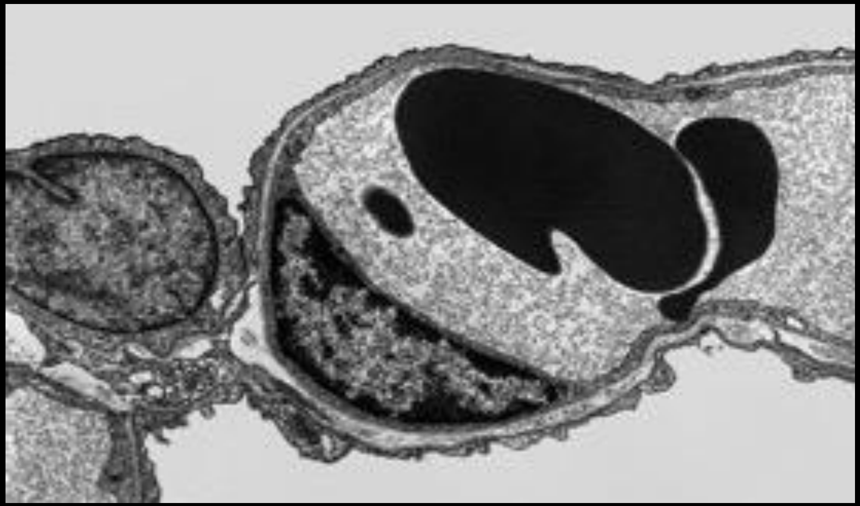


ARDS: Type 1 cell destruction

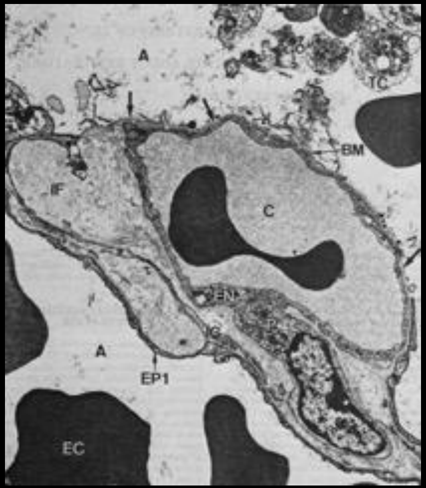


Repair by
Type 2 cell **proliferation**

M.Bachofen 1974, 1977

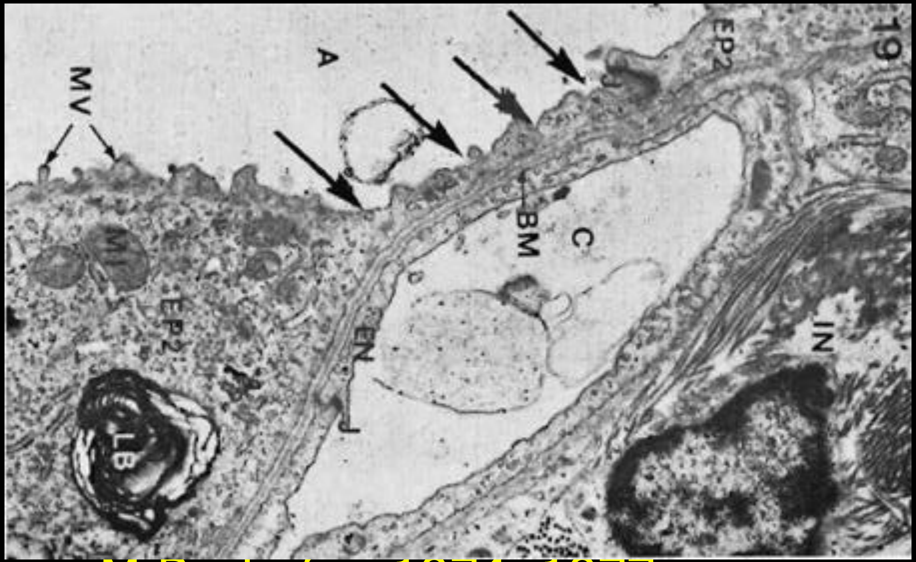


ARDS: Type 1 cell destruction



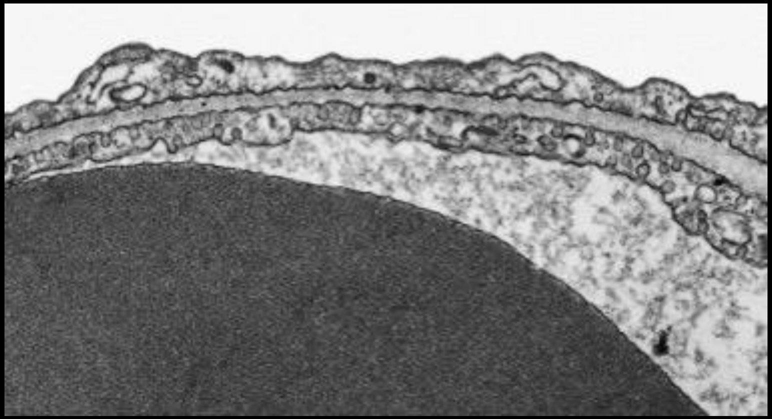
Repair by
Type 2 cell **proliferation**

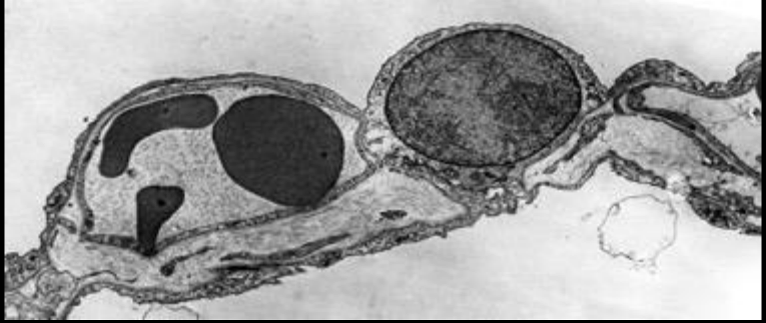
Followed by
Transformation Type 2 to 1



M.Bachofen 1974, 1977

Conclusions (1)



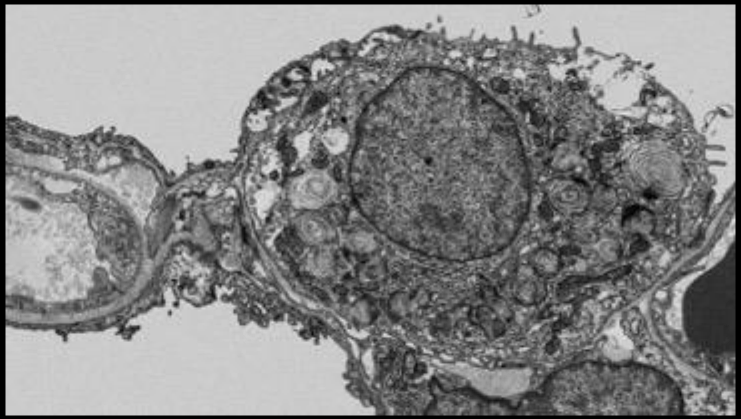


Architecture of Alveolar Type I cell modified from standard epithelial cell model:

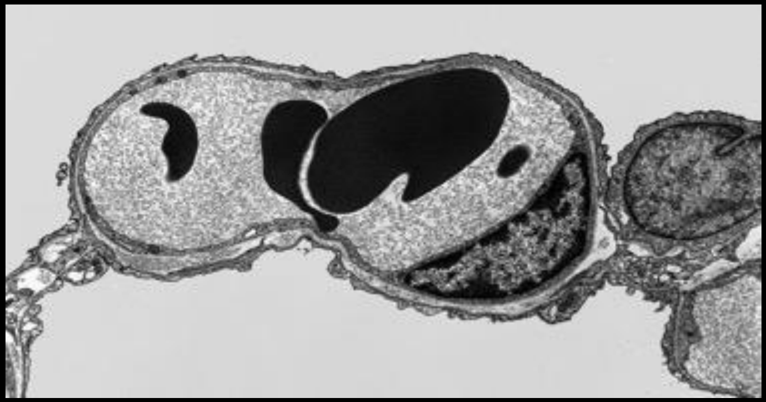
— very thin barrier by extensive spreading to 5000 µm^2
in the interest of efficient gas exchange

— branching cytoplasmic stems shorten distances for nuclear-based support of cell function

Conclusions (2)



Alveolar epithelial cells Type I
derive from Type II cells
as progenitors or stem cells

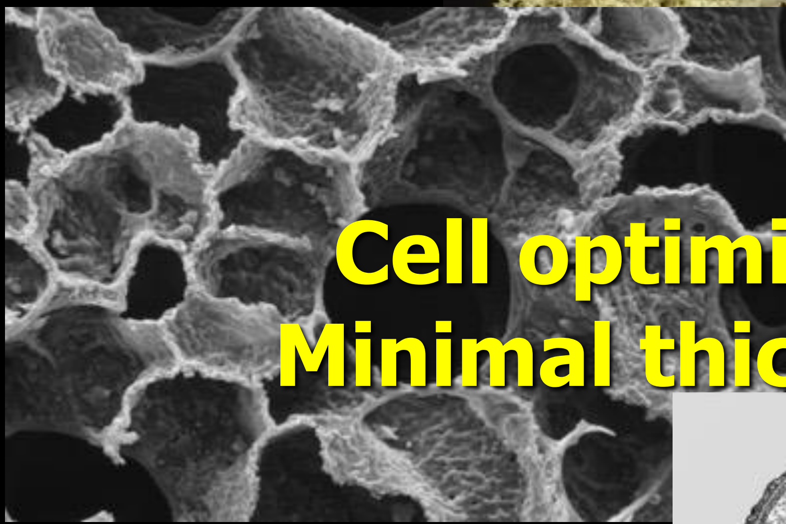


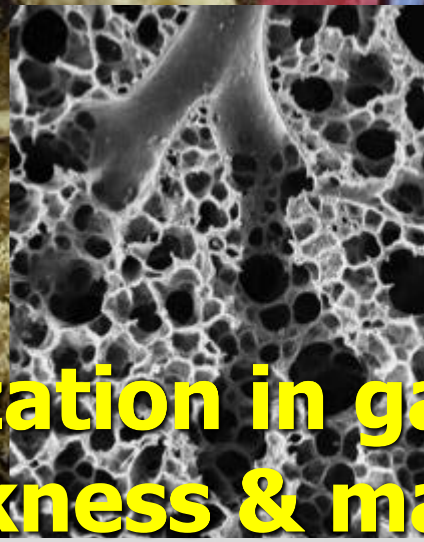
— by transformation into Type I cells

— both in development and repair

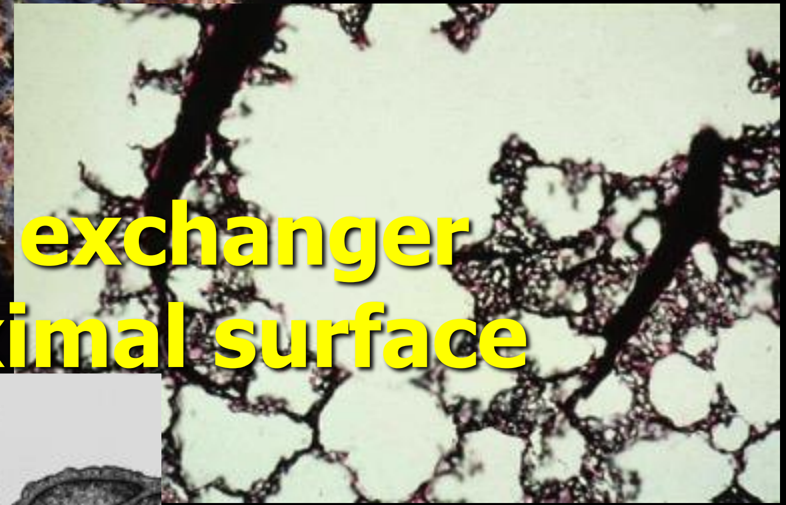
What does it take to make a Good Lung?

Very large surface of air-blood contact





Correlativity of airways & vessels



Cell optimization in gas exchanger

Minimal thickness & maximal surface

Who‘s done the work ?

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Thank you !