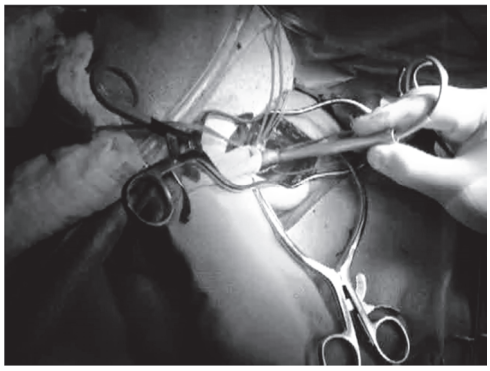
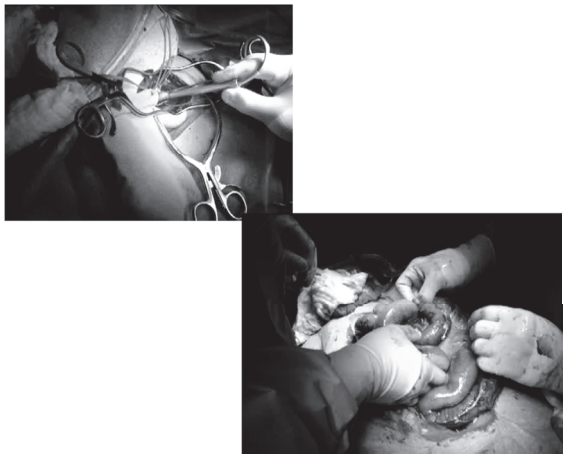
Glycocalyx: What is it and what is it important?

Ulises Baltazar, MD, FACS, CLT
Vascular Surgery
Assistant Professor of Vascular Surgery Weill-Cornell University
Director of the Veno-Lymphatic Service

Houston Methodist Hospital Sugar Land
Sugar Land, Texas

"When you are a hammer….
everything looks like a nail"



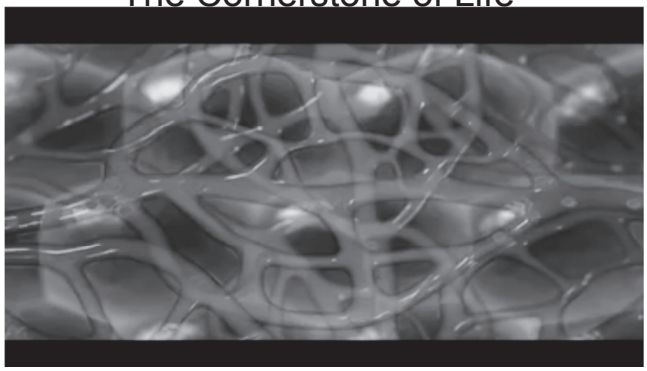


What is

The Cornerstone of Life?

Microcirculation

The Cornerstone of Life



Microcirculation

- Dynamic “organized chaos”
- Empty-filled capillaries
- Fluxmotion

Metabolic

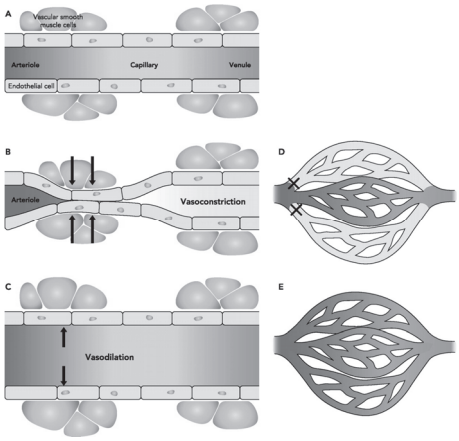
Physical

Humoral

Nervous

“Microcirculation in insulin resistance and diabetes: more than and compilation”
Wienersperger NF, Bouskela, E
Diabetes Metab 2003:29, 6S77-6S87

Microcirculation



Microcirculation

Microcirculation

- Capillary flow regulation (Getting the blood there)
- Hydrostatic - Oncotic equilibrium (Osmosis Starling principle)
- Filtration (Lymph formation revised Starling principle)

Microcirculation

- Capillary flow regulation

Microcirculation

- Capillary flow regulation
  - Arteriolar myogenic response
  - Venoarteriolar reflex
  - Pre capillary arteriolar vasomotion

“Microcirculation in insulin resistance and diabetes: more than and compilation”
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Diabetes Metab 2003:29, 6S77-6S87

Microcirculation

- Arteriolar vasomotion
  - Nitric Oxide (NO)
  - Endothelium-Derived Hyperpolarizing Factor (EDHF)

"A unique role of NO in the control of blood flow" Pohl U, De Wit C, News Physiol Sci, 19, 74-80, 1999

Microcirculation

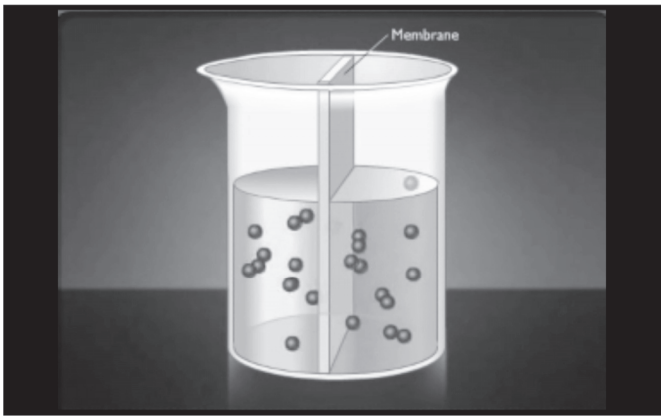
- Arteriolar vasomotion
  - Slow-wave
    - Arteriolar contraction oscillations of membrane potential
  - High amplitude
  - 1-10 Hz

"Vasomotion and flow motion: physiological mechanisms and clinical evidence" Intlagietta M, Vasc Med Rev, 1, 101-112, 1990
"Electrophysiolocial basis of arteriolar vasomotion in vivo" Bartlet II, Crane GJ, Neidl T, et al, J Vasc Res, 37, 568-575, 2000

Microcirculation

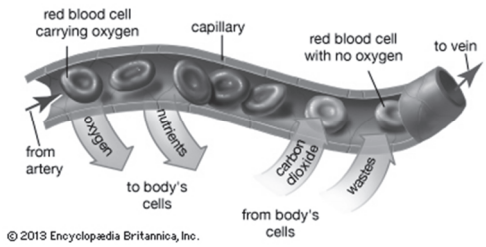
- Hydrostatic - Oncotic equilibrium

Microcirculation



Microcirculation

Hydrostatic-Oncotic pressure
Arterioles-Venues



Microcirculation

- Filtration

Microcirculation

Carl Friedrich Weilheim Ludwig
1816-1895

- Suggested that lymph was formed by plasma filtration through capillary walls

Microcirculation

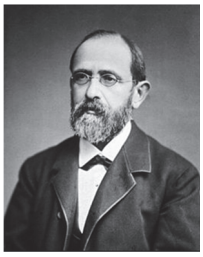
Julius Friedrich Cohnheim
1839-1884

- Expanded Ludwig's concept to vascular pressure and different capillary permeability throughout the body

Microcirculation

Rudolph Peter Heinrich Heidenhain
1834-1897

- 1854 published his secretion theory and his work on lymphagogues substances (crayfish extract)



Microcirculation

Ernest Henry Starling
1866-1927

- 1893 Intravenous injection of peptones

Microcirculation

Starling Principle

Ernest Henry Starling
1866-1927

- 1896 Basic concept of tissue fluid absorption
- Incomplete

Microcirculation

ON THE ABSORPTION OF FLUIDS FROM THE CONNECTIVE TISSUE SPACES. By ERNEST H. STARLING. (Two Figures in Text.)

(*From the Physiological Laboratory, Guy's Hospital.*)

Until within the last few years, all workers, who investigated the question of absorption by the blood vessels, confined their experiments to cases in which some substance, not occurring normally in the blood, was introduced into some connective tissue space. That, under these conditions, absorption by the blood vessels does take place, was shown by Majendie, and confirmed in recent years by Ascher[1] as well as by Tubby and myself[2]. Although the ease, with which this interchange by a process of diffusion between blood and extravascular fluids takes place, must be of great importance for the normal metabolism of the tissues (as, *e.g.* the much discussed supply of CaO to the mammary gland-cells), yet such processes will not serve to explain the absorption by the blood vessels of fluids having the same tonicity and the same approximate constitution as the circulating plasma. The fluids contained in the tissue-spaces have the same tonicity and the same composition in salts as blood-plasma. We have to inquire first whether the blood vessels do absorb such isotonic fluids, and secondly the manner in which this absorption takes place.

Evidence as to Absorption by Blood Vessels.

1. *Absorption from the serous cavities.*

A number of experiments have been made recently on the subject of the absorption of isotonic fluids (*e.g.* 1 % salt solution or serum) from the serous cavities. Orlow[3] showed that isotonic fluids were absorbed from the peritoneal cavity with considerable rapidity without producing any corresponding lymph-flow from the thoracic duct, and concluded

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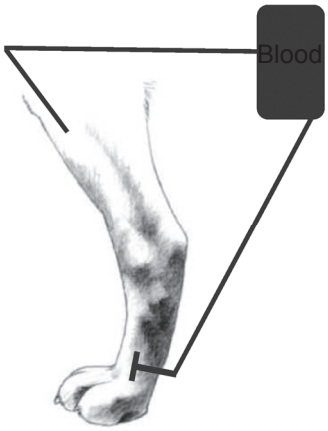
[2] *Pflüger's Archiv*, LXX. 170. 1894.
[3] This *Journal*, XVI. 140. 1894.

Microcirculation



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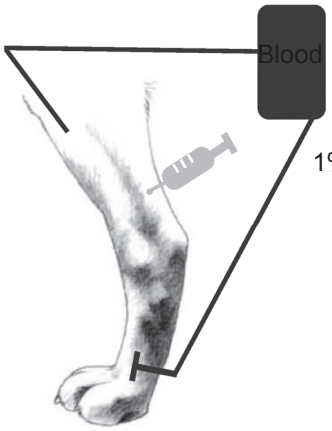
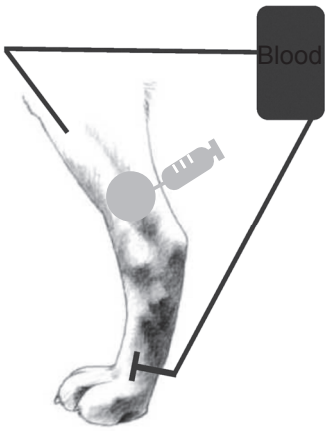
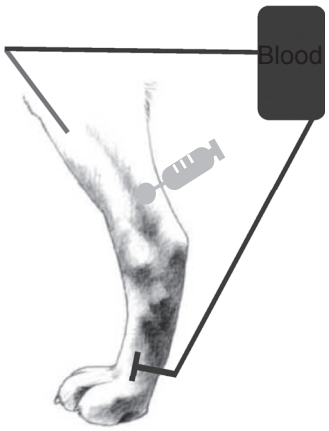


Microcirculation



Microcirculation



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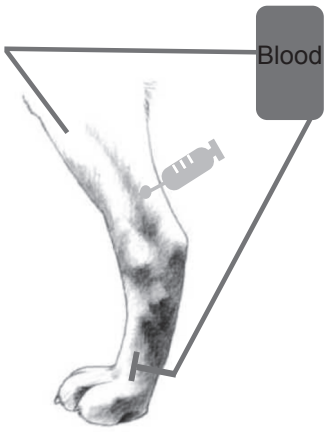

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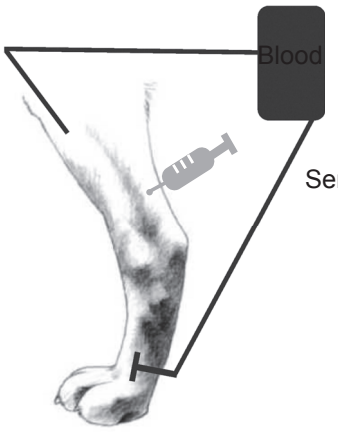
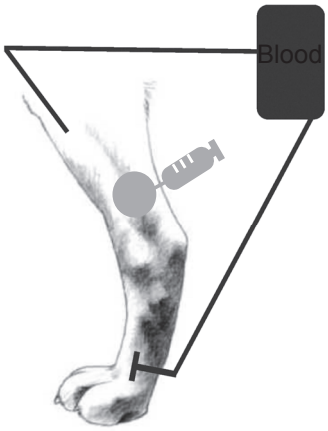
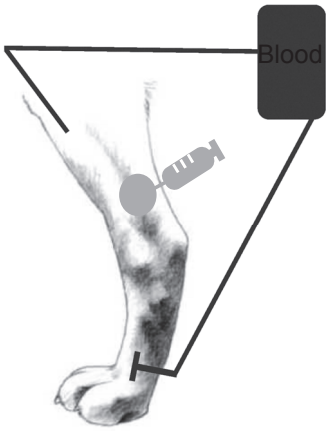


Microcirculation



Microcirculation



Microcirculation

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[3] *Pflüger's Archiv*, lix. 170. 1894.

Microcirculation

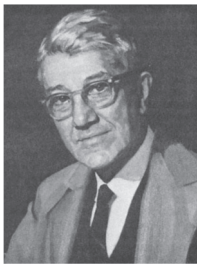
William D Haliburton
1860-1931

- 1904 disputed Starling's discoveries and he believed that filtration dominated over secretion

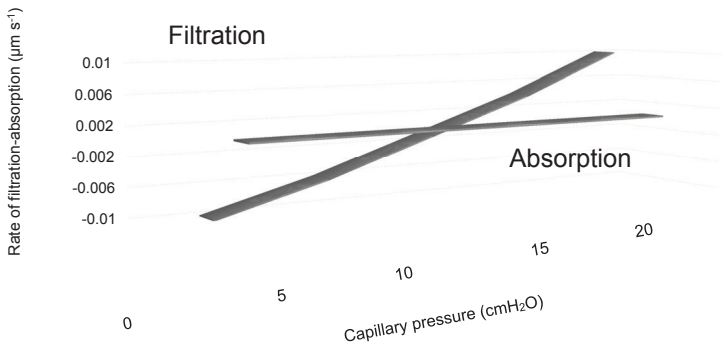
Microcirculation

Eugene Markley Landis
1901-1987

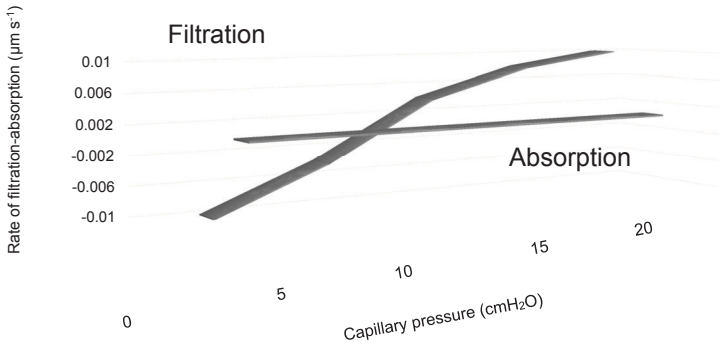
- 1927 first direct experimental evidence of Starling's principle



Microcirculation

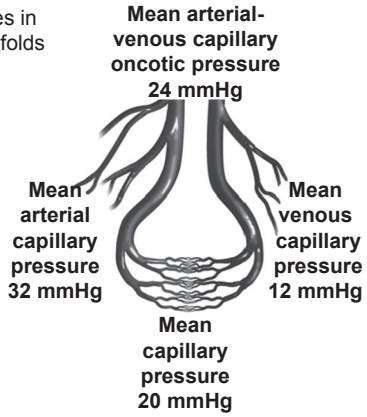


Microcirculation

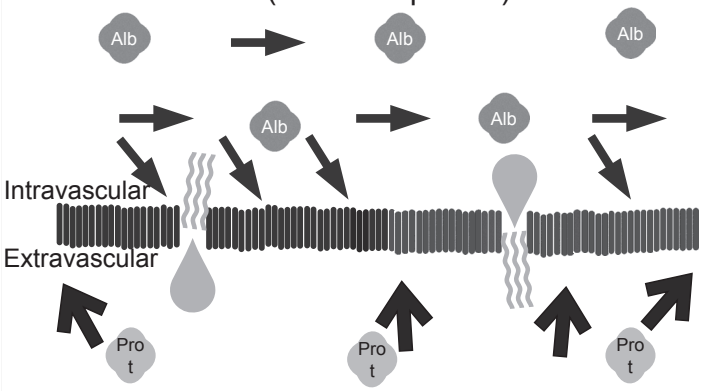


Microcirculation

- 1930 Landis measured capillary pressures in human fingernail folds at heart level



Starling's Principle (Landis' equation)



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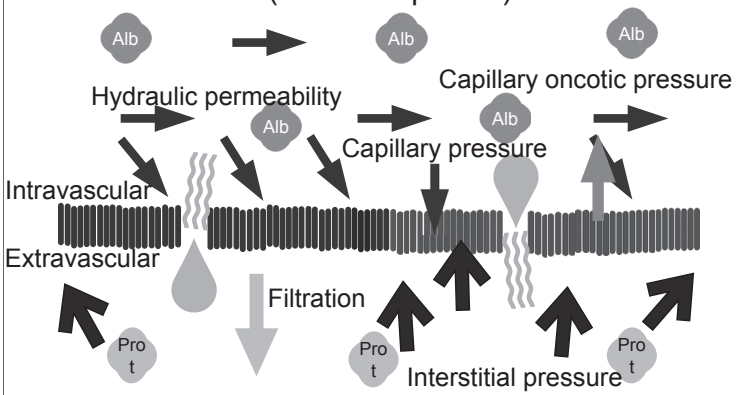


$$Jv/A = L_p((P_c - P_i) - (\Pi_c - \Pi_i))$$

Microcirculation

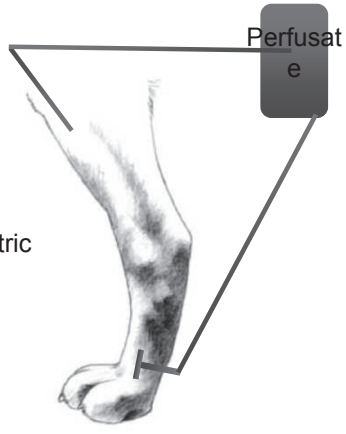
Armando Soto-Rivera
1920-2004

John Richard Pappenheimer
1915-2007

- 1948 they proposed the term isogravimetric state

Microcirculation

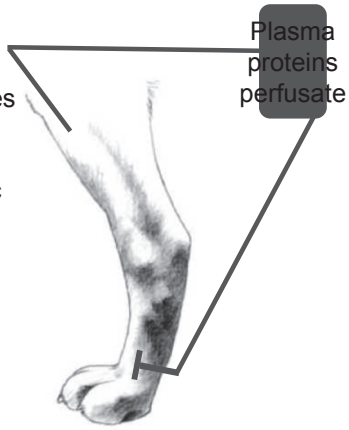
Constant limb weight=0 net fluid movement=isogravimetric state



Microcirculation

Capillary pressure varies according the plasma oncotic pressure to achieve isogravimetric state

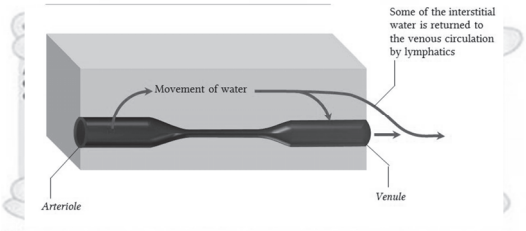
Rate of filtration-reabsorption=P_c-$P_{c(iso)}$



Microcirculation

Classic Starling Principle

- Landis, Pappenheimer and Soto-Rivera
- Krogh, Landis and Turner 1931
  - Hydrostatic and oncotic pressures



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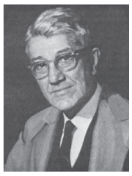
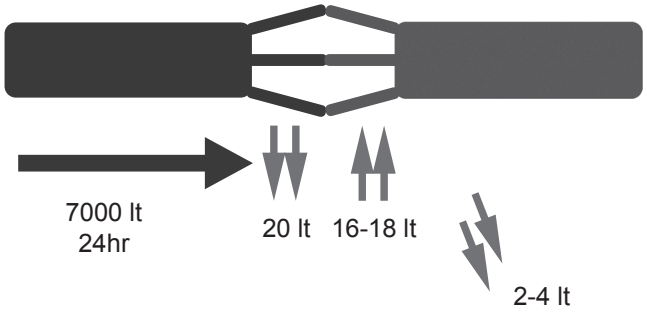


Eugene Markley Landis
1901-1987

John Richard Pappenheimer
1915-2007

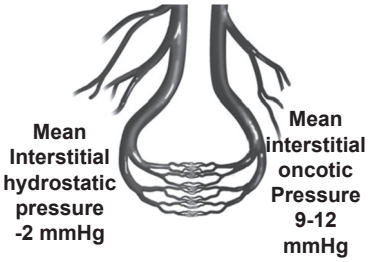
- 1963 quatinfied the values of filtration-absorption

Microcirculation

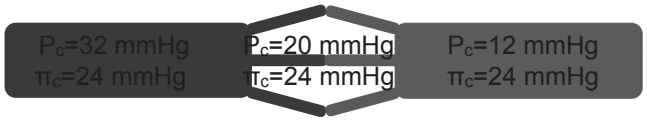


Microcirculation

- 1963 Guyton measured the interstitial hydrostatic and oncotic pressures



Microcirculation



P_i=-2 mmHg
π_i=9-12 mmHg

P_i=0 mmHg
π_i=9-12 mmHg

P_i=0 mmHg
π_i=9-12 mmHg

Microcirculation

Ernest Ruska
1906-1988

Max Knoll
1897-1969

- 1931 developed the electron microscope. 10 nm resolution
- 1944 2 nm resolution

Microcirculation

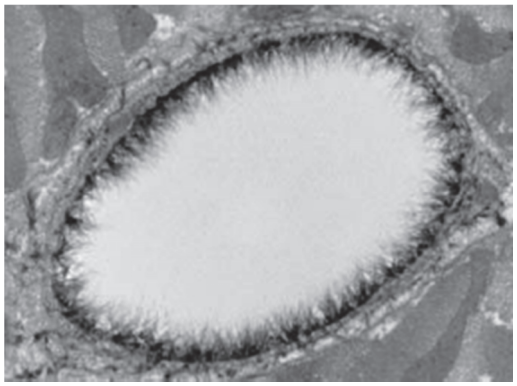
James Frederic Danielli
1911-1984

- 1940 First postulated the presence of the Glycocalyx

Microcirculation
Glycocalyx

- Hydrogel-like layer
- Hemodynamic function 1970
- Main structure
  - Glycoproteins y proteoglycans

Microcirculation
Glycocalyx



Microcirculation

1951 Staverman's Reflection Coefficient

NON-EQUILIBRIUM THERMODYNAMICS OF MEMBRANE PROCESSES

By A. J. Staverman
Plastics Research Institute T.N.O., Delft, Netherlands

Received 21st May, 1951 ; *in final form* 10th *August*, 1951

By applying the theory of non-equilibrium thermodynamics to membrane processes it is found that the action of a membrane in a system containing n components is completely characterized by $\frac{1}{2}n(n+1)$ thermodynamical constants.

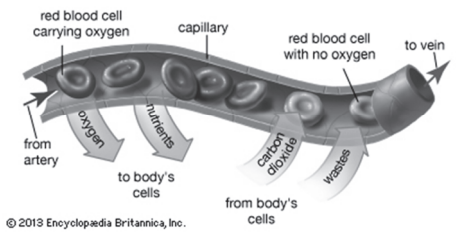
In measurements of transference numbers, membrane potentials and electrokinetic constants, a set of phenomenological constants can be determined from which, if sufficient independent data are obtained, the thermodynamical constants may be computed.

The relations between phenomenological and thermodynamical constants are given. Also a number of relations between different phenomenological constants is given, which must hold independently of any model of the action of the membrane. Some of these relations, such as Nernst's equation for the diffusion potential and some relations between electrokinetic constants have been derived before by quasi-thermodynamical reasonings or from calculations on models. Others, such as the relation between mechanical and

Microcirculation

1951 Staverman's Reflection Coefficient

Vessel Permeability
Tight or moderate
<3nm
Fenestration
>3nm

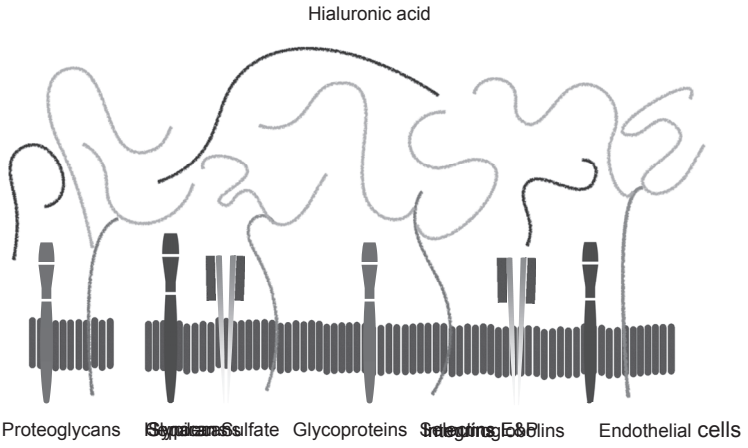


Lymphedema

Glycocalyx

- 500-2000 nm
- Total surface 4000 - 7000 m^2 (0.98 - 1.7 acres)
- Negative net charge
- Rheologic function and microenviroment control

Glycocalyx model



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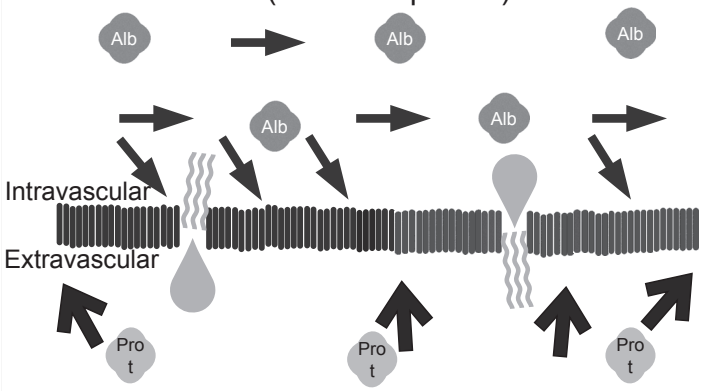
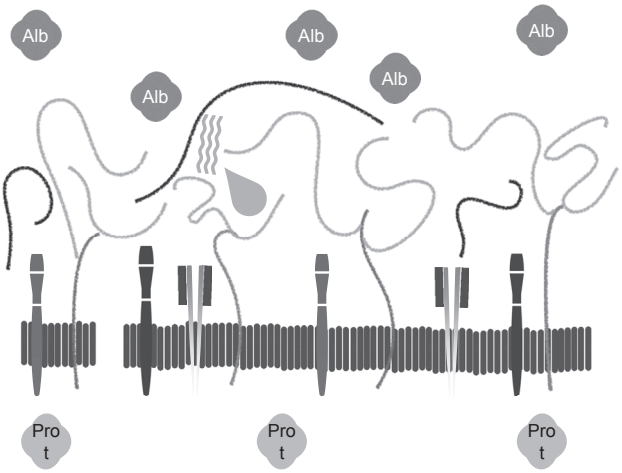


Glycocalyx model



Microcirculation

Charles C Michel

Roger H Adamson

J Rodney Levick

Sheldon Weinbaum

Microcirculation

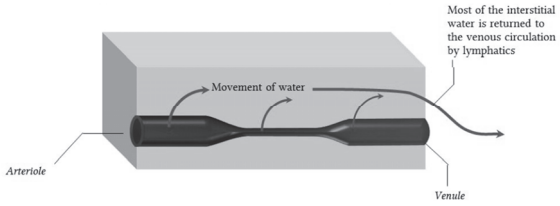
Charles C Michel

- 70's-60's replicated Starling's findings
- 1987 Transient-state and Steady-state of absorption

Lymphedema

Revised Starling Principle

- Adamson 2004- Levick and Michel 2010
  - Glycocalyx function



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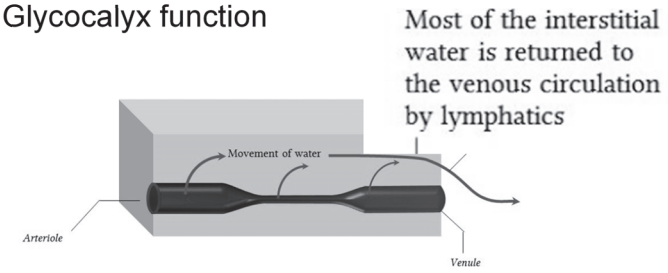
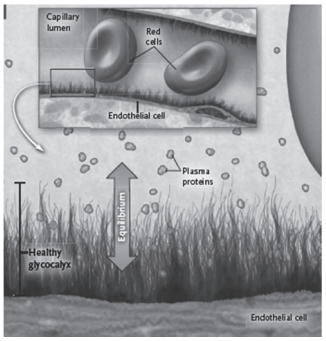


Lymphedema

Glycocalyx model



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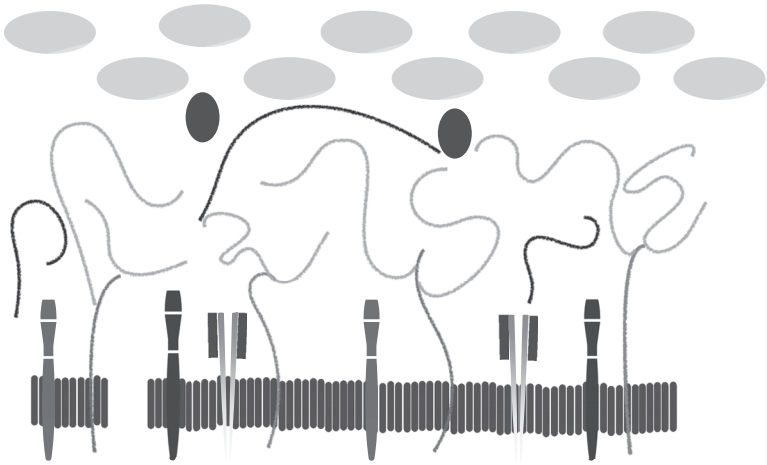

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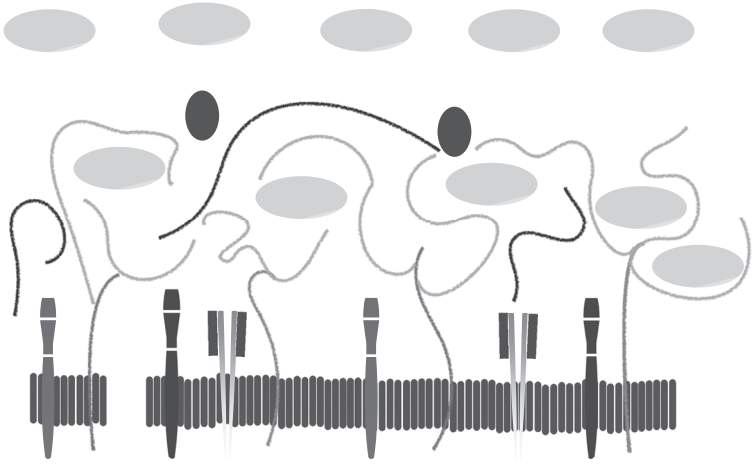

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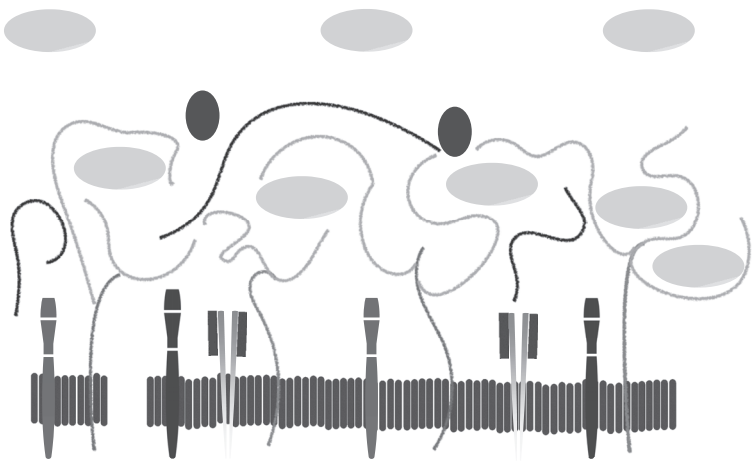

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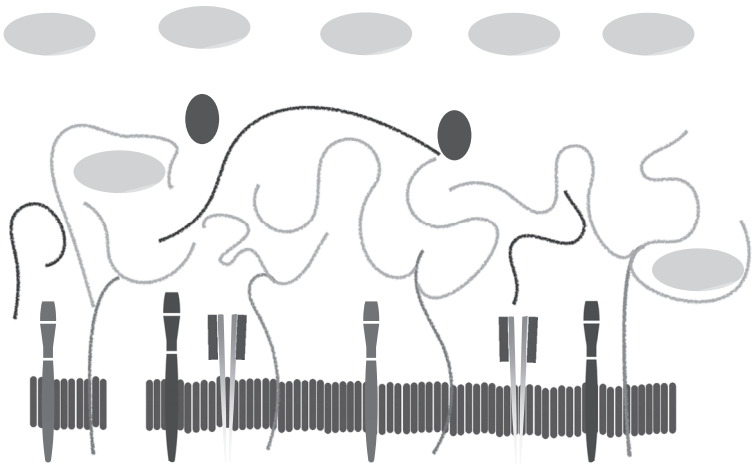
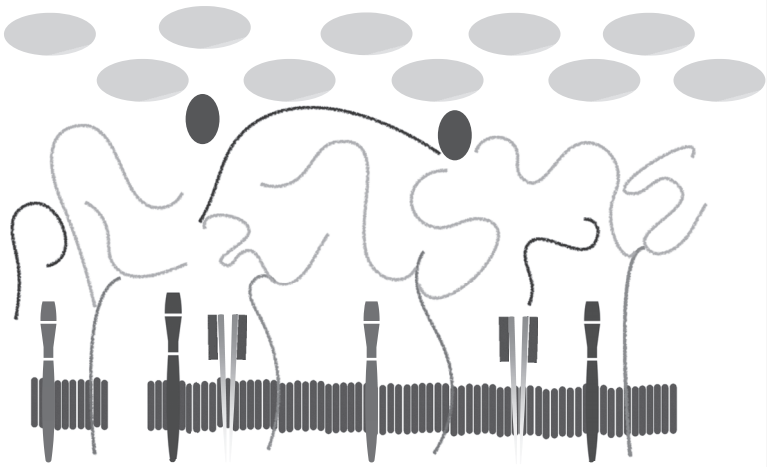
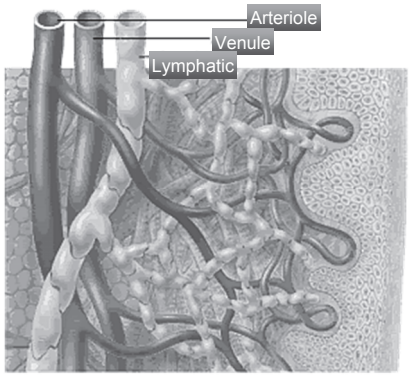


Glycocalyx model



1-1.5 liters of fluid

Microcirculation



Lymphedema

Földiklinik
Fachklinik für Lymphologie

- Tobias Bertsch, MD
- Guenter Klose, CLT

TEAM EFFORT!!!!

Sadly some patients can't be helped